Metoprolol Succinate Extended-Release Tablets

DEFINITION
Metoprolol Succinate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metoprolol succinate [(C15H25NO3)2·C4H6O4].

IDENTIFICATION
- **A. INFRARED ABSORPTION (197K)**
  - Sample solution: Equivalent to 200 mg of metoprolol succinate from 1 or more Tablets to a stoppered centrifuge tube. Add 20 mL of pH 6.8 Phosphate Buffer (see Reagents, Indicators, and Solutions—Buffer Solutions) and 20 mL of methylene chloride, and shake for 5 min. Centrifuge, filter, and use the aqueous phase as the Sample solution.
  - Sample: Transfer 3 mL of the Sample 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.
  - Acceptance criteria: The IR spectrum of the Sample 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)**
  - Sample: Transfer 5 mL of the Sample solution prepared in Identification test A into 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.
  - Acceptance criteria: The IR spectrum of the Sample exhibits maxima only at the same wavelengths as that obtained from a similar preparation of succinic acid (presence of succinate).

ASSAY
- **PROCEDURE**
  - Analysis: Determine the mean percentage value of the labeled amount of metoprolol succinate [(C15H25NO3)2·C4H6O4] from the Tablets analyzed in the test for Uniformity of Dosage Units (905).
  - Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION (711)**
  - **Test 1** (08 1-Aug-2012)
    - Medium: pH 6.8 Phosphate Buffer (see Reagents, Indicators, and Solutions—Buffer Solutions); 500 mL
    - Apparatus 2: 50 rpm
    - Time: 1, 4, 8, and 20 h
    - Buffer, Mobile phase, and Standard solution: Proceed as directed in the test for Uniformity of Dosage Units (905).
    - Analysis: Proceed as directed in the test for Uniformity of Dosage Units (905), except use 5.0 mL of a filtered portion of the solution under test as the Sample solution, and use Medium as the blank, in comparison with a Standard solution having a known concentration of USP Metoprolol Succinate RS in the same Medium.
  - **Acceptance criteria:** *See Table 1.*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 25</td>
</tr>
<tr>
<td>4</td>
<td>20–40</td>
</tr>
<tr>
<td>8</td>
<td>40–60</td>
</tr>
<tr>
<td>20</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metoprolol succinate [(C15H25NO3)2·C4H6O4] dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

- **Test 2:** If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.
  - Medium: Simulated gastric fluid without enzyme, pH 1.2; 500 mL
  - Apparatus 2: 75 rpm
  - Time: 1, 4, 8, and 20 h
  - Buffer: 1 M monobasic sodium phosphate, 1 M phosphoric acid, and water (50:8:942). If necessary, adjust with 1 M monobasic sodium phosphate or 1 M phosphoric acid to a pH of 3.0.
  - Mobile phase: Acetonitrile and Buffer (250:750)
  - Standard solution: Prepare a solution of USP Metoprolol Succinate RS in Medium as directed in Table 2.

<table>
<thead>
<tr>
<th>Tablet Strength (mg as metoprolol succinate)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>0.380</td>
</tr>
<tr>
<td>100</td>
<td>0.190</td>
</tr>
<tr>
<td>50</td>
<td>0.095</td>
</tr>
<tr>
<td>25</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Sample solution: Pass the solution under test thorough a suitable filter.

Chromatographic system
(See Chromatography (621), System Suitability.)

| Mode: | LC |
| Detector: | UV 280 nm |
| Column: | 4.0-mm x 12.5-cm; 4-µm packing L7 |
| Flow rate: | 1 mL/min |
| Injection volume: | See Table 3. |

<table>
<thead>
<tr>
<th>Tablet Strength (mg as metoprol succinate)</th>
<th>Volume (µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>200</td>
<td>5</td>
</tr>
</tbody>
</table>
Metoprolol

System suitability
Sample: Standard solution
Suitability requirements
Column efficiency: NLT 1500 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis:
Samples: Standard solution and Sample solution
Calculate the concentration, \( C_i \) in mg/mL of metoprolol succinate dissolved in Medium at each time point, \( t_i \)

\[
\text{Result}_i = \left( \frac{r_i}{r_S} \right) \times C_i
\]

\( r_i \) = peak response of metoprolol from the Sample solution
\( r_S \) = peak response of metoprolol from the Standard solution
\( C_i \) = concentration of USP Metoprolol Succinate RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of metoprolol succinate \( \left( \left[ \left( C_i \times (V - V_i) \right) \right] \times \left( V - V_i \right) \right) \times \left( \frac{1}{V_i} \right) \times \left( \frac{1}{V_L} \right) \times 100 \)

\( r_i \) = peak response of metoprolol from the Sample solution
\( r_S \) = peak response of metoprolol from the Standard solution
\( C_i \) = concentration of USP Metoprolol Succinate RS in the Standard solution (mg/mL)
\( V \) = volume of Medium; 500 mL
\( V_i \) = volume of the Sample solution withdrawn from the Medium (mL)
\( L \) = label claim (mg/Tablet)
Tolerances: See Table 4.

| Time Point (hr) | Time Point (hr) | Amount Dissolved (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>20-40</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>55-85</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metoprolol succinate \( \left( \left[ \left( C_i \times (V - V_i) \right) \right] \times \left( V - V_i \right) \right) \times \left( \frac{1}{V_i} \right) \times \left( \frac{1}{V_L} \right) \times 100 \) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).</p>

**Unifomity of Dosage Units (905):** Meet the requirements

Procedure for content uniformity
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:** Acetonitrile and Buffer (250:750)

**Standard solution:** 0.05 mg/mL of USP Metoprolol Succinate RS in Mobile phase

**Sample stock solution:** Nominally 1 mg/mL of metoprolol succinate prepared as follows. Transfer 1 Tablet to a suitable volumetric flask, add about 5 mL of water, and allow the Tablet to disintegrate. Add a volume of alcohol to fill 30% of final volume, and shake for 30 min. Add a portion of 0.1 N hydrochloric acid to fill 50% of the flask volume, and shake for an additional 30 min. Dilute with 0.1 N hydrochloric acid to volume. Filter, and discard the first 10 mL of the filtrate.

**Sample solution:** Nominally 0.05 mg/mL of metoprolol succinate from the Sample stock solution in Mobile phase

**Chromatographic system**
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 280 nm
Column: 4-mm × 12.5-cm; packing L7
Flow rate: 1 mL/min
Injection volume: 40 µL

**System suitability**
Sample: Standard solution
Suitability requirements
Relative standard deviation: NMT 2.0%
Analysis:
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of metoprolol succinate \( \left( \left[ \left( C_i \times (V - V_i) \right) \right] \times \left( V - V_i \right) \right) \times \left( \frac{1}{V_i} \right) \times \left( \frac{1}{V_L} \right) \times 100 \) dissolved in

\( r_i \) = peak response of metoprolol from the Sample solution
\( r_S \) = peak response of metoprolol from the Standard solution
\( C_i \) = concentration of USP Metoprolol Succinate RS in the Standard solution (mg/mL)
\( C_U \) = nominal concentration of metoprolol succinate in the Sample solution (mg/mL)

**ADDITIONAL REQUIREMENTS**
- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

**Change to read:**
- **Labeling:** Label it to indicate the content of metoprolol succinate and its equivalent, expressed as metoprolol tartrate \( \left( \left[ \left( C_i \times (V - V_i) \right) \right] \times \left( V - V_i \right) \right) \times \left( \frac{1}{V_i} \right) \times \left( \frac{1}{V_L} \right) \times 100 \). When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
- **USP Reference Standards (11)**
  USP Metoprolol Succinate RS