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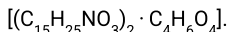
Metoprolol Succinate Extended-Release Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click

<https://www.uspnf.com/rb-metoprolol-succinate-ert-20240927>.

DEFINITION

Metoprolol Succinate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of metoprolol succinate



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	 Documents NMT 20 Document Sharing Hub

Time Point (i)	Time (h)	Amount Dissolved (%)
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>i</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_p) 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.