Morphine Sulfate Extended-Release Capsules

Type of Posting	Revision Bulletin
Posting Date	26–Oct–2018
Official Date	01–Nov–2018
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 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 [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$].

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 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
33	100	0
44	85	15
54	85	15
55	100	0
65	100	0

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 [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$] in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Morphine Sulfate RS in the *Standard solution* (mg/mL), calculated on the anhydrous basis
C_U = nominal concentration of morphine sulfate pentahydrate in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of morphine sulfate pentahydrate, 758.83
M_{r2} = 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 1.01 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

Column: 3.9-mm × 30-cm; 10-µm packing L1
Flow rate: 2 mL/min
Injection volume: 25 µL
System suitability
Sample: *System suitability solution*
[NOTE—The relative retention times for phenol and morphine sulfate are about 0.8 and 1.0, respectively.]
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 2

Time (h)	Amount Dissolved (%)
1	NMT 10
4	25–50
6	50–90
9	NLT 85

The percentage of the labeled amount of morphine sulfate pentahydrate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$] dissolved in 1 h conforms to *Dissolution* ⟨711⟩, *Acceptance Table 3*. The percentages of the labeled amount of morphine sulfate pentahydrate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$)] dissolved at the other 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
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 × 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
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Replace the *Acid stage* under *Medium* immediately after 1 h with the *Buffer stage* under *Medium*.
Calculate the concentration (C_i) of morphine sulfate pentahydrate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$] in the sample withdrawn from the vessel at each time point (*i*):

$$\text{Result}_i = (r_U/r_S) \times C_S$$

r_U = peak response of morphine from the *Sample solution* at each time point (*i*)
r_S = peak response of morphine from the appropriate *Standard solution* at each time point (*i*)
C_S = concentration of USP Morphine Sulfate RS in the appropriate *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of morphine sulfate pentahydrate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$] dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = C_2 \times V \times (1/L) \times 100$$
$$\text{Result}_3 = \{[C_3 \times (V - V_S)] + (C_2 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of morphine sulfate pentahydrate [$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$] in the portion of the sample withdrawn at each time point (*i*) (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Capsule)
V_S = volume of *Medium* taken (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 10
2	4	10–35
3	6	50–70
4	9	NLT 80

The percentages 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 4

Time (h)	Amount Dissolved (%)
1	NMT 10
4	36–56

Table 4 *(continued)*

Time (h)	Amount Dissolved (%)
6	74–94
9	NLT 85

The percentage of the labeled amount of morphine sulfate pentahydrate $[(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O]$ dissolved in 1 h conforms to *Dissolution* ⟨711⟩, *Acceptance Table 3*. The percentages of the labeled amount of morphine sulfate pentahydrate $[(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O)]$ 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 morphine related compound A and morphine related compound B in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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_S = concentration of USP Morphine Related Compound A RS or USP Morphine Related Compound B RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any unspecified impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of any individual unspecified impurity from the *Sample solution*

r_T = 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 ▲5▲ (RB 1-Nov-2018)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Morphine related compound A[a]	1.4	0.5
Morphine sulfate	1.0	—
Morphine related compound B[b]	2.3	0.5
Any unspecified impurity	—	0.2
Total impurities	—	1.5

[a] 7,8-Didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol, *N*-oxide.
[b] 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-4,5α-epoxy-17-methylmorphinan-3,6α-diol, *N*-oxide.
$C_{17}H_{19}NO_4$ 301.34

USP Morphine Related Compound B RS
2,2′-Bimorphine.
$C_{34}H_{36}N_2O_6$ 568.66

USP Morphine Sulfate RS