Metoprolol Succinate Extended-Release Tablets

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Posting Date: 27–Jul–2018
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Expert Committee: Chemical Medicines Monographs 2
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Metoprolol Succinate Extended-Release Tablets monograph. The purpose for the revision is to add Dissolution Test 4 to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests. The revision also necessitates a change in the table numbering in the Organic Impurities test.

- Dissolution Test 4 was validated using a Hypersil BDS C18 brand of L1 column. The typical retention time for metoprolol is about 4 min.

The Metoprolol Succinate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

See below for additional information about the proposed text.¹

Should you have any questions, please contact Donald Min, Ph.D., Senior Scientific Liaison (301-230-7457 or ddm@usp.org).

¹ The addition of Dissolution Test 3 (which includes Table 5) to the Metoprolol Succinate Extended-Release Tablets monograph is currently being proposed under the Pending monograph process.
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 \([\text{C}_{15}\text{H}_{25}\text{NO}_{3}\cdot\text{C}_{4}\text{H}_{6}\text{O}_{2}]\).

IDENTIFICATION
- A. INFRARED ABSORPTION (197K)
  Sample solution: Equivalent to 200 mg of metoprolol succinate from NLT 1 Tablet in a stoppered centrifuge tube. Add 40 mL of pH 6.8 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions) and 40 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 separation funnel. 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 those 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 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 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 those obtained from a similar preparation of succinic acid (presence of succinate).

Add the following:

- C. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

Change to read:

- PROCEDURE
  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 a suitable number of Tablets to a suitable volumetric flask, add about 5 mL of water, and allow the Tablets to disintegrate. Add a volume of alcohol to fill 30% of the flask 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; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 40 µL

System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of metoprolol succinate \([\text{C}_{15}\text{H}_{25}\text{NO}_{3}\cdot\text{C}_{4}\text{H}_{6}\text{O}_{2}]\) in the portion of Tablets taken:

\[
\text{Result} = \frac{(r_0/r_1)}{(C_1/C_0)} \times 100
\]

\[r_0 = \text{peak response of metoprolol from the Sample solution}\]
\[r_1 = \text{peak response of metoprolol from the Standard solution}\]
\[C_1 = \text{concentration of USP Metoprolol Succinate RS in the Standard solution (mg/mL)}\]
\[C_0 = \text{nominal concentration of metoprolol succinate in the Sample solution (mg/mL)}\]

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- DISSOLUTION (711)
  Test 1
  Medium: pH 6.8 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions); 500 mL
  Apparatus 2: 50 rpm
  Times: 1, 4, 8, and 20 h
  Buffer, Mobile phase, and Standard solution: Prepare as directed in the Assay.
  Analysis: Proceed as directed in the Assay 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 with 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 \([\text{C}_{15}\text{H}_{25}\text{NO}_{3}\cdot\text{C}_{4}\text{H}_{6}\text{O}_{2}]\) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 2.
Prepare a solution of USP Metoprolol Succinate RS in Medium as directed in Table 2.

**Medium:** Simulated gastric fluid without enzyme, pH 1.2; 500 mL

**Apparatus 2:** 75 rpm

**Times:** 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.

**Sample solution:** Pass the solution under test through a suitable filter.

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

**Mode:** LC

**Detector:** UV 280 nm

**Column:** 4.0-mm × 12.5-cm; 4-µm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** See Table 3.

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

<table>
<thead>
<tr>
<th>Column efficiency</th>
<th>NLT 1500 theoretical plates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tailing factor</td>
<td>NMT 2.0</td>
</tr>
<tr>
<td>Relative standard deviation</td>
<td>NMT 2.0%</td>
</tr>
</tbody>
</table>

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration (C) of metoprolol succinate dissolved in Medium at each time point (t):

\[
C = \frac{(C_i \times (V - 2 \times V_i)) + (C_i \times C_i \times V_i)) \times (1/L) \times 100}{(1/L) \times 100}
\]

Result = \(C_1 \times (1/L) \times 100\)

Result = \(C_2 \times (1/L) \times 100\)

Result = \(C_3 \times (1/L) \times 100\)

Result = \(C_4 \times (1/L) \times 100\)

**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>

**Table 3**

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

The percentages of the labeled amount of metoprolol succinate dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 4:** If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 4.

**Medium:** Phosphate buffer, pH 6.8 (dissolve 6.8 g of monobasic potassium phosphate and 0.93 g of sodium hydroxide in 1 L of water; adjust with sodium hydroxide to a pH of 6.8); 500 mL

**Apparatus 2:** 50 rpm

**Times:** 1, 4, 8, and 24 h

**Buffer:** 5.0 mL/L of triethylamine in water. Adjust with phosphoric acid to a pH of 3.0.

**Mobile phase:** Methanol and Buffer (40:60)

**Standard solution:** Prepare a solution of USP Metoprolol Succinate RS in Medium as directed in Table 5.

**Table 4**

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</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>

**Table 5**

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>200</td>
<td>0.4</td>
</tr>
<tr>
<td>100</td>
<td>0.2</td>
</tr>
<tr>
<td>50</td>
<td>0.1</td>
</tr>
<tr>
<td>25</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Sample solution:** Withdraw a 10-mL aliquot at each time point. Pass the solution under test through a suitable filter of 0.45-µm pore size. Replace the portion withdrawn with an equal volume of Medium.

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

**Mode:** LC

**Detector:** UV 223 nm

**Column:** 4.6-mm × 25-cm; 5-µm packing L1

**Column temperature:** 30° C

**Flow rate:** 1.5 mL/min

**Injection volume:** 5 µL

**Run time:** NLT 2 times the retention time of metoprolol.

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System suitability
Sample: Standard solution
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration (C) of metoprolol succinate dissolved in Medium at each time point (i):

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

where:
- \( r_i \) = peak response of each unspecified degradation product from the Sample solution
- \( r_d \) = 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 \([(C_{15}H_{25}NO_3)_2 \cdot C_6H_5O_2] \) dissolved \((Q_i)\) at each time point (i):

\[ \text{Result}_1 = C_i \times V \times \frac{1}{L} \times 100 \]
\[ \text{Result}_2 = \left( C_i \times V \right) + \left( C_i \times V_j \right) \times \frac{1}{L} \times 100 \]
\[ \text{Result}_3 = \left( C_i \times V \right) + \left( C_i \times C_d \times V_j \right) \times \frac{1}{L} \times 100 \]

where:
- \( V \) = volume of Medium, 500 mL
- \( L \) = label claim (mg/Tablet)
- \( V_j \) = volume of the Sample solution withdrawn from the Medium (mL)

Tolerances: See Table 6.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (Tablet labeled 25 mg) (%)</th>
<th>Amount Dissolved (Tablets labeled 50, 100, and 200 mg) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT.20</td>
<td>NMT.20</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>20-40</td>
<td>5-35</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>42-67</td>
<td>38-64</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT.80</td>
<td>NLT.80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metoprolol succinate \([(C_{15}H_{25}NO_3)_2 \cdot C_6H_5O_2] \) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.\(^\text{R8 1-Aug-2018}\)

Change to read:

**Uniformity of Dosage Units (905):** Meet the requirements \(^\text{▲ USP41}\)

**Impurities**

Change to read:

\(^\text{▲ Organic Impurities}\)

Buffer: 1.15 mL of phosphoric acid in 2 L of water. Add 2.6 g of sodium dodecyl sulfate. Sonicate to dissolve.

Solution A: Methanol and Buffer (30:70)

Solution B: Acetonitrile and Buffer (75:25)

Mobile phase: See Table 7

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>20</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>25</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>30</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>35</td>
<td>35</td>
<td>65</td>
</tr>
<tr>
<td>37</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>50</td>
<td>65</td>
<td>35</td>
</tr>
</tbody>
</table>

Diluent: Acetonitrile and Buffer (40:60)

System suitability solution: 3 µg/mL of USP Metoprolol Related Compound A RS and 1 mg/mL of USP Metoprolol Succinate RS in Diluent

Standard solution: 3 µg/mL of USP Metoprolol Succinate RS in Diluent

Sensitivity solution: 0.5 µg/mL of USP Metoprolol Succinate RS from Standard solution in Diluent

Sample solution: Nominally 1 mg/mL of metoprolol succinate from Tablets prepared as follows. Transfer a portion of finely powdered Tablets (NLT 20), equivalent to 50 mg of metoprolol succinate, to a 50-mL volumetric flask. Add Diluent to fill 60% of the flask volume and sonicate for 30 min with intermittent shaking. Dilute with Diluent to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

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

Mode: LC

Detector: UV 223 nm

Column: 4.6-mm x 15-cm; 5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability
Samples: System suitability solution, Standard solution, and Sensitivity solution

Suitability requirements
Resolution: NLT 2.0 between metoprolol related compound A and metoprolol, System suitability solution

Relative standard deviation: NMT 5.0%, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each unspecified degradation product in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_i}{r_d} \right) \times \left( \frac{C_i}{C_d} \right) \times 100 \]

where:
- \( r_i \) = peak response of each unspecified degradation product from the Sample solution
- \( r_d \) = peak response of metoprolol from the Standard solution
- \( C_i \) = concentration of USP Metoprolol Succinate RS in the Standard solution (µg/mL)
- \( C_d \) = nominal concentration of metoprolol succinate in the Sample solution (µg/mL)

Acceptance criteria: See Table 8.\(^\text{R8 1-Aug-2018}\) Reporting threshold: 0.05%.
### Table 8

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinic acid&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.1</td>
<td>—</td>
</tr>
<tr>
<td>Metoprolol related compound A</td>
<td>0.83</td>
<td>—</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>0.20</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<sup>a</sup> Counter ion included for identification only.

**ADDITIONAL REQUIREMENTS**

- **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 succinate \([\text{C}_{15}\text{H}_{25}\text{NO}_3\text{O}_{3}\] \cdot \text{C}_4\text{H}_6\text{O}_6\). When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

**Change to read:**

- **USP REFERENCE STANDARDS (11)**
  - USP Metoprolol Related Compound A RS
  - USP Metoprolol Succinate RS

  \[\text{C}_{14}\text{H}_{23}\text{NO}_3\quad 253.34\] USP41

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