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Nadolol and Bendroflumethiazide Tablets

DEFINITION

Nadolol and Bendroflumethiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of nadolol ($C_{17}H_{27}NO_4$) and bendroflumethiazide ($C_{15}H_{14}F_3N_3O_4S_2$).

IDENTIFICATION

Change to read:

• **A.** The retention times of the two major peaks of the *Sample solution* correspond to ▲those▲ (USP 1-May-2021) of the *Standard solution*, ▲as obtained▲ (USP 1-May-2021) in the *Assay*.

Add the following:

▲• **B.** The UV spectra of the two major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

[**Caution—**Use low-actinic glassware for the *Sample solution* and the *Standard solution*.]

Mobile phase: Transfer 5.62 g of anhydrous sodium chloride and 1.97 g of sodium acetate to 1000 mL of water in a 2-L volumetric flask. Add 4.0 mL of glacial acetic acid and 800 mL of methanol. Dilute with water to volume.

System suitability solution: 0.4 mg/mL each of USP Nadolol RS and USP 2,4-Disulfamyl-5-trifluoromethylaniline RS in methanol

Standard solution: 0.4 mg/mL of USP Nadolol RS and 0.4*J* mg/mL of USP Bendroflumethiazide RS in methanol, where *J* is the ratio of the labeled amount of bendroflumethiazide, in milligrams, to the labeled amount of nadolol, in mg/Tablet

Sample solution: Nominally equivalent to 0.4 mg/mL of nadolol in methanol prepared as follows. Transfer a portion of finely powdered Tablets (NLT 20), equivalent to 40 mg of nadolol, to a 100-mL volumetric flask. Add methanol, and sonicate for 15 min with occasional shaking. Dilute with methanol to volume, and centrifuge.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm.▲For *Identification B*, use a diode array detector in the range of 210–400 nm.▲ (USP 1-May-2021)

Column: ▲3.9-mm▲ (USP 1-May-2021) × 30-cm; ▲10-µm▲ (USP 1-May-2021) packing L11

Flow rate: 1.5 mL/min

Injection volume: 20 µL

▲**Run time:** NLT 2 times the retention time of bendroflumethiazide▲ (USP 1-May-2021)

System suitability

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

[Note—The relative retention times for nadolol and bendroflumethiazide are about 0.3 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.4 between the solvent and 2,4-disulfamyl-5-trifluoromethylaniline peaks; NLT 1.4 between the 2,4-disulfamyl-5-trifluoromethylaniline and nadolol peaks, ▲*System suitability solution;*▲ (USP 1-May-2021) and NLT 1.7 between the nadolol and bendroflumethiazide peaks, ▲*Standard solution*▲ *(USP 1-May-2021)*

Relative standard deviation: NMT 3.0% ▲for the nadolol and bendroflumethiazide peaks,▲ (USP 1-May-2021) *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

r_U = peak response of 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 = nominal concentration of nadolol in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of bendroflumethiazide ($C_{15}H_{14}F_3N_3O_4S_2$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩, *Procedure, Apparatus 1 and Apparatus 2, Immediate-Release Dosage Forms, Procedure for a pooled sample for immediate-release dosage forms*

[**Caution—**Protect solutions from light throughout this test.]

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: Dissolve USP Nadolol RS and USP Bendroflumethiazide RS in a minimal amount of methanol, and dilute with *Medium* to the desired concentrations.

Sample solution: ▲Pass a▲ (USP 1-May-2021) portion of the solution under test ▲through a suitable filter.▲ (USP 1-May-2021) Dilute with *Medium* to a concentration that is similar to the *Standard solution*.

Chromatographic system and **System suitability:** Proceed as directed in the *Assay*.

▲**Analysis**

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of nadolol ($C_{17}H_{27}NO_4$) or bendroflumethiazide ($C_{15}H_{14}F_3N_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times D \times V \times (1/L) \times 100$$

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

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

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

D = dilution factor of the *Sample solution*

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)▲ (USP 1-May-2021)

Tolerances: NLT 80% (Q) of the labeled amount of nadolol ($C_{17}H_{27}NO_4$) and bendroflumethiazide ($C_{15}H_{14}F_3N_3O_4S_2$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩, *Content Uniformity*: Meet the requirements

IMPURITIES

Add the following:

▲• **Organic Impurities, Procedure 1: Nadolol Related Impurities**

[**Caution—**Protect all solutions containing nadolol from light.]

Buffer: Transfer 3.85 g of ammonium acetate into 1000 mL of water. Adjust with 5 N hydrochloric acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (89:11)

Standard solution: 0.016 mg/mL of USP Nadolol RS in *Mobile phase*

Sensitivity solution: 0.0016 mg/mL of USP Nadolol RS from the *Standard solution* in *Mobile phase*

Sample solution: Nominally 3.2 mg/mL of nadolol prepared as follows. Transfer a suitable amount, equivalent to 160 mg of nadolol, from finely powdered Tablets (NLT 20) to a suitable volumetric flask. Add *Mobile phase* to 80% of the volume of the flask. Shake and mix for 15

min. Dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 25-cm; 5-µm packing L3

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of nadolol

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[NOTE—The relative retention times for bendroflumethiazide and nadolol are 0.17 and 1.00, respectively.]

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any nadolol related 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 any nadolol related unspecified degradation product 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 = nominal concentration of nadolol in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 1*. The reporting threshold is 0.05%.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Bendroflumethiazide	0.17	—
Nadolol	1.00	—
Any nadolol related unspecified degradation product	—	0.2▲ (USP 1-May-2021)

Change to read:

• **▲ORGANIC IMPURITIES, PROCEDURE 2: BENDROFLUMETHIAZIDE RELATED IMPURITIES**

[**CAUTION—**Protect all solutions containing bendroflumethiazide from light.]

Buffer: Transfer 6.8 g of monobasic potassium phosphate into 1000 mL of water. Add 1 mL of phosphoric acid and mix. Adjust with phosphoric acid to a pH of 2.0.

Mobile phase: Acetonitrile and *Buffer* (38:62)

Standard stock solution A: 0.25 mg/mL of USP 2,4-Disulfamyl-5-trifluoromethylaniline RS in *Mobile phase*

Standard stock solution B: 0.25 mg/mL of USP Bendroflumethiazide RS in acetonitrile

Standard solution: 1.0 µg/mL each of USP 2,4-Disulfamyl-5-trifluoromethylaniline RS and USP Bendroflumethiazide RS in *Mobile phase* from *Standard stock solution A* and *Standard stock solution B*

Sensitivity solution: 0.1 µg/mL each of USP 2,4-Disulfamyl-5-trifluoromethylaniline RS and USP Bendroflumethiazide RS from the *Standard solution* in *Mobile phase*

Sample solution: Nominally 200 µg/mL of bendroflumethiazide prepared as follows. Transfer a suitable amount, equivalent to 10 mg of bendroflumethiazide, from finely powdered Tablets (NLT 20) to a suitable volumetric flask. Add *Mobile phase* to 80% of the volume of the flask. Shake and mix for 15 min. Dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter. Use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Autosampler temperature: 2°–8°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of bendroflumethiazide

System suitability

Samples: *Standard solution* and *Sensitivity solution*

[NOTE—The relative retention times for nadolol, 2,4-disulfamyl-5-trifluoromethylaniline, and bendroflumethiazide are 0.11, 0.21, and 1.00, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for both 2,4-disulfamyl-5-trifluoromethylaniline and bendroflumethiazide, *Standard solution*

Relative standard deviation: NMT 2.0% for both 2,4-disulfamyl-5-trifluoromethylaniline and bendroflumethiazide, *Standard solution*

Signal-to-noise ratio: NLT 10 for both 2,4-disulfamyl-5-trifluoromethylaniline and bendroflumethiazide, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of 2,4-disulfamyl-5-trifluoromethylaniline in the portion of Tablets taken:

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

r_U = peak response of 2,4-disulfamyl-5-trifluoromethylaniline from the *Sample solution*

r_S = peak response of 2,4-disulfamyl-5-trifluoromethylaniline from the *Standard solution*

C_S = concentration of USP 2,4-Disulfamyl-5-trifluoromethylaniline RS in the *Standard solution* (µg/mL)

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

Calculate the percentage of any bendroflumethiazide related 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 any bendroflumethiazide related unspecified degradation product from the *Sample solution*

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

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is ▲▲ (ERR 1-May-2021) 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Nadolol	0.11	—
2,4-Disulfamyl-5-trifluoromethylaniline	0.21	1.5
Bendroflumethiazide	1.00	—
Any bendroflumethiazide related unspecified degradation product	—	0.2
Total impurities[a]	—	2.0▲ (USP 1-May-2021)

[a] Total impurities include the sum of all nadolol related unspecified degradation products (see *Table 1*), 2,4-disulfamyl-5-trifluoromethylaniline, and all bendroflumethiazide related unspecified degradation products.

ADDITIONAL REQUIREMENTS

Change to read:

• **PACKAGING AND STORAGE:** Preserve in tight, ▲light-resistant▲ (USP 1-May-2021) containers. ▲Store at controlled room temperature.▲ (USP 1-May-2021)

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Bendroflumethiazide RS USP 2,4-Disulfamyl-5-trifluoromethylaniline RS USP Nadolol RS	$C_7H_8F_3N_3O_4S_2$	319.29

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

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

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