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Propranolol Hydrochloride and Hydrochlorothiazide Tablets

DEFINITION

Propranolol Hydrochloride and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

Change to read:

• **A.** ▲The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Aug-2022)

Change to read:

• **B.** ▲The UV spectrum of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-Aug-2022)

ASSAY

Change to read:

• **Procedure**

Solution A: ▲Tetrabutylammonium hydroxide, 40% in water▲ (USP 1-Aug-2022)

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water. Add 3.4 mL of phosphoric acid and a volume of *Solution A* equivalent to 2.6 g of tetrabutylammonium hydroxide, and dilute with water to 2000 mL. Adjust, if necessary, with phosphoric acid or 10 N potassium hydroxide to a pH of 2.5. ▲▲ (USP 1-Aug-2022)

Mobile phase: Methanol and *Buffer* (15:85) ▲▲ (USP 1-Aug-2022)

Standard solution A: 0.25 mg/mL of USP Hydrochlorothiazide RS prepared as follows. Transfer 25 mg of USP Hydrochlorothiazide RS to a 100-mL volumetric flask. Add 15 mL of methanol, and dilute with *Buffer* to volume.

Standard solution B: Dissolve a quantity of USP Propranolol Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of 0.25*J* mg/mL, with *J* being the ratio of the labeled quantity, in milligrams, of propranolol hydrochloride to the labeled quantity, in milligrams, of hydrochlorothiazide per Tablet.

Standard solution: 50 µg/mL of USP Hydrochlorothiazide RS and 50*J* µg/mL of USP Propranolol Hydrochloride RS in *Mobile phase* prepared as follows. Mix 5.0 mL of *Standard solution A* and 5.0 mL of *Standard solution B* in a 25-mL volumetric flask, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 50 µg/mL of hydrochlorothiazide prepared as follows. Transfer an equivalent to 25 mg of hydrochlorothiazide, from finely powdered Tablets (NLT 20), to a 500-mL volumetric flask. Add 5 mL of water, mix, and allow to stand for 5 min, with occasional swirling. Add 75 mL of methanol, mix, and sonicate for 10 min, with occasional swirling, adding ice to the bath, if necessary, to maintain the temperature at NMT 20°. Add about 350 mL of *Buffer* to the flask, and sonicate for 10 min, with occasional swirling, maintaining the temperature of the bath at NMT 20°. Dilute with *Buffer* to volume. Centrifuge a portion of this solution, if necessary, to obtain a clear solution.

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 200–400 nm.▲ (USP 1-Aug-2022)

Column: 4-mm × 15-cm; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 50 µL

▲**Run time:** NLT 3 times the retention time of propranolol▲ (USP 1-Aug-2022)

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for ▲▲ (USP 1-Aug-2022) hydrochlorothiazide and propranolol are about ▲▲ (USP 1-Aug-2022) 0.4 and 1.0, respectively.]

Suitability requirements

▲▲ (USP 1-Aug-2022)

Tailing factor: NMT 1.5 for the propranolol and hydrochlorothiazide peaks

Relative standard deviation: NMT ▲1.0% for the propranolol and hydrochlorothiazide peaks▲ (USP 1-Aug-2022)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

r_U = peak response of propranolol or hydrochlorothiazide from the *Sample solution*

r_S = peak response of propranolol or hydrochlorothiazide from the *Standard solution*

C_S = concentration of USP Propranolol Hydrochloride RS or USP Hydrochlorothiazide RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of propranolol hydrochloride or hydrochlorothiazide in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

▲[NOTE—Analyze the sample under test using either the *Instrumental procedure* or *Chromatographic procedure*.]

Instrumental procedure▲ (USP 1-Aug-2022)

Standard solution: Transfer a mixture of 5.0 mL of an aqueous solution having a known concentration of USP Propranolol Hydrochloride RS and 5.0 mL of a 0.005 N sodium hydroxide solution having a known concentration of USP Hydrochlorothiazide RS to a suitable capped bottle, and add 5.0 mL of water, 1.0 mL of 5 N sodium hydroxide, and 25.0 mL of *n*-heptane. Cap the bottle, shake by mechanical means for 5 min, and allow the layers to separate, centrifuging if necessary, to obtain clear upper (*n*-heptane) and lower (aqueous) extracts.

Sample solution: Filter a portion of the solution under test, transfer 10.0 mL of the filtrate to a suitable capped bottle, and add 5.0 mL of water, 1.0 mL of 5 N sodium hydroxide, and 25.0 mL of *n*-heptane. Cap the bottle, shake by mechanical means for 5 min, and allow the layers to separate, centrifuging if necessary, to obtain clear upper (*n*-heptane) and lower (aqueous) extracts.

Blank solution: Transfer 10.0 mL of water to a suitable capped bottle, and add 5.0 mL of water, 1.0 mL of 5 N sodium hydroxide, and 25.0 mL of *n*-heptane. Cap the bottle, shake by mechanical means for 5 min, and allow the layers to separate, centrifuging if necessary, to obtain clear upper (*n*-heptane) and lower (aqueous) extracts.

Instrumental conditions

Mode: UV

Analytical wavelength: 293 nm for *n*-heptane layer (propranolol hydrochloride); 273 nm for aqueous layer (hydrochlorothiazide)

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank solution*

▲Calculate the percentage of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) dissolved:

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

A_U = absorbance from the *Sample solution*

A_S = absorbance from the *Standard solution*

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

V = volume of *Medium*, 900 (mL)

L = label claim for propranolol hydrochloride (mg/Tablet)

D = dilution factor for *Sample solution*, 2.5

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

A_U = absorbance from the *Sample solution*

A_S = absorbance from the *Standard solution*

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

V = volume of *Medium*, 900 (mL)

L = label claim for hydrochlorothiazide (mg/Tablet)

D = dilution factor for *Sample solution*, 1.6

Chromatographic procedure

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Methanol and *Buffer* (10:90)

Diluent 1: 0.01 N hydrochloric acid

Diluent 2: Methanol and 0.01 N hydrochloric acid (10:90)

Standard stock solution A: 0.8 mg/mL of USP Propranolol Hydrochloride RS in methanol

Standard stock solution B: 0.25 mg/mL of USP Hydrochlorothiazide RS in methanol

Standard solution: 0.04 mg/mL of USP Propranolol Hydrochloride RS and 0.0125 mg/mL of USP Hydrochlorothiazide RS in *Diluent 1* from *Standard stock solution A* and *Standard stock solution B*, respectively

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute 5.0 mL of the filtrate with 5.0 mL of *Diluent 2*. Mix.

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 15-cm; 5-µm packing L10

Column temperature: 35°

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of propranolol

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 4.0 between propranolol and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for propranolol and hydrochlorothiazide

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) and the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

r_U = peak response of propranolol or hydrochlorothiazide from the *Sample solution*

r_S = peak response of propranolol or hydrochlorothiazide from the *Standard solution*

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

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*, 2

L = label claim (mg/Tablet) ▲ (USP 1-Aug-2022)

Tolerances: NLT 80% (*Q*) of the labeled amount of propranolol hydrochloride ($C_{16}H_{21}NO_2 \cdot HCl$) and NLT 80% (*Q*) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements ▲▲ (USP 1-Aug-2022)

IMPURITIES

Change to read:

• **Organic Impurities**

▲**Buffer:** Dissolve 5.75 g of monobasic ammonium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile, methanol, and *Buffer* (15:10:75)

Standard stock solution A: 4.0 mg/mL of USP Propranolol Hydrochloride RS in *Mobile phase*. Sonicate to dissolve, if necessary.

Standard stock solution B: 2.5 mg/mL of USP Hydrochlorothiazide RS prepared as follows. Transfer an appropriate amount of USP Hydrochlorothiazide RS into a suitable volumetric flask. Add methanol to 20% of the flask volume and sonicate. Dilute with *Mobile phase* to volume.

Standard stock solution C: 0.05 mg/mL of USP Benzothiadiazine Related Compound A RS in *Mobile phase*. Sonicate to dissolve, if necessary.

Standard stock solution D: 0.025 mg/mL of USP Chlorothiazide RS in *Mobile phase*. Sonicate to dissolve, if necessary.

System suitability solution: 0.2 mg/mL of USP Propranolol Hydrochloride RS, 0.125 mg/mL of USP Hydrochlorothiazide RS, 1.25 µg/mL of USP Benzothiadiazine Related Compound A RS, and 0.625 µg/mL of USP Chlorothiazide RS in *Mobile phase* from *Standard stock solution A*, *Standard stock solution B*, *Standard stock solution C*, and *Standard stock solution D*, respectively

Standard solution: 2.0 µg/mL of USP Propranolol Hydrochloride RS and 0.625 µg/mL of USP Hydrochlorothiazide RS in *Mobile phase* from *Standard stock solution A* and *Standard stock solution B*, respectively

Sensitivity solution: 0.2 µg/mL of USP Propranolol Hydrochloride RS and 0.0625 µg/mL of USP Hydrochlorothiazide RS in *Mobile phase* from the *Standard solution*

Sample stock solution: Nominally the concentrations given in *Table 1* are prepared as follows. Transfer NLT 10 Tablets into a suitable volumetric flask. Add *Mobile phase* to at least 70% volume of the flask and sonicate. Mix well and dilute with *Mobile phase* to volume. Centrifuge and use the supernatant.

Table 1

Tablet Strength Propranolol Hydrochloride/Hydrochlorothiazide (mg/mg)	Nominal Concentration of Propranolol Hydrochloride (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
40/25	4	2.5
80/25	4	1.25

Sample solution: Nominal concentrations in *Mobile phase* from the *Sample stock solution* are given in *Table 2*.

Table 2

Tablet Strength Propranolol Hydrochloride/Hydrochlorothiazide (mg/mg)	Nominal Concentration of Propranolol Hydrochloride (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
40/25	0.2	0.125
80/25	0.2	0.063

Chromatographic system

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

Mode: LC

Detector: UV 233 nm for degradation products related to propranolol and UV 272 nm for degradation products related to hydrochlorothiazide

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2.5 times the retention time of propranolol

System suitability

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

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between benzothiadiazine related compound A and chlorothiazide at both 233 and 272 nm, *System suitability solution*

Relative standard deviation: NMT 5.0% for propranolol and hydrochlorothiazide, *Standard solution*

Signal-to-noise ratio: NLT 10 for propranolol and hydrochlorothiazide, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any unspecified degradation product related to propranolol in the portion of Tablets taken:

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

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

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

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

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

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

Calculate the percentage of benzothiadiazine related compound A and any unspecified degradation products related to hydrochlorothiazide in the portion of Tablets taken:

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

r_U = peak response of benzothiadiazine related compound A or unspecified degradation product from the *Sample solution*

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

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

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

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

Acceptance criteria: See *Table 3*. The reporting threshold is 0.1%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	0.12	0.71	1.0
Chlorothiazide[a]	0.14	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Hydrochlorothiazide	0.15	—	—
Propranolol	1.0	—	—
Any unspecified degradation product[b]	—	1.0[c]	0.2
Total degradation products	—	—	1.5▲ (USP 1-Aug-2022)

[a] For resolution measurement only.

[b] For any unspecified degradation product detected at 233 and 272 nm.

[c] The relative response factor of 1.0 is assigned for any unspecified degradation product detected at 233 and 272 nm.

ADDITIONAL REQUIREMENTS

Change to read:

• **Packaging and Storage:** Preserve in well-closed containers. ▲Store at controlled room temperature.▲ (USP 1-Aug-2022)

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

$C_6H_8ClN_3O_4S_2$ 285.73

▲USP Chlorothiazide RS▲ (USP 1-Aug-2022)

USP Hydrochlorothiazide RS

USP Propranolol Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
PROPRANOLOL HYDROCHLORIDE AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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