Metoprolol Succinate Extended-Release Tablets

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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 5 to accommodate drug products that were approved with different conditions and tolerances than the existing dissolution tests. The revision also necessitates a change in the table numbering in the Organic Impurities test.

- Dissolution Test 5 was validated using an Agilent Eclipse XDB C8 brand of L7 packing. The typical retention time for metoprolol is about 2.2 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 to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).

¹ The addition of Dissolution Test 3 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 [(C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>)<sub>2</sub>·C<sub>6</sub>H<sub>5</sub>O<sub>2</sub>] in the portion of Tablets taken.

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 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 those obtained from a similar preparation of the 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 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 those obtained from a similar preparation of succinic acid (presence of succinate).
• 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
• 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 x 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 [(C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>)<sub>2</sub>·C<sub>6</sub>H<sub>5</sub>O<sub>2</sub>] in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_o} \right) \times 100 \]

where:
- \( r_u \) = peak response of metoprolol from the Sample solution
- \( r_s \) = peak response of metoprolol from the Standard solution
- \( C_u \) = concentration of USP Metoprolol Succinate RS in the Standard solution (mg/mL)
- \( C_o \) = 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 [(C<sub>9</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>)<sub>2</sub>·C<sub>6</sub>H<sub>5</sub>O<sub>2</sub>] 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.
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)
**2 Metoprolol**

**Standard solution:** Prepare a solution of USP Metoprolol Succinate RS in Medium as directed in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablet Strength (mg, as metoprolol succinate)</td>
</tr>
<tr>
<td>200</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>25</td>
</tr>
</tbody>
</table>

**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.

**Table 3**

<table>
<thead>
<tr>
<th>Tablet Strength (mg, as metoprolol 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>

**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) of metoprolol succinate dissolved in Medium at each time point (t):

\[ \text{Result} = (r_0/r_s) \times C_s \]

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

Calculate the percentage of the labeled amount of metoprolol succinate \([\text{C}_{15}H_{25}NO_3 \cdot \text{C}_4\text{H}_9\text{O}_4] \) dissolved (Q), at each time point (t):

\[ \text{Result}_1 = C_s \times V \times (1/L) \times 100 \]
\[ \text{Result}_2 = \left( \left[ C_s \times [V - (V \times V_0)] \right] + (C_s \times V_0) \right) \times (1/L) \times 100 \]
\[ \text{Result}_3 = \left( \left[ C_s \times [V - (3 \times V_0)] \right] + [C_s + C_2 \times V_0] \right) \times (1/L) \times 100 \]
\[ \text{Result}_4 = \left( \left[ C_s \times [V - (3 \times V_0)] \right] + [C_1 + C_2 + C_3 \times V_0] \right) \times (1/L) \times 100 \]

\[ C_s = \text{concentration of metoprolol succinate in the portion of sample withdrawn at time point (t) (mg/mL)} \]
\[ V = \text{volume of Medium, 500 mL} \]
\[ L = \text{label claim (mg/Tablet)} \]

\[ V_s = \text{volume of the Sample solution withdrawn from the Medium (mL)} \]

**Tolerances:** See Table 4.

| Table 4 |
|---|---|---|
| Time Point (t) | Time (h) | Amount Dissolved (%) |
| 1    | 1   | NMT 20 |
| 2    | 4   | 20–40 |
| 3    | 8   | 55–85 |
| 4    | 20  | NLT 80 |

The percentages of the labeled amount of metoprolol succinate \([\text{C}_{15}H_{25}NO_3 \cdot \text{C}_4\text{H}_9\text{O}_4] \) 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 5 |
|---|---|
| Tablet Strength (mg) | Concentration (mg/mL) |
| 200 | 0.4 |
| 100 | 0.2 |
| 50  | 0.1 |
| 25  | 0.05 |

**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) of metoprolol succinate dissolved in Medium at each time point (t):

\[ \text{Result} = (r_0/r_s) \times C_s \]
Calculating the percentage of the labeled amount of metoprolol succinate ([C₁₅H₂₃NO₃]₂·C₃H₇O₄) dissolved (Q), at each time point (i):

$$
\text{Result}_1 = C_i \times V \times (1/L) \times 100
$$

$$
\text{Result}_2 = [(C_i \times V) + (C_i \times V_i)] \times (1/L) \times 100
$$

$$
\text{Result}_3 = [(C_i \times V) + ([C_i + C_i] \times V_i)] \times (1/L) \times 100
$$

$$
\text{Result}_4 = [(C_i \times V) + ([C_i + C_i + C_i] \times V_i)] \times (1/L) \times 100
$$

where:

- $C_i$ = concentration of metoprolol succinate in the portion of sample withdrawn at time point (i) (mg/mL)
- $V$ = volume of Medium, 500 mL
- $L$ = label claim (mg/Tablet)
- $V_i$ = volume of the Sample solution withdrawn from the Medium (mL)

**Tolerances:** See Table 6.

<table>
<thead>
<tr>
<th>Time Point (i)</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>15–35</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 ([C₁₅H₂₃NO₃]₂·C₃H₇O₄) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2. ▲ (RB 1-Aug-2018)

**Test 5:** If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 5. Medium: Phosphate buffer, pH 6.8 (dissolve 27.22 g of monobasic potassium phosphate and 3.6 g of sodium hydroxide in 4 L of water; adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.8); 500 mL Apparatus 2: 50 rpm, with sinkers Times: 1, 4, 8, and 20 h Buffer: Transfer 3.0 mL of triethylamine and 1.0 mL of phosphoric acid to a 1000-mL volumetric flask that contains 600 mL of water. Dilute with water to volume. Mobile phase: Acetonitrile and Buffer (25:75) Standard solution: Prepare a solution of USP Metoprolol Succinate RS in Medium as directed in Table 7.

**Table 7**

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

The percentages of the labeled amount of metoprolol succinate ([C₁₅H₂₃NO₃]₂·C₃H₇O₄) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2. ▲ (RB 1-Dec-2018)

**Table 6**

<table>
<thead>
<tr>
<th>Time Point (i)</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>15–35</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>

**Table 8**

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT:10</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>5–30</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>30–55</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>NLT:75</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of metoprolol succinate ([C₁₅H₂₃NO₃]₂·C₃H₇O₄) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2. ▲ (RB 1-Dec-2018)
Change to read:

### IMPURITIES

#### 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 9.

**Table 9**

<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 × 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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \(r_U\) = peak response of each unspecified degradation product from the Sample solution
- \(r_S\) = peak response of metoprolol from the Standard solution
- \(C_S\) = concentration of USP Metoprolol Succinate RS in the Standard solution (µg/mL)
- \(C_U\) = nominal concentration of metoprolol succinate in the Sample solution (µg/mL)

**Acceptance criteria:** See Table 10.

**Table 10**

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinic acid(^a)</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>

\(^a\) 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[(C\(_15\)H\(_25\)NO\(_3\))\(_2\)· C\(_4\)H\(_6\)O\(_6\)]. 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 Related Compound A RS
  - C\(_{14}\)H\(_{23}\)NO\(_3\) 253.34
  - USP Metoprolol Succinate RS