Telmisartan and Hydrochlorothiazide Tablets

Type of Posting: Revision Bulletin
Posting Date: 26–Jan–2018
Official Date: 01–Feb–2018
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 Expert Committee 2 has revised the Telmisartan and Hydrochlorothiazide Tablets monograph. The purpose for the revision is to add Dissolution Test 3 to accommodate FDA approved drug products.

Dissolution Test 3 was validated using a Symmetry C18 brand of L1 column from Waters. The typical retention time for hydrochlorothiazide is about 4 minutes and for telmisartan is about 9 minutes.

Telmisartan and Hydrochlorothiazide Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement to USP 41–NF 36.

Should you have any questions, please contact Donald Min, Ph.D, Senior Scientific Liaison (301–230–7457 or DDM@USP.org.)
Telmisartan and Hydrochlorothiazide Tablets

**DEFINITION**

Telmisartan and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of telmisartan (C33H30N4O2) and NLT 90.0% and NMT 107.5% of the labeled amount of hydrochlorothiazide (C8H7ClN3O4S2).

**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>
<thead>
<tr>
<th>Time (min)</th>
<th>Buffer (%)</th>
<th>Solution A (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>3.50</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>3.50</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>7.70</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>12.0</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>12.1</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>15.5</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

  **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°C 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 x 12.5-cm; 5-µm packing L7

  **Column temperature:** 40°C

  **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 (C33H30N4O2) and hydrochlorothiazide (C8H7ClN3O4S2) in the portion of Tablets taken:

  \[
  \text{Result} = \frac{(r_U/r_S) \times (C_U/C_S)}{100}
  \]

  \(r_U\) = peak response of telmisartan or hydrochlorothiazide from the Sample solution

  \(r_S\) = peak response of telmisartan or hydrochlorothiazide from Standard solution A

  \(C_U\) = concentration of USP Telmisartan RS or USP Hydrochlorothiazide RS in Standard solution A (mg/mL)

  \(C_S\) = 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**

  **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°C

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>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>1.50</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>1.51</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>5.00</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>5.01</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>6.20</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>6.21</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>9.70</td>
<td>85</td>
<td>15</td>
</tr>
</tbody>
</table>

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 (C33H30N4O2) or hydrochlorothiazide (C13H8ClN3O4S2) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times 100 \]

\( r_U = \) 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 (C33H30N4O2) or hydrochlorothiazide (C13H8ClN3O4S2) dissolved:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times C_T \times V \times (1/L) \times 100 \]

\( r_U = \) peak response of telmisartan or hydrochlorothiazide from the Sample solution

\( r_S = \) peak response of telmisartan from the Standard solution

\( C_T = \) concentration of USP Telmisartan RS or USP Hydrochlorothiazide RS in the Standard solution (mg/mL)
Telmisartan

Official February 1, 2018

Revision Bulletin

Solution B: Acetonitrile

System suitability

Mobile phase: See Chromatographic system

Sample solution:

0.9 mg/mL of Hydrochlorothiazide standard solution:

Dilute the solution of Hydrochlorothiazide standard stock solution: 1.25 mg/mL solution for a Tablet strength of 80 mg/12.5 mg, and 0.5 µg/mL solution for Tablet strengths 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 a suitable volumetric flask, add methanol to about 10% of the total volume. Sonicate to dissolve. Dilute with Hydrochlorothiazide Medium to volume.

Telmisartan standard solution: Dilute the Telmisartan standard stock solution with Telmisartan Medium to obtain a solution having a known concentration of telmisartan similar to that of the Sample solution.

Hydrochlorothiazide standard solution: Dilute the Hydrochlorothiazide standard stock solution with Hydrochlorothiazide Medium to obtain a solution having a known concentration of hydrochlorothiazide similar to that of the Sample solution.

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 270 nm: For hydrochlorothiazide
UV 298 nm: For telmisartan

Column: 4.6-mm × 25-cm; 5-μm packing L1
Flow rate: 1 mL/min
Injection volume: 10 μL
Run time: NLT 2 times the retention time of telmisartan

System suitability
Samples: Telmisartan standard solution and Hydrochlorothiazide standard solution

[NOTE—The relative retention times for hydrochlorothiazide and telmisartan are 0.44 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for both telmisartan and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for both telmisartan and hydrochlorothiazide

Analysis

Samples: Telmisartan standard solution, Hydrochlorothiazide standard solution, and Sample solution

Calculate the percentage of the labeled amount of telmisartan (C33H30N4O2) or hydrochlorothiazide (C7H8ClN3O4S2) dissolved:

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

\( r_U \) = peak response of telmisartan or hydrochlorothiazide from the Sample solution

\( r_S \) = peak response of telmisartan or hydrochlorothiazide from the Telmisartan standard solution or Hydrochlorothiazide standard solution

\( C_S \) = concentration of USP Telmisartan RS or USP Hydrochlorothiazide RS in the Telmisartan standard solution or Hydrochlorothiazide 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 (C33H30N4O2) and hydrochlorothiazide (C7H8ClN3O4S2) is dissolved.

• Uniformity of Dosage Units (905): Meet the requirements

IMPURITIES

• Organic Impurities


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:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\( r_U = \) 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 Telmisartan RS in Standard solution B (mg/mL)
\( C_U = \) nominal concentration of telmisartan in the Sample solution (mg/mL)

Calculate the percentage of each unspecified degradation impurity related to hydrochlorothiazide in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

\( r_U = \) peak response of each unspecified degradation impurity at 270 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.
• 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. \( C_{19}H_{18}ClN_3O_4S_2 \) 285.73
  USP Hydrochlorothiazide RS
  USP Telmisartan RS