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Lisinopril and Hydrochlorothiazide Tablets

DEFINITION

Lisinopril and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of lisinopril ($C_{21}H_{31}N_3O_5$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

• **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

The Tablets must be assayed within 24 h of the time they are put in the solution.

Buffer: Dissolve 4.08 g of monobasic potassium phosphate in 800 mL of water. Adjust with phosphoric acid to a pH of 2.5, and dilute with water to 1 L.

Mobile phase: Acetonitrile, triethylamine, water, and phosphoric acid (280:3:1480:15)

Lisinopril standard stock solution: 0.5 mg/mL of USP Lisinopril RS in *Buffer*

Hydrochlorothiazide standard stock solution: 3.12 mg/mL of USP Hydrochlorothiazide RS in methanol

Lisinopril related compound A stock solution: 0.05 mg/mL of USP Lisinopril Related Compound A RS in methanol

Benzothiadiazine related compound A stock solution: 0.016 mg/mL of USP Benzothiadiazine Related Compound A RS in methanol

Standard solution: 0.1 mg/mL of USP Lisinopril RS, 0.125 mg/mL of USP Hydrochlorothiazide RS, 2 µg/mL of USP Lisinopril Related Compound A RS, and 1.3 µg/mL of USP Benzothiadiazine Related Compound A RS in *Buffer* from *Lisinopril standard stock solution, Hydrochlorothiazide standard stock solution, Lisinopril related compound A stock solution*, and *Benzothiadiazine related compound A stock solution*. For Tablet strengths 20/12.5 of lisinopril/hydrochlorothiazide, the concentration of USP Lisinopril RS and USP Lisinopril Related Compound A RS in the *Standard solution* is 0.2 mg/mL and 4 µg/mL, respectively.

Sample stock solution: Transfer 10 Tablets to a suitable volumetric flask. Add *Buffer* (0.25 mL/mg of total lisinopril), sonicate for 5 min, and then add methanol (0.5 mL/mg of total lisinopril). Sonicate for an additional 10 min. Add more *Buffer* (0.75 mL/mg of total lisinopril), and mix by mechanical means for 20 min. Dilute with water to volume to prepare solutions as described in *Table 1*.

Table 1

Tablet Strength of Lisinopril/ Hydrochlorothiazide (mg/Tablet)	Nominal Concentration of Lisinopril/ Hydrochlorothiazide (mg/mL)
10/12.5	0.4/0.5
20/12.5	0.4/0.25
20/25	0.4/0.5

Sample solution: Dilute the *Sample stock solution* with *Buffer* to prepare solutions as described in *Table 2*. Pass a portion through a suitable filter of 0.45-µm pore size.

Table 2

Tablet Strength of Lisinopril/ Hydrochlorothiazide (mg/Tablet)	Nominal Concentration of Lisinopril/ Hydrochlorothiazide (mg/mL)
10/12.5	0.1/0.12
20/12.5	0.2/0.125
20/25	0.1/0.12

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 10 min

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 3.0 between lisinopril and benzothiadiazine related compound A and NLT 4.0 between hydrochlorothiazide and benzothiadiazine related compound A

Tailing factor: NMT 2 for both the lisinopril and hydrochlorothiazide peaks

Relative standard deviation: NMT 2.0% for both the lisinopril and hydrochlorothiazide peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of lisinopril ($C_{21}H_{31}N_3O_5$) 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 lisinopril or hydrochlorothiazide from the *Sample solution*

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

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

C_U = nominal concentration of lisinopril or hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 45 min for hydrochlorothiazide; 30 min for lisinopril

Buffer and **Mobile phase:** Prepare as directed in the *Assay*.

Lisinopril standard stock solution: 0.5 mg/mL of USP Lisinopril RS in *Buffer*

Hydrochlorothiazide standard stock solution: 0.44 mg/mL of USP Hydrochlorothiazide RS in methanol

Standard solution: Prepare solutions in *Medium* as described in *Table 3* from the *Lisinopril standard stock solution* and *Hydrochlorothiazide standard stock solution*.

Table 3

Tablet Strength of Lisinopril/ Hydrochlorothiazide (mg/Tablet)	Nominal Concentration of Lisinopril/ Hydrochlorothiazide (mg/mL)
10/12.5	0.01/0.013
20/12.5	0.02/0.013
20/25	0.02/0.026

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

Chromatographic system: Proceed as directed in the *Assay*, except use an injection volume of 20 µL.

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 4.0 between the lisinopril and hydrochlorothiazide peaks

Tailing factor: NMT 2 for both the lisinopril and hydrochlorothiazide peaks

Column efficiency: NLT 6000 theoretical plates for the hydrochlorothiazide peak

Relative standard deviation: NMT 2.0% for both the lisinopril and hydrochlorothiazide peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of lisinopril ($C_{21}H_{31}N_3O_5$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

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

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

C_S = concentration of lisinopril and hydrochlorothiazide in the *Standard solution* from *Table 3* (mg/mL)

L = labeled amount of lisinopril and hydrochlorothiazide (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amounts of lisinopril ($C_{21}H_{31}N_3O_5$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

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

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Times: 30 min for both lisinopril and hydrochlorothiazide

Buffer: 2.76 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (6:94)

Standard stock solution 1 (for Tablets labeled to contain 10 mg/12.5 mg or 20 mg/25 mg of lisinopril/hydrochlorothiazide)**:** 0.11 mg/mL of USP Lisinopril RS and 0.14 mg/mL of USP Hydrochlorothiazide RS, prepared as follows. Add acetonitrile to fill 1.5% of the total volume, sonicate until dissolved, and dilute with *Medium* to volume.

Standard stock solution 2 (for Tablets labeled to contain 20 mg/12.5 mg of lisinopril/hydrochlorothiazide)**:** 0.22 mg/mL of USP Lisinopril RS and 0.14 mg/mL of USP Hydrochlorothiazide RS, prepared as follows. Add acetonitrile to fill 1.5% of the total volume, sonicate until dissolved, and dilute with *Medium* to volume.

Standard solution: Prepare solutions, in *Medium*, of lisinopril and hydrochlorothiazide as described in *Table 4* from either *Standard stock solution 1* or *Standard stock solution 2*.

Table 4

Tablet Strength of Lisinopril/ Hydrochlorothiazide (mg/Tablet)	Nominal Concentration of Lisinopril/ Hydrochlorothiazide (mg/mL)
10/12.5	0.011/0.014
20/12.5	0.022/0.014
20/25	0.022/0.028

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

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 20-cm; 5-µm packing L7

Column temperature: 50°

Flow rate: 1.0 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.8 for the lisinopril peak and NMT 1.5 for the hydrochlorothiazide peak

Resolution: NLT 3.5 between the lisinopril and hydrochlorothiazide peaks

Relative standard deviation: NMT 2.0% for both peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of lisinopril ($C_{21}H_{31}N_3O_5$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

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

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

C_S = concentration of lisinopril or hydrochlorothiazide in the *Standard solution* (mg/mL)

L = labeled amounts of lisinopril or hydrochlorothiazide (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of lisinopril ($C_{21}H_{31}N_3O_5$) and NLT 75% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

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

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, Benzothiadiazine related compound A stock solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Standard solution 1: Use the *Standard solution*, prepared as directed in the *Assay*.

Standard solution 2: 1.28 µg/mL of USP Benzothiadiazine Related Compound A RS in *Buffer* from the *Benzothiadiazine related compound A stock solution*

Analysis

Samples: *Standard solution 1*, *Standard solution 2*, and *Sample solution*

Calculate the percentage of lisinopril related compound A and benzothiadiazine related compound A in the portion of Tablets taken:

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

r_U = peak response of lisinopril related compound A or benzothiadiazine related compound A from the *Sample solution*

r_S = peak response of lisinopril related compound A or benzothiadiazine related compound A from *Standard solution 1* or *Standard solution 2*

C_S = concentration of USP Lisinopril Related Compound A RS in *Standard solution 1* or USP Benzothiadiazine Related Compound A RS in *Standard solution 2* (mg/mL)

C_U = nominal concentration of lisinopril or hydrochlorothiazide in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of lisinopril, 405.5, for calculating the percentage of lisinopril related compound A; or molecular weight of hydrochlorothiazide, 297.74, for calculating the percentage of benzothiadiazine related compound A

M_{r2} = molecular weight of lisinopril related compound A, 387.47; or benzothiadiazine related compound A, 285.73

Acceptance criteria

Individual impurities: NMT 2% of lisinopril related compound A; NMT 1% of benzothiadiazine related compound A

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed 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.
- **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 Hydrochlorothiazide RS

USP Lisinopril RS

USP Lisinopril Related Compound A RS

(*S*)-2-{(3*S*,8a*S*)-3-(4-Aminobutyl)-1,4-dioxohexahydropyrrolo[1,2-a]pyrazin-2(1*H*)-yl}-4-phenylbutanoic acid.

$C_{21}H_{29}N_3O_4$ 387.47

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

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

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