Metoprolol Succinate Extended-Release Tablets

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In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Metoprolol Succinate Extended-Release Tablets monograph. The purpose of this revision is to add *Dissolution Test 9* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). The revision also necessitates a change in the table numbering in the test for *Organic Impurities*.

- *Dissolution Test 9* was validated using the Ultimate XB-C8 brand of column with L7 packing. The typical retention time for metoprolol succinate is about 2.5 min.

The Metoprolol Succinate Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Brice Wagner, Scientist III (301-998-6832 or brice.wagner@usp.org).

Revision Bulletin
Official: September 13, 2024

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.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

● **B.** The UV spectrum 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* (25:75)

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. For *Identification B*, use a diode array detector in the range of 200–400 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)

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 and **Mobile phase:** Prepare as directed in the *Assay*.

Standard solution: A known concentration of USP Metoprolol Succinate RS in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter.

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 $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4]$ dissolved at each time point.

Tolerances: 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)	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)	Volume (µL)
25	40
50	20
100	10
200	5

Run time: NLT 2 times the retention time of metoprolol

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 a sodium hydroxide solution 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 (Tablets 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*.

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

Tablet Strength (mg)	Concentration (mg/mL)
200	0.2
100	0.2
50	0.05
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 280 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 40 µL for 25 and 50 mg; 10 µL for 100 and 200 mg

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 3.0%

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 8*.

Table 8

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 10
2	4	5–30
3	8	30–55
4	20	NLT 75

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 7: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 7*.

Medium: Phosphate buffer, pH 6.8 (dissolve 6.8 g of monobasic potassium phosphate and 0.9 g of sodium hydroxide in 1 L of water; adjust with 1 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8), deaerated; 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, 12, and 24 h for Tablets labeled 25 and 50 mg and 1, 4, 8, and 20 h for Tablets labeled 100 and 200 mg

Buffer: Mix 50 mL of 1 M monobasic sodium phosphate dihydrate and 8.0 mL of 1 M phosphoric acid, and dilute with water to 1000 mL. Adjust with 1 M monobasic sodium phosphate dihydrate or 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (22:78)

Standard solution: Known concentrations of USP Metoprolol Succinate RS in *Medium* are listed in *Table 9*.

Table 9

Tablet Strength (mg)	Concentration (mg/mL)
100	0.2
50/200	0.1
25	0.05

Sample solution: Withdraw an 8-mL aliquot of the solution under test at each time point. For Tablets labeled 25, 50, and 100 mg, no further dilution is required. For Tablets labeled 200 mg, transfer 5.0 mL of the aliquot withdrawn to a 20-mL volumetric flask, and dilute with *Medium* to volume. Centrifuge, if needed. Pass the supernatant through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 0.9 mL/min

Injection volume: 10 µL

Run time: NLT 2.6 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 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 for 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):

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

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

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

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

$$\text{Result}_5 = (\{C_5 \times [V - (4 \times V_S)]\} + [(C_4 + C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 of metoprolol succinate (mg/Tablet)

V_S = volume of the sample withdrawn at each time point, 8 mL

Tolerances: See *Table 10* and *Table 11*.

Table 10

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 25 and 50 mg) (%)
1	1	NMT 15
2	4	10–30
3	8	35–55
4	12	55–75
5	24	NLT 80

Table 11

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
1	1	NMT 17
2	4	17–37

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
3	8	42–62
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 8: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 8*.

Medium: Phosphate buffer, pH 6.8; 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, and 24 h

Solution A: Dissolve 156.0 g of monobasic sodium phosphate dihydrate in 1 L of water.

Solution B: Dissolve 68.2 mL of phosphoric acid in 1 L of water.

Solution C: Dissolve 136.0 g of monobasic potassium phosphate in 1 L of water.

Buffer: Mix 50 mL of *Solution A* and 8.0 mL of *Solution B*, and dilute with water to 1000 mL. Adjust with *Solution C* or *Solution B* 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: At the *Times* specified, withdraw a known volume of the solution under test and replace with an equal volume of fresh *Medium*. Pass through a suitable filter of 0.45-µm pore size, discarding the first 1 mL of filtrate. Dilute the filtrate with *Medium* to a concentration similar to that of the *Standard solution*.

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 40 µL

Run time: NLT 1.8 times the retention time of metoprolol

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of metoprolol succinate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_4$] in the sample withdrawn from the vessel 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 for 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 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 at each time point (i) and replaced with *Medium* (mL)

Tolerances: See *Table 12*.

Table 12

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	4	20–40
3	8	42–62
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*.

▲**Test 9:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 9*.

Medium: Phosphate buffer, pH 6.8; 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, 20, and 24 h

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. 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: At the times specified, withdraw a portion of the solution under test, and pass the solution under test through a suitable filter of 0.45-µm pore size.

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: 10 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 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 at each time point (i):

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

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

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

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

$$\text{Result}_5 = (\{C_5 \times [V - (4 \times V_S)]\} + [(C_4 + C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 of metoprolol succinate (mg/Tablet)

V_S = volume of the sample withdrawn at each time point (i) (mL)

Tolerances: See *Table 13*.

Table 13

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	1	NMT 20
2	4	20–40
3	8	40–60
4	20	68–88
5	24	NLT 75

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 13-Sep-2024)

Test 10: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 10*.

Medium: Phosphate buffer, pH 6.8; 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, and 20 h

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* (25:75)

Standard solution: (*L*/500) mg/mL of USP Metoprolol Succinate RS in *Medium*, where *L* is the label claim of metoprolol succinate in mg/Tablet. Sonicate to dissolve, if necessary.

Sample solution: At the *Times* specified, withdraw an aliquot and replace the portion withdrawn with an equal volume of *Medium*. Pass the solution under test through a suitable filter of 0.10-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 12.5-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: See ▲*Table 14*.

Table 14 ▲ (RB 13-Sep-2024)

Tablet Strength (mg)	Volume (µL)
25	40
50	20

Tablet Strength (mg)	Volume (µL)
100/200	10

Run time: NLT 2.1 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 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 at each time point (i) and replaced with *Medium* (mL)

Tolerances: See ▲*Table 15*.

Table 15▲ (RB 13-Sep-2024)

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 25 and 50 mg) (%)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
1	1	NMT 15	NMT 15

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 25 and 50 mg) (%)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
2	4	12–32	12–32
3	8	36–56	33–53
4	20	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*.

Test 11: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 11*.

Medium: Phosphate buffer, pH 6.8 (Dissolve 6.8 g of monobasic potassium phosphate and 0.9 g of sodium hydroxide in 1 L of water; adjust with a sodium hydroxide solution or phosphoric acid to a pH of 6.8.); 500 mL

Apparatus 2: 50 rpm

Times: 2, 8, 16, and 30 h

Buffer: Dissolve 1.7 g of monobasic sodium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Standard solution: 0.2 mg/mL of USP Metoprolol Succinate RS in *Medium*. Sonicate to dissolve, if necessary.

Sample solution: At the *Times* specified, withdraw a portion of the solution under test and pass through a suitable filter of 45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 7.5-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 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 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 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 of metoprolol succinate (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (i) from the *Medium* (mL)

Tolerances: See ▲*Table 16*.

Table 16▲ (RB 13-Sep-2024)

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 25 and 50 mg) (%)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
1	2	NMT 10	NMT 10
2	8	20–40	10–30
3	16	65–85	50–70
4	30	NLT 85	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 12: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 12*.

Medium: Phosphate buffer, pH 6.8 (Dissolve 6.8 g of monobasic potassium phosphate and 0.9 g of sodium hydroxide in 1 L of water; adjust with 2 N sodium hydroxide solution to a pH of 6.8.); 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, and 20 h

Buffer: Dissolve 7.8 g monobasic sodium phosphate dihydrate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (25:75)

Standard solution: (*L*/500) mg/mL of USP Metoprolol Succinate RS in *Medium*, where *L* is the label claim of metoprolol succinate in mg/Tablet. Sonicate to dissolve, if necessary.

Sample solution: At the *Times* specified, withdraw an aliquot and replace the portion withdrawn with an equal volume of *Medium*. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

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 for 25 and 50 mg; 10 µL for 100 and 200 mg

Run time: NLT 1.8 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 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 at each time point (*i*) and replaced with *Medium* (mL)

Tolerances: See ▲*Table 17*.

Table 17▲ (RB 13-Sep-2024)

Time (h)	Amount Dissolved (%)
1	NMT 25
4	15–35
8	35–55
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 13: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 13*.

Medium: Phosphate buffer, pH 6.8 (Dissolve 6.8 g of monobasic potassium phosphate in 250 mL of water, add 112 mL of 0.2 N sodium hydroxide and 500 mL of water, adjust with 0.2 N sodium hydroxide or 2 N hydrochloric acid to a pH of 6.8. Dilute with water to 1000 mL.); 500 mL

Apparatus 2: 50 rpm

Times: 1, 4, 8, and 20 h for Tablets labeled 25 and 50 mg; 1, 4, 10, and 24 h for Tablets labeled 100 and 200 mg

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* (25:75)

Standard solution: (*L*/500) mg/mL of USP Metoprolol Succinate RS in *Medium*, where *L* is the label claim of metoprolol succinate in mg/Tablet. Sonicate to dissolve, if necessary.

Sample solution: At the *Times* specified, withdraw an aliquot and replace the portion withdrawn with an equal volume of *Medium*. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

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: 10 µL

Run time: NLT 2.0 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 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 at each time point (i) and replaced with *Medium* (mL)

Tolerances: See ▲*Table 18* and *Table 19*.

Table 18▲ (RB 13-Sep-2024)

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 25 mg) (%)	Amount Dissolved (Tablets labeled 50 mg) (%)
1	1	NMT 20	NMT 20
2	4	15–35	15–35
3	8	38–58	35–55
4	20	NLT 80	NLT 80

▲**Table 19**▲ (RB 13-Sep-2024)

Time Point (*i*)	Time (h)	Amount Dissolved (Tablets labeled 100 and 200 mg) (%)
1	1	NMT 20
2	4	10–30
3	10	40–60
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*.

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

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 20*.

▲Table 20▲ (RB 13-Sep-2024)

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*

[Note—The relative retention times for succinic acid (the counter ion), metoprolol related compound A, and metoprolol are about 0.1, 0.83, and 1.0, respectively.]

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 any unspecified impurity in the portion of Tablets taken:

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

r_U = peak response of any unspecified impurity 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: The reporting threshold is 0.05%.

Any unspecified impurity: NMT 0.20%

Total impurities: NMT 0.75%

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 tartrate $[(C_{15}H_{25}NO_3)_2 \cdot C_4H_6O_6]$. When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.
- **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

USP Metoprolol Succinate RS

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