Morphine Sulfate Extended-Release Capsules

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<thead>
<tr>
<th>Type of Posting</th>
<th>Revision Bulletin</th>
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<tr>
<td>Posting Date</td>
<td>26–Oct–2018</td>
</tr>
<tr>
<td>Official Date</td>
<td>01–Nov–2018</td>
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<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 2</td>
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<td>Reason for Revision</td>
<td>Compliance</td>
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</tbody>
</table>

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Morphine Sulfate Extended-Release Capsules monograph. The purpose for the revision is to add Dissolution Test 3 to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- The same test procedure as in Dissolution Test 1 was used for Dissolution Test 3. The typical retention time for morphine is about 5 min with a MicroBondapak C18 brand of column with L1 packing.

The revision also necessitates a change in the table numbering in the Organic Impurities test.

The Morphine Sulfate Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Hillary Cai, Senior Scientific Liaison (301-230-3379 or hzc@usp.org).
Morphine Sulfate Extended-Release Capsules

**DEFINITION**
Morphine Sulfate Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of morphine sulfate pentahydrate [(C$_9$H$_{14}$NO$_3$)$_2$·H$_2$SO$_4$·5H$_2$O)].

**IDENTIFICATION**

- **A.** Standard solution and Sample solution: Prepare as directed in the Assay.

  Analysis: Inject 10 µL each of the Standard solution and the Sample solution using the Chromatographic system except for the Injection volume in the Assay.

  Acceptance criteria: The UV absorption spectrum of the morphine peak of the Sample solution and of the Standard solution exhibits maxima and minima at the same wavelengths, as obtained in the Assay.

- **B.** 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**

  Diluent: Water. Adjust with phosphoric acid to a pH of 3.6.

  Buffer solution: 13.8 mg/mL of monobasic sodium phosphate

  Solution A: Acetonitrile, triethylamine, Buffer solution, and water (25: 0.5: 100: 874.5). Adjust with phosphoric acid to a pH of 3.6.

  Solution B: Acetonitrile

  Mobile phase: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>44</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>54</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>55</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>65</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

  System suitability solution: 400 µg/mL of USP Morphine Sulfate RS and 10 µg/mL each of USP Morphine Related Compound A RS and USP Morphine Related Compound B RS (pseudomorphine) in Diluent

  Standard solution: 1.0 mg/mL of USP Morphine Sulfate RS in Diluent

  Sample stock solution: Transfer a weighed portion of the contents from NLT 20 Capsules, nominally equivalent to 250 mg of morphine sulfate pentahydrate, to a 100-mL volumetric flask. Add 5 mL of methanol and mix well for NLT 30 min with gentle swirling about every 5 min. Add Diluent up to half of the flask volume and sonicate for NLT 5 min to dissolve. Dilute with Diluent to volume.

  Sample solution: Nominally 1.0 mg/mL of morphine sulfate pentahydrate from the Sample stock solution in Diluent. Pass through a suitable filter and use the clear filtrate.

  Chromatographic system

  (See Chromatography (621), System Suitability.)

  Mode: LC

  Detector: UV 245 nm. For Identification A, use a diode array detector in the range of 200–400 nm.

  Columns

  Guard: Packing L1

  Analytical: 3.9-mm × 30-cm; 10-µm packing L1

  Flow rate: 2 mL/min

  Injection volume: 40 µL

  **System suitability**

  Samples: System suitability solution and Standard solution

  **Suitability requirements**

  Resolution: NLT 2.0 between the morphine related compound A and morphine sulfate peaks, System suitability solution

  Relative standard deviation: NMT 2.0%, Standard solution

  **Analysis**

  Samples: Standard solution and Sample solution

  Calculate the percentage of the labeled amount of morphine sulfate pentahydrate [(C$_9$H$_{14}$NO$_3$)$_2$·H$_2$SO$_4$·5H$_2$O] in the portion of Capsules taken:

  \[
  \text{Result} = \left( \frac{r_1}{r_2} \right) \times \left( \frac{C_1}{C_0} \right) \times \left( \frac{M_1}{M_2} \right) \times 100
  \]

  \( r_1 \) = peak response from the Standard solution

  \( r_2 \) = peak response from the Sample solution

  \( C_1 \) = concentration of USP Morphine Sulfate RS in the Standard solution (mg/mL), calculated on the anhydrous basis

  \( C_0 \) = nominal concentration of morphine sulfate pentahydrate in the Sample solution (mg/mL)

  \( M_{11} \) = molecular weight of morphine sulfate pentahydrate, 758.83

  \( M_{12} \) = molecular weight of anhydrous morphine sulfate, 668.77

  Acceptance criteria: 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Test 1**

  **pH 7.5 phosphate buffer:** 6.8 mg/mL of monobasic potassium phosphate and 1.6 mg/mL of sodium hydroxide. Adjust with phosphoric acid or 2 N sodium hydroxide to a pH of 7.5.

  **Medium:** Prepare as directed in Dissolution (711). Procedure, Apparatus 1 and Apparatus 2, Delayed-Release Dosage Forms, Method B Procedure, observing the following exceptions. Perform Acid Stage testing, using 500 mL of 0.1 N hydrochloric acid for 1 h; and perform Buffer Stage testing, using 500 mL of pH 7.5 phosphate buffer for NLT 8 h.

  **Apparatus 1:** 100 rpm

  **Times:** 1, 4, 6, and 9 h

  **Mobile phase:** Methanol, glacial acetic acid, and water (280:10:720), containing 0.73 g of sodium 1-heptanesulfonate for each 0.091 L of the solvent mixture

  **System suitability solution:** 0.1 mg/mL each of phenol and USP Morphine Sulfate RS in Mobile phase

  **Standard solution:** USP Morphine Sulfate RS in pH 7.5 phosphate buffer to obtain a solution with a known concentration corresponding to that of the Sample solution

  **Sample solution:** Sample per Dissolution (711).

  Chromatographic system

  (See Chromatography (621), System Suitability.)

  **Mode:** LC

  **Detector:** UV 284 nm
2 Morphine

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Column: 3.9-mm x 30-cm; 10-µm packing L1
Flow rate: 2 mL/min
Injection volume: 25 µL

System suitability
Sample: System suitability solution

Suitability requirements
Resolution: NLT 2.0 between the phenol and morphine sulfate peaks
Tailing factor: NMT 2.0 for the morphine sulfate peak
Relative standard deviation: NMT 2.0% for the morphine sulfate peak

Analysis
Samples: Standard solution and Sample solution

Tolerances: See Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of morphine sulfate pentahydrate \([C_{17}H_{19}NO_2\cdot H_2SO_4\cdot 5H_2O]\) dissolved in 1 h conforms to Dissolution (711), Acceptance Table 3. The percentages of the labeled amount of morphine sulfate pentahydrate \([C_{17}H_{19}NO_2\cdot H_2SO_4\cdot 5H_2O]\) dissolved at each time point 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
Acid stage: 0.1 N hydrochloric acid (HCl); 500 mL
Buffer stage: pH 7.5 phosphate buffer (dissolve 40.8 g of monobasic potassium phosphate and 9.6 g of sodium hydroxide in 6 L of water; adjust with phosphoric acid or 2 N sodium hydroxide to a pH of 7.5); 500 mL
Apparatus 1: 100 rpm
Times: 1, 4, 6, and 9 h
Solution A: 0.1% phosphoric acid and 0.1% triethylamine in water
Mobile phase: Solution A and methanol (93:7)
Standard stock solution: 2.0 mg/mL of USP Morphine Sulfate RS in water
Standard solution: 0.16 mg/mL of USP Morphine Sulfate RS in either the Acid stage under Medium or in the Buffer stage under Medium, from Standard stock solution
Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size. Centrifuge the filtrate if necessary.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm x 15-cm; 5-µm packing L7
Column temperature: 25°
Flow rate: 1.5 mL/min
Injection volume: 5 µL
Run time: NLT 2 times the retention time of morphine

System suitability
Sample: Standard solution

Suitability requirements
Resolution: NLT 2.0 between the phenol and morphine sulfate peaks
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution

Tolerances: See Table 3.

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Point (h)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of morphine sulfate pentahydrate released at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP Dissolution Test 3. Proceed as directed in Test 1, except for Tolerances.

Tolerances: See Table 4.

<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Table 4 (continued)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>74-94</td>
</tr>
<tr>
<td>9</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of morphine sulfate pentahydrate \([(C_{17}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O]\) dissolved in 1 h conforms to Dissolution (711), Acceptance Table 3. The percentages of the labeled amount of morphine sulfate pentahydrate \([(C_{17}H_{21}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O)] dissolved at the other times specified conform to Dissolution (711), Acceptance Table 2. ▲ (RB 1-Nov-2018)

**• UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

**IMPURITIES**

**Change to read:**

- **ORGANIC IMPURITIES**
  - Diluent, Solution A, System suitability solution, Chromatographic system, and Sample solution:
    Proceed as directed in the Assay.
  - Sensitivity solution: 0.5 µg/mL of USP Morphine Sulfate RS in Diluent
  - Standard solution: 0.002 mg/mL of USP Morphine Sulfate RS and 0.005 mg/mL each of USP Morphine Related Compound A RS and USP Morphine Related Compound B RS (pseudomorphine) in Diluent
  - System suitability
    - Samples: System suitability solution, Standard solution, and Sensitivity solution
    - Suitability requirements
      - Resolution: NLT 2.0 between the morphine related compound A and morphine sulfate peaks, System suitability solution
      - Signal-to-noise ratio: NLT 10 for morphine sulfate, Sensitivity solution
      - Relative standard deviation: NMT 5% for morphine related compound A, morphine sulfate, and morphine related compound B, Standard solution
  - Analysis
    - Samples: Diluent, Standard solution, and Sample solution
    - Calculate the percentage of the morphine related compound A and morphine related compound B in the portion of Capsules taken:
      
      \[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_u}{C_s} \right) \times 100 \]
      
      \( r_u \) = peak response of morphine related compound A or morphine related compound B from the Sample solution
      \( r_s \) = peak response of USP Morphine Related Compound A RS or USP Morphine Related Compound B RS from the Standard solution
      \( C_u \) = nominal concentration of morphine sulfate pentahydrate in the Sample solution (mg/mL)
      \( C_s \) = concentration of USP Morphine Related Compound A RS or USP Morphine Related Compound B RS in the Standard solution (mg/mL)
      
      Calculate the percentage of any unspecified impurity in the portion of Capsules taken:
      
      \[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times 100 \]
      
      \( r_u \) = peak response of any individual unspecified impurity from the Sample solution
      \( r_s \) = peak response of morphine sulfate from the Sample solution

  - Acceptance criteria: See Table 5, ▲ (RB 1-Nov-2018) Disregard any peaks below 0.05% and the peaks corresponding to those from the Diluent.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine related compound A*</td>
<td>1.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Morphine sulfate</td>
<td>1.0</td>
<td>-</td>
</tr>
<tr>
<td>Morphine related compound B*</td>
<td>2.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Any unspecified impurity</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* 7,8-Didehydro-4,5a-epoxy-17-methylmorphinan-3,6a-diol, N-oxide.
* 2,2'-Bimorphine.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at controlled room temperature.
- **Labeling:** When more than one test for Dissolution is given, the Labeling section states the test for Dissolution used only if Test 1 is not used.
- **USP Reference Standards** (11)
  - USP Morphine Related Compound A RS
  - 7,8-Didehydro-4,5a-epoxy-17-methylmorphinan-3,6a-diol, N-oxide.
  - \( \text{C}_{17}\text{H}_{21}\text{NO}_3 \) 301.34
  - USP Morphine Related Compound B RS
  - 2,2'-Bimorphine.
  - \( \text{C}_{16}\text{H}_{21}\text{N}_{2}\text{O}_3 \) 568.66
  - USP Morphine Sulfate RS

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