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Losartan Potassium and Hydrochlorothiazide Tablets

DEFINITION

Losartan Potassium and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) 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*.
- **B.** The UV spectra of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **Procedure**

Buffer A: 2.76 g/L of ▲monobasic sodium phosphate▲ (ERR 1-Nov-2020) in water. Adjust with phosphoric acid to a pH of 2.5.

Buffer B: 1.25 g/L of monobasic potassium phosphate and 1.5 g/L of dibasic sodium phosphate in water. The pH of the resulting solution is about 7.0–7.5.

Solution A: Acetonitrile and *Buffer B* (7:93)

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
12	92	8
28	38	62
30	100	0
35	100	0

Diluent: Acetonitrile and *Buffer A* (60:40)

Standard solution: Transfer appropriate amounts of USP Losartan Potassium RS and USP Hydrochlorothiazide RS into a suitable volumetric flask, and dissolve in *Diluent* (50% of the volume of the flask). Dilute with *Buffer A* to volume to obtain a solution having concentrations as directed in *Table 2*. Pass a portion of the solution through a PTFE or equivalent filter of 0.45-µm pore size.

Table 2

Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)	Concentration of USP Losartan Potassium RS (mg/mL)	Concentration of USP Hydrochlorothiazide RS (mg/mL)
50/12.5	0.4	0.1
100/12.5	0.4	0.05
100/25	0.4	0.1

Sample stock solution: Transfer 10 Tablets into a suitable volumetric flask and add *Diluent* as directed in *Table 3*. Mix well and mechanically shake or stir until the solid is dispersed. Dilute with *Buffer A* to volume, and sonicate.

Table 3

Tablet Strength Losartan Potassium/ Hydrochlorothiazide (mg)	Flask Size (mL)	Volume of Diluent (mL)
50/12.5	250	210
100/12.5	500	420
100/25	500	420

Sample solution: Dilute a portion of the *Sample stock solution* first with acetonitrile (20% of the volume of the flask) and then with *Buffer A* to obtain a solution having nominal concentrations of losartan potassium and hydrochlorothiazide similar to those of the *Standard solution*. Pass a portion of this solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm. For *Identification B*, use a diode array detector in the range of 190–400 nm.

Column: 3.9-mm × 15-cm; 5-µm packing L7

Column temperature: 35°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for hydrochlorothiazide and losartan are 1.0 and 3.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.5 for the losartan peak

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) or 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 losartan or hydrochlorothiazide from the *Sample solution*

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

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

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: Water; 900 mL, deaerated

Apparatus 1: 100 rpm

Time: 30 min for both losartan and hydrochlorothiazide

Buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (40:60)

Losartan potassium stock solution: 0.44 mg/mL of USP Losartan Potassium RS in *Medium*

Hydrochlorothiazide stock solution: 0.14 mg/mL of USP Hydrochlorothiazide RS prepared by dissolving in methanol (10% of the volume of the flask). Dilute with *Medium* to volume.

Standard solution: Transfer the appropriate volumes of *Losartan potassium stock solution* and *Hydrochlorothiazide stock solution* to a 100-mL volumetric flask according to the dilution schemes in *Table 4*. Dilute with *Medium* to volume.

Table 4

Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)	Aliquot of Losartan Potassium Stock Solution (mL)	Aliquot of Hydrochlorothiazide Stock Solution (mL)
50/12.5	12.5	10.0
100/12.5	25.0	10.0
100/25	25.0	20.0

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 230 nm

Column: 4.6-mm × 25-cm; 10-µm packing L7

Column temperature: 35°

Flow rate: 2.3 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of the losartan peak

System suitability

Sample: *Standard solution*

[Note—The relative retention times for hydrochlorothiazide and losartan are 1.0 and 2.7, respectively.]

Suitability requirements

Resolution: NLT 2 between the hydrochlorothiazide and losartan peaks

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) or hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 85% (*Q*) of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) and NLT 75% (*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 the product meets USP *Dissolution Test 2*.

Medium, Apparatus 1, and **Time:** Proceed as directed in *Test 1*.

Buffer: 1.78 g/L of dibasic sodium phosphate dihydrate in water. Adjust with phosphoric acid to a pH of 6.5.

Mobile phase: Acetonitrile and *Buffer* (32:68)

Diluent: Acetonitrile and water (40:60)

Standard stock solution 1: 1.1 mg/mL of USP Losartan Potassium RS in *Diluent*. Sonication may be necessary for complete dissolution.

Standard stock solution 2: 0.28 mg/mL of USP Hydrochlorothiazide RS in *Diluent*. Sonication may be necessary for complete dissolution.

Standard solution: Transfer appropriate volumes of *Standard stock solution 1* and *Standard stock solution 2* to a 100-mL volumetric flask according to the dilution schemes in *Table 5*. Dilute with *Medium* to volume.

Table 5

Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)	Aliquot of Standard Stock Solution 1 (mL)	Aliquot of Standard Stock Solution 2 (mL)
50/12.5	5	5
100/12.5	10	5
100/25	10	10

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 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Autosampler temperature: 8°

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of the losartan peak

System suitability

Sample: *Standard solution*

[Note—The relative retention times for hydrochlorothiazide and losartan are 1.0 and 1.4, respectively.]

Suitability requirements

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

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

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

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 85% (*Q*) of the labeled amount of losartan potassium ($C_{22}H_{22}ClKN_6O$) and 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 A, Buffer B, Solution A, Solution B, Mobile phase, Diluent, Standard solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Chlorothiazide standard solution: 0.1 mg/mL of USP Chlorothiazide RS prepared by dissolving in *Diluent* (50% of the volume of the flask). Dilute with *Buffer A* to volume, and sonicate.

Benzothiadiazine related compound A standard solution: 0.1 mg/mL of USP Benzothiadiazine Related Compound A RS prepared by dissolving in *Diluent* (50% of the volume of the flask). Dilute with *Buffer A* to volume, and sonicate.

Stressed losartan solution: [Note—This solution contains the degradates 1-*H*-dimer and 2-*H*-dimer and losartan potassium.] Weigh 12 mg of the USP Losartan Potassium RS in a 50-mL flask. Dissolve in 5 mL of water. Pipet 5.0 mL of 0.1 N *hydrochloric acid* into this solution, and place it in an oven at 105° for 1–2 h. Remove from the oven and allow to cool to room temperature. Pipet 5.0 mL of 0.1 N *sodium hydroxide* into the flask, and dilute with water to volume.

Diluted standard solution: Dilute portions of the *Standard solution* and *Benzothiadiazine related compound A standard solution* first with acetonitrile (30% of the volume of the flask), then with *Buffer A* to obtain a solution having nominal concentrations based on Tablet strength as listed in *Table 6*.

Table 6

Tablet Strength Losartan Potassium/ Hydrochlorothiazide (mg)	Concentration of USP Losartan Potassium RS (µg/mL)	Concentration of USP Hydrochlorothiazide RS (µg/mL)	Concentration of USP Benzothiadiazine Related Compound A RS (µg/mL)
50/12.5	4	1	1
100/12.5	4	0.5	1
100/25	4	1	1

System suitability solution: Dissolve weighed quantities of USP Losartan Potassium RS and USP Hydrochlorothiazide RS in a suitable volumetric flask in *Diluent* (50% of the volume of the flask). Add the *Stressed losartan solution,* about 25% of the volume of the flask, into the same flask. Transfer appropriate amounts of *Chlorothiazide standard solution* and *Benzothiadiazine related compound A standard solution* into the same flask, and dilute with *Buffer A* to volume to obtain a solution having a known concentration of about 0.4 mg/mL of losartan, 0.1 mg/mL of hydrochlorothiazide, and 0.001 mg/mL each of benzothiadiazine related compound A and chlorothiazide. Adjust with phosphoric acid to a pH of 2.5, and mix well. Pass an aliquot of the solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Sensitivity solution: Pipet 5.0 mL of the *Diluted standard solution* into a 50-mL volumetric flask. Add 15 mL of acetonitrile, dilute with *Buffer A* to volume, and mix well.

System suitability

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

[NOTE—The run time is about 1.6 times the retention time of the losartan peak. See *Table 7* for the relative retention times.]

Suitability requirements

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

Tailing factor: NMT 2.5 for the losartan peak, *Standard solution*

Relative standard deviation: NMT 2.0% for both the hydrochlorothiazide and losartan peaks, *Standard solution*; NMT 10.0% for both the hydrochlorothiazide and losartan peaks, *Diluted standard solution*

Signal-to-noise ratio: NLT 10 for each component from the first injection. If this is not met, then the signal-to-noise ratio must be greater than 3 with a relative standard deviation of area counts less than 25% for 3 replicate injections, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Diluted standard solution*

Calculate the percentage of benzothiadiazine related compound A (expressed as hydrochlorothiazide equivalent) 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 benzothiadiazine related compound A from the *Sample solution*

r_S = peak response of benzothiadiazine related compound A from the *Diluted standard solution*

C_S = concentration of USP Benzothiadiazine Related Compound A RS in the *Diluted standard solution* (mg/mL)

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

M_{r1} = molecular weight of hydrochlorothiazide, 298

M_{r2} = molecular weight of benzothiadiazine related compound A, 286

Calculate the percentage of each specified impurity in the portion of Tablets taken:

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

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

r_S = peak response of losartan from the *Diluted standard solution*

C_S = concentration of USP Losartan Potassium RS in the *Diluted standard solution* (mg/mL)

C_U = nominal concentration of losartan potassium in the *Sample solution* (mg/mL)

For Tablet strengths of 50/12.5 and 100/25 mg for losartan potassium/hydrochlorothiazide, respectively, calculate the percentage of any other impurity in the portion of Tablets taken:

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

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

r_S = peak response of losartan from the *Diluted standard solution*

C_S = concentration of USP Losartan Potassium RS in the *Diluted standard solution* (mg/mL)

C_U = nominal concentration of losartan potassium in the *Sample solution* (mg/mL)

For a Tablet strength of 100/12.5 mg for losartan potassium/hydrochlorothiazide, calculate the percentage of any other impurity in the portion of Tablets taken:

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

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

r_S = peak response of hydrochlorothiazide from the *Diluted standard solution*

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

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

Acceptance criteria See *Table 7*.

Table 7

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Chlorothiazide[a]	0.57	—
Benzothiadiazine related compound A	0.69	1.0
Hydrochlorothiazide	1.0	—
Losartan	2.7	—
1-*H*-Dimer[b]	3.3	0.5
2-*H*-Dimer[c]	3.5	0.5
Any unspecified degradation product	—	0.2
Total impurities[d]	—	2.0

[a] This process impurity (not a degradation product) is related to hydrochlorothiazide and is controlled in the drug substance.

[b] Related to losartan potassium: 5-[4'-({2-Butyl-5-[(5-{4'-[(2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl)methyl]biphenyl-2-yl}-1*H*-tetrazol-1-yl)methyl]-4-chloro-1*H*-imidazol-1-yl}methyl)biphenyl-2-yl]tetrazol, potassium salt.

[c] Related to losartan potassium: 5-[4'-({2-Butyl-5-[(5-{4'-[(2-butyl-4-chloro-5-hydroxymethyl-1*H*-imidazol-1-yl)methyl]biphenyl-2-yl}-2*H*-tetrazol-2-yl)methyl]-4-chloro-1*H*-imidazol-1-yl}methyl)biphenyl-2-yl]tetrazol, potassium salt.

[d] Total impurities include the sum of all the specified impurities and the unspecified impurities that are equal to or greater than 0.1%.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tightly closed containers protected from light, and store at controlled room temperature.
- **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* 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 Chlorothiazide RS

USP Hydrochlorothiazide RS

USP Losartan Potassium RS

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

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

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