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Fosinopril Sodium and Hydrochlorothiazide Tablets

DEFINITION

Fosinopril Sodium and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of fosinopril sodium ($C_{30}H_{45}NNaO_7P$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: **197F**▲ (CN 1-May-2020)

Fosinopril Sodium: Transfer an amount equivalent to 25 mg of fosinopril sodium from finely powdered Tablets to a 100-mL beaker containing 40 mL of water. Heat at 30° for 5 min with stirring, and filter through a fritted disk of medium pore size. Centrifuge the filtrate at 2500 rpm for 30 min. Adjust the filtrate with hydrochloric acid to a pH of 1 to precipitate the fosinopril, and filter through a fritted-disk funnel. Dissolve the precipitate by passing methyl isobutyl ketone through the filter, and evaporate the filtrate to dryness under a stream of nitrogen. Proceed as directed, using the oily residue so obtained and a similarly prepared residue from 25 mg of USP Fosinopril Sodium RS.

Hydrochlorothiazide: Transfer an amount equivalent to 37.5 mg of hydrochlorothiazide from finely powdered Tablets to a 250-mL beaker containing 120 mL of water, heat at 30° for 5 min with stirring, and filter through a a fritted disk of medium pore size. Wash the precipitate with 60 mL of methylene chloride and glacial acetic acid (90:10) mixture, and discard the filtrate. Dissolve the precipitate by passing 10 mL of methyl isobutyl ketone through the filter, and evaporate the filtrate to dryness under a stream of nitrogen. Proceed as directed, using the waxy residue so obtained and a similarly prepared residue from 37 mg of USP Hydrochlorothiazide RS.

Acceptance criteria: Meet the requirements

• **B.** The retention times of fosinopril and hydrochlorothiazide peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: 0.01 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 2.0.

Solution A: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Buffer (%)	Solution A (%)
0	88	12
2	88	12
20	10	90
28	10	90
37	88	12

Diluent A: Acetonitrile and water (1:2)

Diluent B: Acetonitrile and 0.001 N hydrochloric acid (1:2)

System suitability solution: 0.08 mg/mL each of USP Hydrochlorothiazide RS and USP Fosinopril Sodium RS, and 0.025 mg/mL of USP Chlorothiazide RS in *Diluent B*

Standard stock solution A: 2.0 mg/mL of USP Fosinopril Sodium RS in *Diluent A*

Standard stock solution B: 2.0 mg/mL of USP Hydrochlorothiazide RS in *Diluent B*

Standard solution: 0.08 mg/mL each of USP Fosinopril Sodium RS and USP Hydrochlorothiazide RS from *Standard stock solution A* and *Standard stock solution B*, respectively, in *Diluent B*

Sample stock solution: Nominally equivalent to 0.1 mg/mL of fosinopril sodium and 0.125 mg/mL of hydrochlorothiazide in *Diluent B* from NLT 20 finely powdered Tablets. Initially add *Diluent B* to fill 75% of the final volume, and sonicate for about 10 min. Shake by mechanical

means for 15 min, and dilute with *Diluent B* to volume. Pass a portion of this solution through a filter (PTFE or PVDF) of 0.45-µm pore size, and collect the rest of the filtrate.

Sample solution: 0.075 mg/mL of fosinopril sodium in *Diluent B* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 206 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 1.0 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.8 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 fosinopril sodium ($C_{30}H_{45}NNaO_7P$) in the portion of Tablets taken:

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

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

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

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

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

Calculate the percentage of the labeled amount of 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 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 = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of fosinopril sodium ($C_{30}H_{45}NNaO_7P$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$)

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Buffer: 0.01 M monobasic potassium phosphate; pH 3.0

Mobile phase: Methanol, acetonitrile, and *Buffer* (350:200:450)

Standard stock solution A: 0.1 mg/mL of USP Fosinopril Sodium RS. Initially add 0.3 mL of methanol per mg of USP Fosinopril Sodium RS, and dilute with water to final concentration.

Standard stock solution B: 0.1 mg/mL of USP Hydrochlorothiazide RS. Initially add 0.3 mL of methanol per mg of USP Fosinopril Sodium RS, and dilute with water to final concentration.

Standard solution: Mix 25 mL of *Standard stock solution B* and *x*25 mL of *Standard stock solution A*, *x* being the ratio of the respective labeled amounts, in mg, of fosinopril sodium to that of hydrochlorothiazide per Tablet, and dilute with water to 200 mL.

System suitability solution: 0.05 mg/mL of USP Fosinopril Related Compound H RS and 0.002 mg/mL of USP Hydrochlorothiazide RS. Initially add 1 mL of methanol per mg of USP Fosinopril Related Compound H RS to dissolve, add *Standard stock solution B*, and dilute with water to final concentration.

Sample solution: Pass portions of the solution under test through an acrylic filter of 1.2-µm pore size. Do not use glass filters.

Chromatographic system

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

Mode: LC

Detectors

UV 215 nm: For *Standard solution* and *System suitability solution*

UV 272 nm: For hydrochlorothiazide from 0 to 5 min

UV 210 nm: For fosinopril sodium from 5 to 9 min

Column: 4.6-mm × 25-cm; 5-µm packing L10

Column temperature: 40°

Flow rate: 1.3 mL/min

Injection volume: 50 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between fosinopril related compound H and hydrochlorothiazide, *System suitability solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of fosinopril sodium ($C_{30}H_{45}NNaO_7P$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved.

Tolerances: NLT 80% (*Q*) of the labeled amount of fosinopril sodium ($C_{30}H_{45}NNaO_7P$) 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**

Solution A, Solution B, Diluent B, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution: 4 µg/mL each of USP Fosinopril Sodium RS and USP Hydrochlorothiazide RS in *Diluent B*

System suitability solution: 5 µg/mL each of USP Chlorothiazide RS, USP Fosinopril Related Compound A RS, and USP Benzothiadiazine Related Compound A RS; and 0.5 mg/mL each of USP Hydrochlorothiazide RS and USP Fosinopril Sodium RS in *Diluent B*

System suitability

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

Suitability requirements

Resolution: NLT 1.8 between chlorothiazide and hydrochlorothiazide, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Measure the peak responses eluting between 2.7 min and 27 min.

Calculate the percentage of any impurity or degradation product 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 each impurity from the *Sample solution*

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

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

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

F = relative response factor of each impurity relative to fosinopril sodium or hydrochlorothiazide (see *Table 2*)

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A[a]	0.81 (relative to hydrochloro thiazide)	1.0	0.5
Fosinopril related compound A[b]	0.72 (relative to fosinopril)	1.2	4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlorothiazide[c]	0.90 (relative to hydrochloro thiazide)	1.7	0.3
Any other individual impurity	—	—	0.2[d]
Total impurities	—	—	5.0

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

b (4*S*)-4-Cyclohexyl-[(4-phenylbutyl)phosphinyl]acetyl-L-proline.

c 6-Chloro-2(*H*)-1,2,4-benzothiazine-7-sulfonamide.

d Relative to hydrochlorothiazide.

ADDITIONAL REQUIREMENTS

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

• **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 Fosinopril Sodium RS

USP Fosinopril Related Compound A RS
(4*S*)-4-Cyclohexyl-[(4-phenylbutyl)phosphinyl]acetyl-L-proline.
$C_{23}H_{34}NO_5P$ 435.49

USP Fosinopril Related Compound H RS
4-Phenylbutyl phosphonic acid.
$C_{10}H_{15}O_3P$ 214.20

USP Hydrochlorothiazide RS

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

Topic/Question	Contact	Expert Committee
FOSINOPRIL SODIUM AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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