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 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.

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.

<table>
<thead>
<tr>
<th>Time (hours)</th>
<th>Amount dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>not more than 25%</td>
</tr>
<tr>
<td>4</td>
<td>between 20% and 40%</td>
</tr>
<tr>
<td>8</td>
<td>between 40% and 60%</td>
</tr>
<tr>
<td>20</td>
<td>not less than 80%</td>
</tr>
</tbody>
</table>

Uniformity of dosage units (905): meet the requirements.

Ampoules or glass containers—Store at 25° ± 2°, excursions permitted between 15° and 30°.

Metoprolol Tartrate—

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

Metoprolol Tartrate contains not less than 99.0 percent and not more than 101.0 percent of \((C_{15}H_{25}NO_3) _2 \cdot C_4H_6O_4\) calculated on the dried basis.

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

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 suitable 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 water) and use the solution of potassium iodide, if necessary (see Section Reagents, Indicators, and Solutions).
bottling 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 (C15H25NO3)2 · C4H6O6.

**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 [(C15H25NO3)2 · C4H6O6].

**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**—Dilute USP Oxprenolol Hydrochloride RS in freshly prepared Mobile phase to obtain a solution containing about 720 µg per mL. Prepare a degassed solution of 9.0 g of sodium chloride in water to make 1000 mL.

**Standard preparation**—Dilute 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 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 1.0 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 [(C15H25NO3)2 · C4H6O6], in each mL of the Injection taken by the formula:

\[
\frac{(L / D) \times (C \times R_u)}{R_i}
\]

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 \(R_i\) 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 [(C15H25NO3)2 · C4H6O6]. Prepare Metoprolol Tartrate Oral Solution 10 mg per mL as follows (see Pharmaceutical Compounding—Nonsterile Preparations (795). See also Metoprolol Tartrate Oral Suspension):

<table>
<thead>
<tr>
<th>Metoprolol Tartrate powder</th>
<th>1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle for Oral Solution</td>
<td>100 mL</td>
</tr>
<tr>
<td>(regular or sugar-free), NF</td>
<td></td>
</tr>
<tr>
<td>, a sufficient quantity to make</td>
<td></td>
</tr>
</tbody>
</table>

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