Losartan Potassium and Hydrochlorothiazide Tablets

Type of Posting	Revision Bulletin
Posting Date	27–May–2016
Official Date	01–Jun–2016
Expert Committee	Chemical Medicines Monographs 2
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Losartan Potassium and Hydrochlorothiazide Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to be consistent with the FDA approved specifications for a generic drug product.

The Liquid Chromatography based procedure for *Dissolution Test 2* is validated using a Symmetry C18 brand of L1 column. The typical retention time for losartan and hydrochlorothiazide are about 4.7 min and 3.3 min respectively.

Minor editorial changes have been made to update the monograph to the current *USP* style.

The Losartan Potassium and Hydrochlorothiazide Tablets Revision Bulletin supersedes the currently official Losartan Potassium and Hydrochlorothiazide Tablets monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35.*

Should you have any questions, please contact Sujatha Ramakrishna, Ph.D., MBA. Senior Scientific Liaison (301–816–8349 or sxr@usp.org).

Losartan Potassium and Hydrochlorothiazide Tablets

DEFINITION

Losartan Potassium and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amounts 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*.

ASSAY

• **PROCEDURE**

Buffer A: 2.76 g/L of monobasic sodium phosphate 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.
Diluent: Acetonitrile and *Buffer A* (3:2)
Solution A: Acetonitrile and *Buffer B* (7:93)
Solution B: Use 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

Standard solution: Transfer 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 as directed in *Table 4*. Pass a portion of this solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Table 4

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

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 280 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*
Suitability requirements
Tailing factor: Less than 2.5 for the losartan peak
Relative standard deviation: Less than 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

Change to read:

- **DISSOLUTION** ⟨**711**⟩

•**Test 1**• (RB 1-Jun-2016)

Medium: Water; 900 mL, deaerated
Apparatus 1: 100 rpm
Time: 30 min for both losartan and hydrochlorothiazide
Buffer: Dissolve 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* (2:3)
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 5*. Dilute with *Medium* to volume.

Table 5

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
System suitability
Sample: *Standard solution*
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:

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

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 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: Dissolve 1.78 g of dibasic sodium phosphate dihydrate in 1 L of 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 6*. Dilute with *Medium* to volume.

Table 6

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
System suitability
Sample: *Standard solution*
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.● (RB 1-Jun-2016)

• **Uniformity of Dosage Units** ⟨905⟩

Procedure for content uniformity

Buffer A: Prepare as directed in the *Assay.*

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

Diluent: Prepare a mixture of acetonitrile and *Buffer A* (3:2).

Mobile phase: Acetonitrile and *Buffer B* (2:3)

Standard stock solution 1: 0.46 mg/mL of USP Losartan Potassium RS prepared by dissolving in *Diluent* (50% of the total volume of the flask). Mechanically shake for 15 min or until dissolved. Dilute with *Buffer A* to volume.

Standard stock solution 2: 0.35 mg/mL of USP Hydrochlorothiazide RS prepared by dissolving in *Diluent* (50% of the total volume of the flask). Mechanically shake for 15 min or until dissolved. Dilute with *Buffer A* to volume.

Standard solution: Transfer aliquots of *Standard stock solution 1* and *Standard stock solution 2* into a suitable volumetric flask, and add *Diluent,* up to 42% of the total volume of the flask. Dilute with *Buffer A* to volume, mix well, and sonicate for 2 min to obtain a solution having concentrations based on Tablet strength as listed in *Table 7*. Pass a portion of the solution through a PTFE or equivalent filter of 0.45-µm pore size, and use the filtrate.

Table 7

Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)	Concentration of USP Losartan Potassium RS (mg/mL)	Concentration of USP Hydrochlorothiazide RS (mg/mL)
50/12.5	0.06	0.014
100/12.5	0.06	0.007
100/25	0.06	0.014

Sample stock solution: Transfer 1 Tablet into a suitable volumetric flask, and add *Diluent* as directed in *Table 8*. Mix well, and mechanically shake for 30 min or until the solid is finely dispersed. Dilute with *Buffer A* to volume, and mix well.

Table 8

Tablet Strength Losartan Potassium/Hydrochlorothiazide (mg)	Flask Size (mL)	Volume of Diluent (mL)
50/12.5	100	50
100/12.5	200	100
100/25	200	100

Sample solution: Dilute 10 mL of the *Sample stock solution* in a 100-mL volumetric flask, with 45 mL of *Diluent,* and then dilute with *Buffer A* to volume. Pass an aliquot of the 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 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

System suitability
Sample: *Standard solution*
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 ($C_7H_8ClN_3O_4S_2$) in the Tablet 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: Meet the requirements

IMPURITIES

• **Organic Impurities**

Buffer A, Buffer B, Diluent, Solution A, Solution B, Mobile phase, 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 9*.

Table 9

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.

Limit of quantitation 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 *Limit of quantitation solution*

Suitability requirements

Resolution: Greater than 1.5 between chlorothiazide and benzothiadiazine related compound A; greater than 1.5 between the benzothiadiazine related compound A and hydrochlorothiazide peak, *System suitability solution*

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

Relative standard deviation: Less than 2.0% for both the hydrochlorothiazide and losartan peaks, *Standard solution*; less than 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 three replicate injections, *Limit of quantitation solution*

Analysis

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

[NOTE—The run time is about 1.6 times the retention time of the losartan peak. Identify the peaks using the relative retention times provided in *Table 10*.]

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 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 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 10*.

Table 10

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
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-[(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-[(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

Add the following:

•• **LABELING:** When more than one *Dissolution* test is given, the labeling states the test used only if *Test 1* is not used.• (RB 1-Jun-2016)

- **PACKAGING AND STORAGE:** Preserve in tightly closed containers protected from light, 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 Hydrochlorothiazide RS
  USP Losartan Potassium RS