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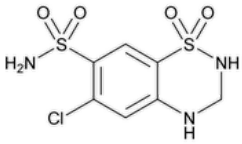
Hydrochlorothiazide



$C_7H_8ClN_3O_4S_2$ 297.74

2*H*-1,2,4-Benzothiadiazine-7-sulfonamide, 6-chloro-3,4-dihydro-, 1,1-dioxide;

6-Chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide CAS RN®: 58-93-5; UNII: 0J48LPH2TH.

DEFINITION

Hydrochlorothiazide contains NLT 98.0% and NMT 102.0% of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), calculated on the dried basis.

IDENTIFICATION

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Sample: Potassium bromide–hydrochlorothiazide mixture, previously heated at 105° for 2 h

Acceptance criteria: Meets the requirements

Delete the following:

▲• **B. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

Sample solution: 10 µg/mL in methanol

Acceptance criteria: Meets the requirements▲ (USP 1-May-2022)

Add the following:

▲• **B.** 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-2022)

ASSAY

Change to read:

• **Procedure**

Buffer: 2.76 g of sodium phosphate, monobasic in a 1000-mL volumetric flask. Add 990 mL of water. Adjust with phosphoric acid to a pH of 2.7 ± 0.1, and dilute with water to volume.

Diluent: Acetonitrile and *Buffer* (30:70)

Solution A: Acetonitrile and methanol (75:25)

Solution B: 0.5% formic acid, anhydrous solution in water

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	3	97
5	3	97
14	36	64

Time (min)	Solution A (%)	Solution B (%)
18	3	97
20	3	97

System suitability solution: 0.32 mg/mL of USP Hydrochlorothiazide RS, 0.0032 mg/mL of USP Chlorothiazide RS, and 0.0032 mg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent*. Sonicate if necessary to dissolve. Pass a portion through a filter of 0.45-µm or finer pore size.

Standard solution: 0.32 mg/mL of USP Hydrochlorothiazide RS in *Diluent*. Sonicate if necessary to dissolve. Pass a portion through a filter of 0.45-µm or finer pore size.

Sample solution: 0.32 mg/mL of Hydrochlorothiazide in *Diluent*, prepared as follows. Transfer 32 mg of Hydrochlorothiazide into a 100-mL volumetric flask. Add 70 mL of *Diluent*, sonicate for 10 min if necessary to dissolve, and allow to cool to ambient temperature. Dilute with *Diluent* to volume. Pass a portion through a filter of 0.45-µm or finer pore size.

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 5-cm; 3.5-µm packing L1

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—See *Table 2* for the relative retention times.]

▲▲ (USP 1-May-2022)

Suitability requirements

Resolution: NLT 2.0 between benzothiadiazine related compound A and chlorothiazide and NLT 1.5 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Tailing factor: ▲NMT 1.5, *Standard solution*▲ (USP 1-May-2022)

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Hydrochlorothiazide 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* (mg/mL)

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

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

IMPURITIES

- **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%
- **CHLORIDE AND SULFATE ⟨221⟩, *Chloride***

Sample solution: Shake 0.50 g with 40 mL of water for 5 min, and filter.

Acceptance criteria: 0.035%; the filtrate shows no more chloride than corresponds to 0.25 mL of 0.020 N hydrochloric acid.

Delete the following:

▲- **SELENIUM ⟨291⟩**

Sample: 200 mg

Acceptance criteria: NMT 30 ppm▲ (USP 1-May-2022)

Change to read:

• **Organic Impurities**

▲**Buffer,**▲ (USP 1-May-2022) **Diluent, Solution A, Solution B, Mobile phase, System suitability solution,** ▲**Sample solution,**▲ (USP 1-May-2022) and **Chromatographic system:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.16 µg/mL of USP Hydrochlorothiazide RS in *Diluent*. Sonicate if necessary to dissolve.

▲▲ (USP 1-May-2022)

System suitability

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

[Note—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between benzothiadiazine related compound A and chlorothiazide and NLT 1.5 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

▲▲ (USP 1-May-2022)

Relative standard deviation: NMT 5.0% for benzothiadiazine related compound A and chlorothiazide, *System suitability solution*; NMT 25% for hydrochlorothiazide, based on 3 replicate injections, *Sensitivity solution*

Analysis

Samples: ▲*Diluent* and▲ (USP 1-May-2022) *Sample solution*

▲[Note—Injection(s) of *Diluent* can be made to correctly identify system peaks, which should be excluded from quantitation.]▲ (USP 1-May-2022)

Calculate the percentage of each impurity in the portion of Hydrochlorothiazide taken:

$$\text{▲Result} = \{ (r_U/F)/[r_S + \Sigma(r_U/F)] \} \times 100$$

r_U = peak response of each impurity from the *Sample solution*

F = relative response factor of each impurity (see *Table 2*)

r_S = peak response of hydrochlorothiazide from the *Sample solution*▲ (USP 1-May-2022)

Acceptance criteria: See *Table 2*. ▲The reporting threshold is 0.05%.▲ (USP 1-May-2022)

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A	0.5	0.54	1.0
Chlorothiazide	0.8	0.63	0.5
Hydrochlorothiazide	1.0	—	—
5-Chlorohydrochlorothiazide▲[a]▲ (USP 1-May-2022)	2.1	1.0	0.5
Hydrochlorothiazide dimer[b]	2.6	1.0	0.5
Any other individual impurity	—	1.0	0.5
Total impurities	—	—	0.9[c]

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

[b] 6-Chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine-4-yl 1,1-dioxide)methyl]3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

[c] Excluding benzothiadiazine related compound A.

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry at 105° for 1 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

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

• **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 Hydrochlorothiazide RS

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

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

Chromatographic Database Information: Chromatographic Database

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