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

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 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

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°
Flow rate: 1.5 mL/min
Injection volume: 5 µL
Run time: NLT 2 times the retention time of metoprolol

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*):

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

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*):

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

C_i = concentration of metoprolol succinate in the portion of sample withdrawn at 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 6*.

Table 6

Time Point (*i*)	Time (h)	Amount Dissolved (Tablet labeled 25 mg) (%)	Amount Dissolved (Tablets labeled 50, 100, and 200 mg) (%)
1	1	NMT 20	NMT 20
2	4	20–40	15–35
3	8	42–67	38–64
4	24	NLT 80	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*.▲ (RB 1-Aug-2018)

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 7*.

Table 7▲ (RB 1-Aug-2018)

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 8*.▲ (RB 1-Aug-2018)Reporting threshold: 0.05%.

▲**Table 8**▲ (RB 1-Aug-2018)

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