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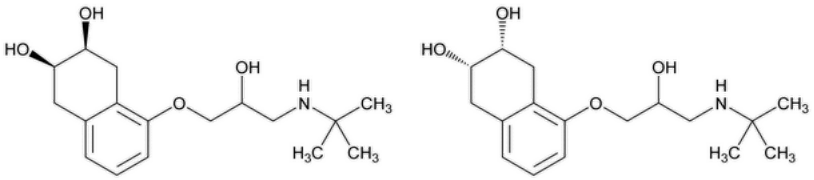
Nadolol

Change to read:



$C_{17}H_{27}NO_4$ 309.40

2,3-Naphthalenediol, 5-[3-[(1,1-dimethylethyl)amino]-2-hydroxypropoxy]-1,2,3,4-tetrahydro-, *cis*-;
1-(*tert*-Butylamino)-3-[(5,6,7,8-tetrahydro-*cis*-6,7-dihydroxy-1-naphthyl)oxy]-2-propanol;
▲(2*RS*,3*SR*)-5-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-1,2,3,4-tetrahydronaphthalene-2,3-diol▲ (USP 1-Dec-2023) CAS RN®: 42200-33-9; UNII: FEN504330V.

DEFINITION
Nadolol contains NLT 98.0% and NMT 102.0% of nadolol ($C_{17}H_{27}NO_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197M ▲or 197A▲ (USP 1-Dec-2023)

• **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

Change to read:

• **Procedure**

Solution A: 0.1% ▲(v/v)▲ (USP 1-Dec-2023) trifluoroacetic acid▲in water prepared as follows. For 1 L, add 1.0 mL of trifluoroacetic acid into 1000 mL of water.▲ (USP 1-Dec-2023)

Mobile phase: Acetonitrile and *Solution A* (15:85)

Standard solution: 0.2 mg/mL of USP Nadolol RS in *Mobile phase*. Sonication and occasional hand shaking may be necessary for complete dissolution.

Sample solution: 0.2 mg/mL of Nadolol in *Mobile phase*. Sonication and occasional hand shaking may be necessary for complete dissolution.

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 1.7 times the retention time of nadolol ▲▲ (USP 1-Dec-2023)

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of nadolol ($C_{17}H_{27}NO_4$) in the portion of Nadolol taken:

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

r_U = peak response of nadolol from the *Sample solution*

r_S = peak response of nadolol from the *Standard solution*

C_S = concentration of USP Nadolol RS in the *Standard solution* (mg/mL)

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

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

OTHER COMPONENTS

Change to read:

• **Racemate Composition**

▲**Mobile phase:** Hexane and alcohol, dehydrated (86:14). For 1 L, add 0.3 mL each of diethylamine and glacial acetic acid into each liter of the mixture.

Standard solution: 0.2 mg/mL of USP Nadolol RS in alcohol, dehydrated

Sample solution: 0.2 mg/mL of Nadolol in alcohol, dehydrated

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 2.1-mm × 15-cm; 3-µm packing L40

Flow rate: 0.2 mL/min

Injection volume: 2 µL

Run time: NLT 2.4 times the retention time of the last eluted isomer

System suitability

Sample: *Standard solution*

[Note—The relative retention times for the four isomers are 0.48, 0.54, 0.84, and 1.0, respectively. The first and last eluted are isomers of nadolol racemate A while the second and third eluted are isomers of nadolol racemate B.]

Suitability requirements

Resolution: NLT 1.0 between the first and the second eluted isomers.

Relative standard deviation: NMT 5.0% for the ratios between the sum of peak responses of isomers of racemate A and the sum of peak responses of isomers of racemate B.

Analysis

Sample: *Sample solution*

Calculate the percentage of racemate A in the portion of Nadolol taken:

$$\text{Result} = r_A/(r_A + r_B) \times 100$$

r_A = sum of peak responses of isomers of nadolol racemate A

r_B = sum of peak responses of isomers of nadolol racemate B

▲ (USP 1-Dec-2023)

Acceptance criteria: 40%–60%

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Change to read:

• **Organic Impurities**

Solution A: Prepare as directed in the *Assay*.

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
3	85	15

Time (min)	Solution A (%)	Solution B (%)
7	50	50
10	50	50
10.5	85	15
15	85	15

Diluent: *Solution B* and *Solution A* (15:85)

▲**System suitability solution:** 14 µg/mL of USP Nadolol RS and 1.4 µg/mL each of USP Nadolol Related Compound A RS, USP Nadolol Related Compound B RS, USP Nadolol Related Compound C RS, USP Nadolol Related Compound F RS, and USP Nadolol Related Compound G RS in *Diluent*▲ (USP 1-Dec-2023)

Standard solution: 7 µg/mL ▲each▲ (USP 1-Dec-2023) of USP Nadolol RS▲and USP Nadolol Related Compound F RS▲ (USP 1-Dec-2023) in *Diluent*. Sonication may be necessary for complete dissolution.

Sensitivity solution: 0.35 µg/mL of USP Nadolol RS from the *Standard solution* in *Diluent*

Sample solution: 700 µg/mL of Nadolol in *Diluent*. Sonication and occasional hand shaking may be necessary for complete dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Samples: ▲*System suitability solution*,▲ (USP 1-Dec-2023) *Standard solution*, and *Sensitivity solution*

▲[NOTE—The relative retention times in *Table 2* are provided as information that could aid in peak assignment.]

Table 2▲ (USP 1-Dec-2023)

Name	Relative Retention Time
▲Nadolol related compound A▲ (USP 1-Dec-2023) [a]	0.78
Nadolol	1.00
▲Nadolol related compound B[a]▲ (USP 1-Dec-2023)	1.53
Nadolol dimer▲[b]▲ (USP 1-Dec-2023)	1.76
▲Nadolol related compound C[a]▲ (USP 1-Dec-2023)	1.83
▲Nadolol related compound F▲ (USP 1-Dec-2023)	2.03
▲Nadolol related compound G▲ (USP 1-Dec-2023)	2.10

[a] ▲Multiple peaks may appear to coelute at this relative retention time▲ (USP 1-Dec-2023) .

▲[b] (2*SR*,3*RS*)-5-{3-[*tert*-Butyl(3-{[(6*RS*,7*SR*)-6,7-dihydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]oxy}-2-hydroxypropyl)amino]-2-hydroxypropoxy}-1,2,3,4-tetrahydronaphthalene-2,3-diol] and *N*,*N*-Bis{2-hydroxy-3-[(6*R*,7*S*)-6,7-dihydroxy-5,6,7,8-tetrahydronaphthalene-1-yloxy]propyl}-*N*-*tert*-butylamine.▲ (USP 1-Dec-2023)

Suitability requirements

▲**Resolution:** NLT 2.0 between nadolol related compound F and nadolol related compound G, *System suitability solution*▲ (USP 1-Dec-2023)

Relative standard deviation: NMT 2.0% ▲for both nadolol and nadolol related compound F,▲ (USP 1-Dec-2023) *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

▲Calculate the percentage of nadolol related compound F in the portion of Nadolol taken:

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

r_U = peak response of nadolol related compound F from the *Sample solution*

r_S = peak response of nadolol related compound F from the *Standard solution*

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

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

▲ (USP 1-Dec-2023)

Calculate the percentage of ▲nadolol related compound A, nadolol related compound B, nadolol dimer, nadolol related compound C, nadolol related compound G, and any unspecified impurity▲ (USP 1-Dec-2023) in the portion of Nadolol taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of ▲nadolol related compound A, nadolol related compound B, nadolol dimer, nadolol related compound C, nadolol related compound G, or any unspecified impurity▲ (USP 1-Dec-2023) from the *Sample solution*

r_S = peak response of nadolol from the *Standard solution*

C_S = concentration of USP Nadolol RS in the *Standard solution* (▲µg/mL▲ (USP 1-Dec-2023))

C_U = concentration of Nadolol in the *Sample solution* (▲µg/mL▲ (USP 1-Dec-2023))

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. ▲The reporting threshold is 0.05%.▲ (USP 1-Dec-2023)

Table 3

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
▲Nadolol related compound A▲ (USP 1-Dec-2023) [a]	1.35	0.20
▲▲ (USP 1-Dec-2023)	▲▲ (USP 1-Dec-2023)	▲▲ (USP 1-Dec-2023)
▲Nadolol related compound B[a]▲ (USP 1-Dec-2023)	1.07	0.20
Nadolol dimer▲▲ (USP 1-Dec-2023)	1.11	0.20
▲Nadolol related compound C[a]▲ (USP 1-Dec-2023)	1.42	0.20
▲ Nadolol related compound F	—▲ (USP 1-Dec-2023)	0.20
▲Nadolol related compound G▲ (USP 1-Dec-2023)	0.78	0.20
Any unspecified impurity	1.00	0.10

Name	Relative Response Factor	Acceptance Criteria, NMT (%)
Total impurities	—	0.50

[a] ▲Assessed as the combined peak response of the coeluting peaks▲ (USP 1-Dec-2023) .

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry under vacuum at 60° for 3 h.

Acceptance criteria: NMT 2.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers.

Change to read:

• **USP Reference Standards ⟨11⟩**

USP Nadolol RS

▲ USP Nadolol Related Compound A RS

(2*RS*,3*SR*)-5-(2,3-Dihydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.

$C_{13}H_{18}O_5$ 254.28

USP Nadolol Related Compound B RS

(2*RS*,3*SR*)-5-(2-Hydroxy-3-methoxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol.

$C_{14}H_{20}O_5$ 268.31

USP Nadolol Related Compound C RS

(2*SR*,3*RS*)-5-(3-{[(6*RS*,7*SR*)-6,7-Dihydroxy-5,6,7,8-tetrahydronaphthalen-1-yl]oxy}-2-hydroxypropoxy)-1,2,3,4-tetrahydronaphthalene-2,3-diol; 1,3-Bis[(6*R*,7*S*)-6,7-dihydroxy-5,6,7,8-tetrahydronaphthalene-1-yloxy]propane-2-ol.

$C_{23}H_{28}O_7$ 416.46

USP Nadolol Related Compound F RS

1-(*tert*-Butylamino)-3-(naphthalen-1-yloxy)propan-2-ol.

$C_{17}H_{23}NO_2$ 273.37

USP Nadolol Related Compound G RS

1-(*tert*-Butylamino)-3-(5,6,7,8-tetrahydronaphthalen-1-yloxy)propan-2-ol.

$C_{17}H_{27}NO_2$ 277.40▲ (USP 1-Dec-2023)

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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