Metoprolol Succinate Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	26–Jan–2018, revised 12–Feb–2018[1]
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Metoprolol Succinate Extended-Release Tablets monograph.

Based on the supporting documents received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Test 3* in *Dissolution* section of the monograph.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph[2]. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

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 notice was revised on February 12, 2018 to make editorial changes and add footnote. No changes were made to the content of the proposed monograph.

[2] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the monograph in effect today. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text as a courtesy to indicate changes that we anticipate will be made official once the product subject to this pending monograph receives FDA approval. Once FDA approval is granted, the official monograph will include the changes indicated herein and any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval.

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 $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$.

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 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).

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*.▲*USP41*

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 $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ in the portion of Tablets taken:

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

  r_U = peak response of metoprolol 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* (mg/mL)
  C_U = nominal concentration of metoprolol succinate in the *Sample solution* (mg/mL)▲*USP41*

  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*.▲*USP41*
  Analysis: Proceed as directed in the ▲*Assay*,▲*USP41* 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 1

Time (h)	Amount Dissolved (%)
1	NMT 25
4	20–40
8	40–60
20	NLT 80

  The percentages of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ 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)
Standard solution: Prepare a solution of USP Metoprolol Succinate RS in *Medium* as directed in *Table 2*.

Table 2

Tablet Strength (mg, as metoprolol succinate)	Concentration (mg/mL)
200	0.380
100	0.190
50	0.095
25	0.048

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

Tablet Strength (mg, as metoprolol succinate)	Volume (µL)
25	40
50	20
100	10
200	5

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

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

r_U = peak response of metoprolol 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* (mg/mL)

Calculate the percentage of the labeled amount of metoprolol succinate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved (Q_i), at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

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

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)
Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	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 $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved 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*.
Medium: pH 6.8 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate and 0.91 g of sodium hydroxide in 1000 mL of water; adjust with 1 N sodium hydroxide to a pH of 6.8); 500 mL
Apparatus 2: 50 rpm
Times: 1, 4, 8, and 24 h
Buffer: Transfer 50 mL of 1 M monobasic sodium phosphate and 8 mL of 1 M phosphoric acid in a 1000-mL volumetric flask. Dilute with water to the volume. 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* (25:75)
Standard solution: 0.05 mg/mL of USP Metoprolol Succinate RS in *Medium*
Sample solution: Withdraw a 10-mL aliquot at each time point. Pass the solution through a suitable filter. Dilute with *Medium* to a concentration similar to that of the *Standard solution*, if needed. Replace the portion withdrawn with an equal volume of *Medium* except for the last time point.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC
Detector: UV 280 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 40 µL
Run time: NLT 3 times the retention time of metoprolol succinate
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_i) of metoprolol succinate dissolved in *Medium* at each time point (*i*):

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

r_U = peak response of metoprolol 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* (mg/mL)
D = dilution factor of the *Sample solution*

Calculate the percentage of the labeled amount of metoprolol succinate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$] dissolved ($Q_i$) at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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

C_i = concentration of metoprolol succinate in the portion of sample withdrawn at the specified time point (*i*) (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim (mg/Tablet)
V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 25
2	4	20–40
3	8	45–65
4	24	NLT 80

The percentages of the labeled amount of metoprolol succinate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$] dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.◄ (TBD)

Change to read:

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements
▲▲*USP41*

IMPURITIES

Change to read:

▲• **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* ►*6.*◄ (TBD)

Table ►6◄ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	65	35
20	65	35
25	40	60
30	35	65
35	35	65
37	65	35
50	65	35

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:

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

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* ►7.◄ (TBD) Reporting threshold: 0.05%.

Table ►7◄ (TBD)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Succinic acid[a]	0.1	—
Metoprolol related compound A	0.83	—
Metoprolol	1.0	—
Any unspecified degradation product	—	0.20
Total impurities	—	0.75

[a] Counter ion included for identification only.

▲*USP41*

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 $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$. 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
  1-Ethylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.
  $C_{14}H_{23}NO_3$ 253.34▲*USP41*
  USP Metoprolol Succinate RS