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Nortriptyline Hydrochloride Capsules

Change to read:

DEFINITION

Nortriptyline Hydrochloride Capsules contain ▲Nortriptyline Hydrochloride▲ (USP 1-May-2024) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of nortriptyline ($C_{19}H_{21}N$).

IDENTIFICATION

Delete the following:

▲• **A. Infrared Absorption**▲ (USP 1-May-2024)

Add the following:

▲• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2024)

Delete the following:

▲• **B.** *Identification Tests—General ⟨191⟩, Chemical Identification Tests, Chloride*▲ (USP 1-May-2024)

Add the following:

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2024)

ASSAY

Change to read:

• **Procedure**

▲**Solution A:** Combine 10 mL of phosphoric acid with 100 mL of water.

Buffer: 1.4 g/L of sodium phosphate, dibasic, anhydrous in water. Adjust with *Solution A* to a pH of 7.7.

Mobile phase: Methanol and *Buffer* (70:30)

Diluent: Methanol and water (70:30)

System suitability solution: 0.11 mg/mL of USP Nortriptyline Hydrochloride RS (equivalent to 0.1 mg/mL of nortriptyline) and 1 µg/mL of USP Cyclobenzaprine Related Compound B RS in *Diluent*

Standard solution: 0.11 mg/mL of USP Nortriptyline Hydrochloride RS (equivalent to 0.1 mg/mL of nortriptyline) in *Diluent*

Sample stock solution: Nominally 1 mg/mL of nortriptyline in *Diluent* prepared as follows. Weigh and combine the contents of Capsules (NLT 20). Transfer a portion of the composite to a suitable volumetric flask, and add *Diluent* to 60% of the flask volume. Shake by mechanical means for 15 min, and sonicate for 10 min. Dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL of nortriptyline in *Diluent* from the *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size, discarding NLT 2 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 45°

Flow rate: 1.2 mL/min

Injection volume: 20 µL

Run time: NLT 1.9 times the retention time of nortriptyline

System suitability

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

[NOTE—The relative retention times for cyclobenzaprine related compound B and nortriptyline are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2 between cyclobenzaprine related compound B and nortriptyline, *System suitability solution*

Tailing factor: NMT 2.5, *Standard solution*

Relative standard deviation: NMT 1.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of nortriptyline ($C_{19}H_{21}N$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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

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

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

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

M_{r1} = molecular weight of nortriptyline, 263.38

M_{r2} = molecular weight of nortriptyline hydrochloride, 299.84

▲ (USP 1-May-2024)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Test 1

Medium: Water; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

▲**Buffer:** 1.63 g/L of monobasic potassium phosphate in water. Adjust with 1 N potassium hydroxide VS to a pH of 6.7.

Mobile phase: Acetonitrile, methanol, and *Buffer* (40:43:17)▲ (USP 1-May-2024)

Standard solution: 0.023 mg/mL of USP Nortriptyline Hydrochloride RS (equivalent to 0.02 mg/mL of nortriptyline) in *Medium*

Sample stock solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Sample solution: Nominally 0.02 mg/mL of nortriptyline from the *Sample stock solution* diluted with *Medium*, if necessary

▲**Chromatographic system**

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

Mode: LC

Detector: UV 239 nm

Column: 4.6-mm × 25-cm; 10-µm packing L10

Flow rate: 2.5 mL/min

Injection volume: 100 µL

Run time: NLT 2 times the retention time of nortriptyline▲ (USP 1-May-2024)

System suitability

Sample: *Standard solution*

Suitability requirement

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of nortriptyline ($C_{19}H_{21}N$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times D \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

D = dilution factor for the *Sample solution*, if necessary

M_{r1} = molecular weight of nortriptyline, 263.38

M_{r2} = molecular weight of nortriptyline hydrochloride, 299.84

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of nortriptyline ($C_{19}H_{21}N$) is dissolved

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 1: 20 mesh basket; 100 rpm

Time: 30 min

Buffer: 3.6 g/L of potassium phosphate dibasic in water. Add 3 mL of butylamine to the solution. Adjust with phosphoric acid to a pH of 6.7.

Mobile phase: Methanol, acetonitrile, and *Buffer* (30:20:50)

Standard stock solution: 1.14 mg/mL of USP Nortriptyline Hydrochloride RS in *Medium*. Sonicate to dissolve, if necessary.

Standard solution: (L/500 × 1.14) mg/mL of USP Nortriptyline Hydrochloride RS from the *Standard stock solution* in *Medium*, where L is the label claim in mg/Capsules

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.0-mm × 15-cm; 5-µm packing L7

Column temperature: 45°

Flow rate: 1.2 mL/min

Injection volume: 5 µL

Run time: NLT 2 times the retention time of nortriptyline

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 nortriptyline ($C_{19}H_{21}N$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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

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

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

V = volume of *Medium*, 500 mL

M_{r1} = molecular weight of nortriptyline, 263.38

M_{r2} = molecular weight of nortriptyline hydrochloride, 299.84

L = label claim (mg/Capsule)

Tolerances: NLT 80% (*Q*) of the labeled amount of nortriptyline ($C_{19}H_{21}N$) is dissolved

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

Add the following:

▲**IMPURITIES**

• **Organic Impurities**

Solution A, Buffer, Mobile phase, Diluent, System suitability solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 1.1 µg/mL of USP Nortriptyline Hydrochloride RS (equivalent to 1 µg/mL of nortriptyline) in *Diluent*

Standard solution: 2.3 µg/mL of USP Nortriptyline Hydrochloride RS (equivalent to 2 µg/mL of nortriptyline) in *Diluent*

Sample solution: Use the *Sample stock solution* from the *Assay*. Pass through a suitable filter of 0.45-µm pore size, discarding NLT 2 mL of filtrate.

System suitability

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

[Note—The relative retention times for cyclobenzaprine related compound B and nortriptyline are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2 between cyclobenzaprine related compound B and nortriptyline, *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 each degradation product in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each degradation product from the *Sample solution*

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

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

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

F = relative response factor (see *Table 1*)

M_{r1} = molecular weight of nortriptyline, 263.38

M_{r2} = molecular weight of nortriptyline hydrochloride, 299.84

Acceptance criteria: See *Table 1*. The reporting threshold is 0.1%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amitriptyline related compound A[a]	0.5	0.65	0.2
Nortriptyline	1.0	—	—
Any unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	1.5

[a] Dibenzosuberone.

▲ (USP 1-May-2024)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

• **Labeling:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.

Change to read:

• **USP Reference Standards** ⟨11⟩

▲ USP Cyclobenzaprine Related Compound B RS

3-(5*H*-Dibenzo[*a*,*d*]cycloheptene-5-ylidene)-*N*-methyl-1-propanamine hydrochloride.

$C_{19}H_{19}N \cdot HCl$ 297.82▲ (USP 1-May-2024)

USP Nortriptyline Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
NORTRIPTYLINE HYDROCHLORIDE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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