Telmisartan and Hydrochlorothiazide Tablets

DEFINITION
Telmisartan and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of telmisartan (\(\text{C}_{33}\text{H}_{30}\text{N}_{4}\text{O}_{2}\)) and NLT 90.0% and NMT 107.5% of the labeled amount of hydrochlorothiazide (\(\text{C}_{7}\text{H}_{8}\text{ClN}_{3}\text{O}_{4}\text{S}_{2}\)).

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.

Performance Tests

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>3.51</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>7.70</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>7.71</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 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 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 \(\times\) 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 (\(\text{C}_{33}\text{H}_{30}\text{N}_{4}\text{O}_{2}\)) and hydrochlorothiazide (\(\text{C}_{7}\text{H}_{8}\text{ClN}_{3}\text{O}_{4}\text{S}_{2}\)) in the portion of Tablets taken:

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

where:
- \(r_U\) = 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.
Telmisartan

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>Table 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
</tr>
<tr>
<td>(min)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1.50</td>
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<tr>
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<tr>
<td>5.00</td>
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<tr>
<td>5.01</td>
</tr>
<tr>
<td>6.20</td>
</tr>
<tr>
<td>6.21</td>
</tr>
<tr>
<td>9.70</td>
</tr>
</tbody>
</table>

System suitability
Samples: Telmisartan standard solution and Hydrochlorothiazide standard solution

Tolerances: NLT 2% for both telmisartan and hydrochlorothiazide

Analysis
Samples: Standard solution and Sample solution

Calculation:

\[ \text{Result} = \left( \frac{r_f}{r_s} \right) \times \left( \frac{C_s}{L} \right) \times V \times 100 \]

Where:
- \( r_f \) = 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

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ORGANIC IMPURITIES

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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.

Analysis

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

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

\[
\text{Result} = \left( \frac{r_1}{r_0} \right) \times \left( \frac{C_A}{C_U} \right) \times 100
\]

where:

- \( r_1 \) = peak response of benzothiadiazine related compound A from the Sample solution
- \( r_0 \) = peak response of benzothiadiazine related compound A from Standard solution B
- \( C_A \) = 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:

\[
\text{Result} = \left( \frac{r_1}{r_0} \right) \times \left( \frac{C_I}{C_U} \right) \times 100
\]

where:

- \( r_1 \) = peak response of each unspecified degradation impurity at 270 nm from the Sample solution
- \( r_0 \) = peak response of hydrochlorothiazide from Standard solution A
- \( C_I \) = concentration of USP Hydrochlorothiazide RS in Standard solution A (mg/mL)
- \( C_U \) = nominal concentration of hydrochlorothiazide 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 7.5% 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.

USP REFERENCE STANDARDS (11)

USP Benzothiadiazine Related Compound A RS
USP Hydrochlorothiazide RS
USP Telmisartan RS