Telmisartan and Hydrochlorothiazide Tablets

DEFINITION

Telmisartan and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) and NLT 90.0% and NMT 107.5% of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩:** The spectrum of the solution under test corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **B.** The retention time of the two major peaks of the *Sample solution* corresponds to that of the two major peaks in *Standard solution A*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Diluent: 0.005 M methanolic solution of sodium hydroxide

Buffer: 2.0 g/L of ammonium dihydrogen phosphate. Adjust with phosphoric acid to a pH of 3.0.

Solution A: Methanol and acetonitrile (1:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Buffer (%)	Solution A (%)
0	85	15
3.50	85	15
3.51	45	55
7.70	45	55
7.71	20	80
12.0	20	80
12.1	85	15
15.5	85	15

Standard stock solution 1: 0.025 mg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent*

Standard stock solution 2: 1.6 mg/mL or 3.2 mg/mL (required for analyzing the Tablet strength of 80 mg/12.5 mg) of USP Telmisartan RS, 0.5 mg/mL of USP Hydrochlorothiazide RS, and 2.5 µg/mL of USP Benzothiadiazine Related Compound A RS (from *Standard stock solution 1*) in *Diluent*

Standard solution A: Dilute *Standard stock solution 2* with a 1:1 solution of *Buffer* and *Solution A* to prepare 0.32 mg/mL of telmisartan, 0.1 mg/mL of hydrochlorothiazide, and 0.5 µg/mL of benzothiadiazine related compound A for Tablet strengths of 80 mg/25 mg and 40 mg/12.5 mg. The final concentrations for analyzing the Tablet strength of 80 mg/12.5 mg are 0.32 mg/mL of telmisartan, 0.05 mg/mL of hydrochlorothiazide solution, and 0.25 µg/mL of benzothiadiazine related compound A.

Sample stock solution: Transfer NLT 10 Tablets to a suitable volumetric flask, add 0.1 N sodium hydroxide solution (5% of the total volume of the flask), and shake until the Tablets have completely disintegrated. Add methanol (80% of the total volume of the flask). Sonicate for 10 min and stir vigorously for 30 min. Allow to cool to room temperature, dilute with methanol to volume, and mix. The concentration of the *Sample stock solution* is about 1.6 mg/mL of telmisartan. [NOTE—The hydrochlorothiazide concentration may vary depending on the ratio of telmisartan to hydrochlorothiazide in the Tablet.] Centrifuge a portion of the solution at 4000 rpm. [NOTE—To prevent heat from degrading the sample, do not extend the sonication time and maintain the bath temperature at NMT 22° by adding ice.]

Sample solution: Dilute 1 mL of the *Sample stock solution* to 5 mL in a 1:1 solution of *Buffer* and *Solution A*.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector
UV 270 nm: For hydrochlorothiazide
UV 298 nm: For telmisartan
Column: 4.0-mm × 12.5-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection volume: 10 µL

System suitability
Sample: *Standard solution A*
Suitability requirements
Resolution: NLT 2.0 between hydrochlorothiazide and benzothiadiazine related compound A
Relative standard deviation: NMT 2.0% for both the telmisartan and hydrochlorothiazide peaks

Analysis
Samples: *Standard solution A* and *Sample solution*
Calculate the percentages of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) 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 telmisartan or hydrochlorothiazide from the *Sample solution*
r_S = peak response of telmisartan or hydrochlorothiazide from *Standard solution A*
C_S = concentration of USP Telmisartan RS or USP Hydrochlorothiazide RS in *Standard solution A* (mg/mL)
C_U = nominal concentration of telmisartan or hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0% of telmisartan and 90.0%–107.5% of hydrochlorothiazide

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION ⟨711⟩**

•Test 1• (RB 1-Apr-2015)
Telmisartan
Medium: pH 7.5 phosphate buffer prepared as follows. 13.61 g/L of monobasic potassium phosphate in water. Adjust with 2 M sodium hydroxide to a pH of 7.5; 900 mL.
Apparatus 2: 75 rpm
Time: 30 min
Hydrochlorothiazide
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Analysis: Determine the amounts of telmisartan and hydrochlorothiazide dissolved by the following method.
Solution A: 5.0 g/L of ammonium dihydrogen phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Solution B: Acetonitrile
Standard stock solution: Appropriate amounts of USP Telmisartan RS and USP Hydrochlorothiazide RS in methanol
Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few mL, and dilute with appropriate *Medium*, if necessary.
Telmisartan standard solution: Dilute the *Standard stock solution* with *Telmisartan Medium* to obtain a solution having a known concentration of telmisartan similar to that expected in the *Sample solution*.
Hydrochlorothiazide standard solution: Dilute the *Standard stock solution* with *Hydrochlorothiazide Medium* to obtain a solution having a known concentration of hydrochlorothiazide similar to that expected in the *Sample solution*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector
UV 270 nm: For hydrochlorothiazide
UV 298 nm: For telmisartan
Column: 3.0-mm × 6-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 0.6 mL/min from 0 to 5.00 min and 1.0 mL/min from 5.01 to 6.20 min. The flow rate goes back to 0.6 mL from 6.21 to 9.70 min.
Injection volume: 4 µL
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	85	15
1.50	85	15
1.51	60	40
5.00	60	40
5.01	20	80
6.20	20	80
6.21	85	15
9.70	85	15

System suitability
Samples: *Telmisartan standard solution* and *Hydrochlorothiazide standard solution*
[NOTE—The relative retention times for hydrochlorothiazide and telmisartan are 0.33 and 1.0, respectively.]
Suitability requirements
Tailing factor: NMT 2.5 for both telmisartan and hydrochlorothiazide
Relative standard deviation: NMT 2%
Calculate the percentage of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) 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 telmisartan or hydrochlorothiazide from the *Sample solution*
r_S = peak response of telmisartan from the *Telmisartan standard solution* or hydrochlorothiazide from the *Hydrochlorothiazide standard solution*
C_S = concentration of telmisartan in the *Telmisartan standard solution* or hydrochlorothiazide in the *Hydrochlorothiazide standard solution* (mg/mL)
L = label claim for telmisartan or hydrochlorothiazide (mg/Tablet)
V = volume of *Medium*, 900 mL
Tolerances: NLT 80% (*Q*) of the labeled amount of telmisartan and hydrochlorothiazide is dissolved.

•**Test 2**
If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: Dissolve 6.8 g of monobasic potassium phosphate and 1.56 g of sodium hydroxide in 1 L of water; adjust with 10% sodium hydroxide solution to a pH of 7.5; 900 mL.
Apparatus 2: 75 rpm
Time: 30 min
Buffer: Dissolve 2.72 g of monobasic potassium phosphate in 1 L of water. Add 2 mL of triethylamine per liter of solution and adjust with phosphoric acid to a pH of 2.4.
Mobile phase: Acetonitrile and *Buffer* (35:65)
Telmisartan standard stock solution: 0.45 mg/mL of USP Telmisartan RS prepared as follows. To a suitable amount of USP Telmisartan RS in a suitable volumetric flask, add methanol to about 50% of the total volume. Sonicate to dissolve, cool to room temperature, and dilute with *Medium* to volume.
Hydrochlorothiazide standard stock solution: 0.28 mg/mL of USP Hydrochlorothiazide RS prepared as follows. To a suitable amount of USP Hydrochlorothiazide RS in a suitable volumetric flask, add methanol to about 50% of the total volume. Sonicate to dissolve, cool to room temperature, and dilute with *Medium* to volume.
Standard solution: (*L*/900) mg/mL each of USP Telmisartan RS and USP Hydrochlorothiazide RS in *Medium*, from *Telmisartan standard stock solution* and *Hydrochlorothiazide standard stock solution*, where *L* is the label claim in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size and discard the first 3 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 270 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 20 µL
Run time: NLT 1.7 times the retention time of telmisartan
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for both telmisartan and hydrochlorothiazide
Column efficiency: NLT 1500 theoretical plates for both telmisartan and hydrochlorothiazide
Relative standard deviation: NMT 2.0% for both telmisartan and hydrochlorothiazide
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) 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 telmisartan or hydrochlorothiazide from the *Sample solution*
r_S = peak response of telmisartan or hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Telmisartan RS or USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)

V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) each of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.• (RB 1-Apr-2015)

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

IMPURITIES

- **Organic Impurities**

Diluent, Buffer, Solution A, Mobile phase, Standard stock solution 1, Standard solution A, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard stock solution 3: 1.6 mg/mL of USP Telmisartan RS and 0.5 mg/mL of USP Hydrochlorothiazide RS in *Diluent* for Tablet strengths of 40 mg/12.5 mg and 80 mg/25 mg. For the Tablet strength of 80 mg/12.5 mg, the concentrations are 1.6 mg/mL of USP Telmisartan RS and 0.25 mg/mL of USP Hydrochlorothiazide RS in *Diluent*.

Standard solution B: 1.25 µg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent* from *Standard stock solution 1*. Dilute further with a 1:1 solution of *Buffer* and *Solution A* to prepare a 0.25-µg/mL solution for a Tablet strength of 80 mg/12.5 mg, and a 0.5-µg/mL solution for Tablet strengths of 40 mg/12.5 mg and 80 mg/25 mg.

Sensitivity solution: Dilute 10 mL of *Standard stock solution 3* with *Diluent* to 100 mL. Combine 1.0 mL of this solution with 2.0 mL of *Standard stock solution 1* and dilute with *Diluent* to 100 mL. Dilute 1 mL of this solution to 5 mL with a 1:1 solution of *Buffer* and *Solution A*.

System suitability

Samples: *Standard solution A* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.0 between hydrochlorothiazide and benzothiadiazine related compound A, *Standard solution A*

Relative standard deviation: NMT 2.0% for both the telmisartan and hydrochlorothiazide peaks, *Standard solution A*

Signal-to-noise ratio: NLT 3.0 for the telmisartan, hydrochlorothiazide, and benzothiadiazine related compound A peaks from the *Sensitivity solution*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

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

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

r_U = peak response of benzothiadiazine related compound A from the *Sample solution*
r_S = peak response of benzothiadiazine related compound A from *Standard solution B*
C_S = concentration of USP Benzothiadiazine Related Compound A RS in *Standard solution B* (mg/mL)
C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified degradation impurity related to hydrochlorothiazide 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 unspecified degradation impurity at 270 nm from the *Sample solution*
r_S = peak response of hydrochlorothiazide from *Standard solution A*
C_S = concentration of USP Hydrochlorothiazide RS in *Standard solution A* (mg/mL)
C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified degradation impurity related to telmisartan 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 unspecified degradation impurity at 298 nm from the *Sample solution*
r_S = peak response of telmisartan from *Standard solution A*
C_S = concentration of USP Telmisartan RS in *Standard solution A* (mg/mL)
C_U = nominal concentration of telmisartan in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: NMT 1.0% of benzothiadiazine related compound A and NMT 0.2% of each individual unspecified degradation impurity related to telmisartan or hydrochlorothiazide

Total impurities: NMT 0.2% of the sum of all degradation products related to telmisartan and NMT 1.5% of the sum of all hydrochlorothiazide degradation products

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers and store at controlled room temperature.

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-Apr-2015)

- **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 Telmisartan RS