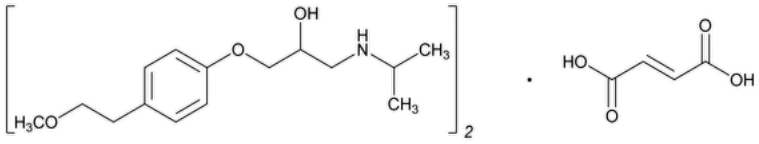
Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-944C29E5-7B48-4E2B-8E3A-6DC8F5247A4B_4_en-US
DOI: https://doi.org/10.31003/USPNF_M53500_04_01
DOI Ref: c96p4

Metoprolol Fumarate



$(C_{15}H_{25}NO_3)_2 \cdot C_4H_4O_4$ 650.80

2-Propanol, 1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-, (±)-, (*E*)-2-butanedioate (2:1) (salt);

(±)-1-(Isopropylamino)-3-[*p*-(2-methoxyethyl)phenoxy]-2-propanol fumarate (2:1) (salt) CAS RN®: 119637-66-0.

DEFINITION

Metoprolol Fumarate contains NLT 98.0% and NMT 102.0% of metoprolol fumarate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_4O_4$], calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**▲ (CN 1-May-2020)

• **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**

Solution A: 1.3 g/L of sodium dodecyl sulfate in 0.1% (w/v) phosphoric acid

Solution B: Acetonitrile

Mobile phase: *Solution A* and *Solution B* (60:40)

Standard solution: 1 mg/mL of USP Metoprolol Fumarate RS in *Mobile phase*

Sample solution: 1 mg/mL of Metoprolol Fumarate in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 223 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 10 min

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of metoprolol fumarate [$(C_{15}H_{25}NO_3)_2 \cdot C_4H_4O_4$] in the portion of Metoprolol Fumarate 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 Fumarate RS in the *Standard solution* (mg/mL)

C_U = concentration of Metoprolol Fumarate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

Solution A: 1.3 g/L of sodium dodecyl sulfate in 0.1% (w/v) phosphoric acid

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	60	40
8	60	40
13	10	90
13.1	60	40
16	60	40

Diluent: *Solution A* and *Solution B* (60:40)

System suitability solution: 5 µg/mL each of USP Metoprolol Fumarate RS, USP Metoprolol Related Compound A RS, USP Metoprolol Related Compound B RS, and USP Metoprolol Related Compound C RS in *Diluent*

Standard solution: 2.5 µg/mL each of USP Metoprolol Fumarate RS, USP Metoprolol Related Compound A RS, USP Metoprolol Related Compound B RS, USP Metoprolol Compound C RS, and USP Metoprolol Related Compound D RS in *Diluent*

Sample solution: 1 mg/mL of Metoprolol Fumarate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 223 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 1.5 between metoprolol related compound A and metoprolol related compound B; NLT 2.5 between metoprolol related compound B and metoprolol related compound C, *System suitability solution*

Relative standard deviation: NMT 2.0% for metoprolol, metoprolol related compound A, metoprolol related compound B, metoprolol related compound C, and metoprolol related compound D, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the corresponding metoprolol related compound in the portion of Metoprolol Fumarate taken:

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

r_U = peak response of the corresponding metoprolol related compound in the *Sample solution*

r_S = peak response of the corresponding metoprolol related compound in the *Standard solution*

C_S = concentration of the corresponding USP Metoprolol Related Compound RS in the *Standard solution* (µg/mL)

C_U = concentration of Metoprolol Fumarate in the *Sample solution* (µg/mL)

Calculate the percentage of any unspecified impurity in the portion of Metoprolol Fumarate taken:

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

r_U = peak response of each unspecified impurity in the *Sample solution*

r_S = peak response of metoprolol in the *Standard solution*

C_S = concentration of USP Metoprolol Fumarate RS in the *Standard solution* (µg/mL)

C_U = concentration of Metoprolol Fumarate in the *Sample solution* (µg/mL)

Acceptance criteria: See *Table 2*. Disregard peaks below 0.03%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Fumaric acid	0.2	—
Metoprolol related compound C[a]	0.6	0.10
Metoprolol related compound B[b]	0.7	0.10
Metoprolol related compound A[c]	0.8	0.10
Metoprolol	1.0	—
Metoprolol related compound D[d]	1.5	0.10
Any individual unspecified impurity	—	0.10
Total impurities	—	1.0

[a] 4-[2-Hydroxy-3-(isopropylamino)propoxy]benzaldehyde hydrochloride.

[b] 1-Chloro-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

[c] 1-Ethylamino-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

[d] *N,N*-Bis{2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl}isopropylamine hydrochloride.

SPECIFIC TESTS

- **pH ⟨791⟩:** 5.5–6.5, in a solution (1 in 10)
- **Loss on Drying ⟨731⟩**

Analysis: Dry under vacuum at 60° for 4 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **USP Reference Standards ⟨11⟩**

USP Metoprolol Fumarate RS

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 Related Compound B RS

1-Chloro-3-[4-(2-methoxyethyl)phenoxy]propan-2-ol.

$C_{12}H_{17}ClO_3$ 244.71

USP Metoprolol Related Compound C RS

4-[2-Hydroxy-3-(isopropylamino)propoxy]benzaldehyde hydrochloride.

$C_{13}H_{19}NO_3 \cdot HCl$ 273.76

USP Metoprolol Related Compound D RS

N,N-Bis{2-hydroxy-3-[4-(2-methoxyethyl)phenoxy]propyl}isopropylamine hydrochloride.

$C_{27}H_{41}NO_6 \cdot HCl$ 512.08

Topic/Question	Contact	Expert Committee
METOPROLOL FUMARATE	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 41(1)

Current DocID: GUID-944C29E5-7B48-4E2B-8E3A-6DC8F5247A4B_4_en-US

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