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Hydrochlorothiazide Capsules

DEFINITION

Hydrochlorothiazide Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **Procedure**

Buffer: 13.8 g/L of monobasic sodium phosphate

Mobile phase: Acetonitrile and *Buffer* (10:90). Adjust with 10% (v/v) phosphoric acid to a pH of 3.0.

System suitability solution: 0.15 mg/mL each of USP Hydrochlorothiazide RS and USP Chlorothiazide RS in *Mobile phase*. Sonicate to completely dissolve.

Standard stock solution: 0.50 mg/mL of USP Hydrochlorothiazide RS prepared as follows. To a suitable amount of USP Hydrochlorothiazide RS in a suitable volumetric flask add acetonitrile to 10% of the final volume and sonicate to dissolve. Dilute with *Buffer* to volume.

Standard solution: 50 µg/mL of USP Hydrochlorothiazide RS in *Mobile phase* from the *Standard stock solution*

Sample stock solution: Nominally 0.25 mg/mL of hydrochlorothiazide prepared as follows. Transfer NLT 10 Capsules into a suitable volumetric flask. Add water to 10% of the final volume, and sonicate for 10 min with vigorous shaking. Add *Buffer* to 20% of the final volume, and again sonicate for 10 min. Add acetonitrile up to 40% of the final volume, and sonicate for 30 min. Dilute with *Buffer* to volume, and pass through a suitable filter of 0.45-µm pore size.

Sample solution: 50 µg/mL of hydrochlorothiazide in *Mobile phase* from the *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 272 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

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of hydrochlorothiazide

System suitability

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

[Note—The relative retention times for chlorothiazide and hydrochlorothiazide are 0.80 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 2.0 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Capsules taken:

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

r_U = peak response of hydrochlorothiazide 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)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard solution: 6.75 µg/mL of USP Hydrochlorothiazide RS prepared as follows. Dissolve a quantity of USP Hydrochlorothiazide RS in 10% of the flask volume of acetonitrile, and dilute with *Medium*. Sonicate to completely dissolve.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Instrumental conditions

Mode: UV

Analytical wavelength: 272 nm

Cell: 1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

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

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Capsule)

D = dilution factor for the *Sample solution*

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 30 min

Standard stock solution: 0.35 mg/mL of USP Hydrochlorothiazide RS in *Medium*. An amount of acetonitrile, not exceeding 25% of the final volume, may be used to help solubilize hydrochlorothiazide.

Standard solution: (L/900) mg/mL of USP Hydrochlorothiazide RS in *Medium*, from the *Standard stock solution*, where L is the label claim in mg/Capsule

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

Empty capsules solution: Place 10 ▲empty capsules▲ (ERR 1-Oct-2019) into a 900-mL volumetric flask. Slowly add 800 mL of *Medium* pre-heated to 37°, and stir until dissolved. Cool to room temperature, and dilute with *Medium* to volume.

Instrumental conditions

Mode: UV

Analytical wavelength: 272 nm

Cell: 1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

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

$$\text{Result} = [(A_U - A_{EC})/A_S] \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_{EC} = absorbance of the *Empty capsules solution*

A_S = absorbance of the *Standard solution*

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, and **System suitability solution:** Prepare as directed in the *Assay*.

Standard stock solution: 0.25 mg/mL of USP Hydrochlorothiazide RS prepared as follows. To a suitable amount of USP Hydrochlorothiazide RS in a suitable volumetric flask add acetonitrile to 10% of the final volume, and sonicate to dissolve. Dilute with *Buffer* to volume.

Standard solution: 0.25 µg/mL of USP Hydrochlorothiazide RS in *Mobile phase* from the *Standard stock solution*

Sample solution: Use the *Sample stock solution* as prepared in the *Assay*.

Chromatographic system: Proceed as directed in the *Assay* except for the *Run time*.

Run time: NLT 4 times the retention time of hydrochlorothiazide

System suitability

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

[Note—See *Table 1* for the relative retention times for chlorothiazide and hydrochlorothiazide.]

Suitability requirements

Resolution: NLT 2.0 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of benzothiadiazine related compound A and any unspecified impurity in the portion of Capsules 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 any unspecified impurity 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 1*)

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A[a]	0.65	0.61	1.0

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlorothiazide[b]	0.80	—	—
Hydrochlorothiazide	1.0	1.0	—
5-Chlorohydrochlorothiazide[b,c]	2.88	—	—
Any unspecified impurity	—	1.0	0.2
Total impurities[d]	—	—	1.5

[a] 4-Amino-6-chloro-1,3-benzenedisulfonamide.

[b] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.

[c] 5,6-Dichloro-3,4-dihydro-2*H*-benzothiadiazine-7-sulfonamide 1,1-dioxide

[d] Total impurities include benzothiadiazine related compound A and all unspecified impurities.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.
- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

  USP Chlorothiazide RS

  USP Hydrochlorothiazide RS

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

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

Chromatographic Database Information: Chromatographic Database

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