Telmisartan and Hydrochlorothiazide Tablets

Telmisartan and Hydrochlorothiazide Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of telmisartan (C₂₉H₃₈N₂O₂: 514.62) and hydrochlorothiazide (C₂H₃ClN₂O₄S₂: 297.74).

Method of preparation Prepare as directed under Tablets, with Telmisartan and Hydrochlorothiazide.

Identification (1) Telmisartan—Perform the test with 5 µL each of the sample solution and standard solution obtained in the Assay (1) as directed under Liquid Chromatography <2.01> according to the following conditions: the retention times of the peaks of telmisartan in the chromatograms obtained from the sample solution and standard solution are the same, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—
Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).
Detector: Photodiode array detector (wavelength: 270 nm; spectrum range of measurement: 210 – 400 nm).
System suitability—
System performance: Proceed as directed in the system suitability in the Assay (1).

(2) Hydrochlorothiazide—Perform the test with 5 µL each of the sample solution and standard solution obtained in the Assay (2) as directed under Liquid Chromatography <2.01> according to the following conditions: the retention times of the peaks of hydrochlorothiazide in the chromatograms obtained from the sample solution and standard solution are the same, and both spectra of these peaks in the chromatograms exhibit similar intensities of absorption at the same wavelengths.

Operating conditions—
Column, column temperature, mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay (1).
Detector: Photodiode array detector (wavelength: 270 nm; spectrum range of measurement: 210 – 400 nm).
System suitability—
System performance: Proceed as directed in the system suitability in the Assay (2).

Purity Related substances—To a quantity of powdered Telmisartan and Hydrochlorothiazide Tablets, equivalent to 12.5 mg of Hydrochlorothiazide, add 40 mL of the dissolving solution, disperse by sonicate, add the dissolving solution to make exactly 50 mL. Centrifuge this solution, and use the supernatant liquid as the sample solution.
Pipet 1 mL of this solution, add the dissolving solution to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 20 µL each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine each peak area by the automatic integration method: the area of the peak, having the relative retention time of about 0.9 to hydrochlorothiazide, obtained from the sample solution is not larger than the peak area of hydrochlorothiazide from the standard solution.

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Operating conditions—
Detector: An ultraviolet absorption photometer (wavelength: 270 nm).
Column: A stainless steel column 4.0 mm in inside diameter and 15 cm in length, packed with octylsilanized silica gel for liquid chromatography (3 µm in particle diameter).
Column temperature: A constant temperature of about 40°C.
Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.
Mobile phase B: Acetonitrile.
Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

<table>
<thead>
<tr>
<th>Time after injection of sample (min)</th>
<th>Mobile phase A (vol%)</th>
<th>Mobile phase B (vol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 8</td>
<td>90 → 50</td>
<td>10 → 50</td>
</tr>
<tr>
<td>8 – 12</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>12 – 18</td>
<td>50 → 20</td>
<td>50 → 80</td>
</tr>
<tr>
<td>18 – 20</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>

Flow rate: 1.0 mL per minute.

System suitability—
Test for required detectability: Pipet 5 mL of the standard solution and add the dissolving solution to make exactly 50 mL. Confirm that the peak area of hydrochlorothiazide obtained with 20 µL of this solution is equivalent to 7 to 13% of that with 20 µL of the standard solution.
System performance: When the procedure is run with 20 µL of the standard solution under the above operating
conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 6000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 20 \( \mu L \) of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 2.0%.

### Uniformity of dosage units <6.02>
Perform the test according to the following method: it meets the requirement of the Content uniformity test.

(1) Telmisartan—To 1 tablet of Telmisartan and Hydrochlorothiazide Tablets add 4V/5 mL of the dissolving solution, disintegrate by sonicating, add the dissolving solution to make exactly \( V \) mL so that each mL contains about 1.6 mg of telmisartan \((C_{32}H_{30}N_{2}O_{7})\). Centrifuge this solution, pipet 5 mL of the supernatant liquid, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Proceed as directed in the Assay (1).

\[
M_{C} = \text{Amount (mg) of telmisartan for assay taken} \times \frac{A_{T}}{A_{S}} \times \frac{V}{50}
\]

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

(2) Hydrochlorothiazide—To 1 tablet of Telmisartan and Hydrochlorothiazide Tablets add 4V/5 mL of the dissolving solution, centrifuge this solution, add the buffer solution to make exactly 25 mL, and use this solution as the sample solution. Proceed as directed in the Assay (2).

\[
M_{C} = \text{Amount (mg) of hydrochlorothiazide RS taken} \times \frac{A_{T}}{A_{S}} \times \frac{V}{50}
\]

### Dissolution <6.10> (1) Telmisartan—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rates in 45 minutes of a telmisartan 40-mg and hydrochlorothiazide 12.5-mg tablet and a telmisartan 80-mg and hydrochlorothiazide 12.5-mg tablet are not less than 85% and not less than 80%, respectively.

Start the test with 1 tablet of Telmisartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 \( \mu m \). Discard the first 15 mL or more of the filtrate, pipet \( V \) mL of the subsequent filtrate, add the dissolution medium to make exactly \( V \) mL so that each mL contains about 4 \( \mu g \) of telmisartan \((C_{32}H_{30}N_{2}O_{7})\), and use this solution as the sample solution. Separately, weigh accurately about 44 mg of telmisartan for assay, previously dried at 105\(^\circ\)C for 4 hours, dissolve in 10 mL of a solution of meglumine in methanol (1 in 250), and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 25 \( \mu L \) each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak areas, \( A_{T} \) and \( A_{C} \), of telmisartan in each solution.

Dissolution rate (%) with respect to the labeled amount of telmisartan \((C_{32}H_{30}N_{2}O_{7})\)
\[
M_{C} = \frac{M_{C}}{M_{C}} = \frac{M_{C}}{M_{C}} = \frac{M_{C}}{M_{C}} \times \frac{V}{50} \times \frac{1}{C} \times \frac{90}{C}
\]

Buffer solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid.

### Operating conditions—
Detector, column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1).

### System suitability—
System performance: When the procedure is run with 25 \( \mu L \) of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of telmisartan are not less than 25,000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 25 \( \mu L \) of the standard solution under the above operating conditions, the relative standard deviation of the peak area of telmisartan is not more than 2.0%.

(2) Hydrochlorothiazide—When the test is performed at 75 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 45 minutes...
of Telmisartan and Hydrochlorothiazide Tablets is not less than 80%.

Start the test with 1 tablet of Telmisartan and Hydrochlorothiazide Tablets, withdraw not less than 20 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 15 mL or more of the filtrate, pipet V mL of the subsequent filtrate, add the dissolution medium to make exactly V mL so that each mL contains about 14 μg of hydrochlorothiazide (C₈H₄ClN₂O₄S₂), and use this solution as the sample solution. Separately, weigh accurately about 14 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and add methanol to make exactly 50 mL. Pipet 5 mL of this solution, add water to make exactly 100 mL, and use this solution as the standard solution. Perform the test with exactly 25 μL each of the sample solution and standard solution as directed under Liquid Chromatography in <2.01> according to the following conditions, and determine the peak areas, Aᵣ and Aₛ, of hydrochlorothiazide in each solution.

Dissolution rate (%) with respect to the labeled amount of hydrochlorothiazide (C₈H₄ClN₂O₄S₂)

\[ Mₛ = \frac{Mₛ \times Aᵣ}{Aₛ \times V'/V \times \frac{1}{C} \times 90} \]

\[ Mₛ: \text{Amount (mg) of Hydrochlorothiazide RS taken} \]

\[ C: \text{Labeled amount (mg) of hydrochlorothiazide} \]

\[ (C₈H₄ClN₂O₄S₂) \text{ in 1 tablet} \]

**Operating conditions—**

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 7.5 cm in length, packed with octylsylanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. To 1000 mL of this solution add 1000 mL of acetonitrile.

Mobile phase B: Acetonitrile.

Flowing of the mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

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<td>2 – 7</td>
<td>90 → 20</td>
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<td>7 – 8</td>
<td>20</td>
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Flow rate: 0.8 mL per minute.

**System suitability—**

System performance: When the procedure is run with 25 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of hydrochlorothiazide are not less than 1000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 25 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 2.0%. Weigh accurately about 80 mg of telmisartan for assay, previously dried at 105°C for 4 hours, and add the dissolving solution to make exactly 50 mL. Pipet 5 mL of this solution, add the buffer solution to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography in <2.01> according to the following conditions, and determine the peak areas, Aᵣ and Aₛ, of telmisartan in each solution.

\[ \text{Amount (mg) of telmisartan (C₃₈H₅₀N₃O₄)} \]

\[ = Mₛ \times \frac{Aᵣ}{Aₛ} \]

\[ Mₛ: \text{Amount (mg) of telmisartan for assay taken} \]

Dissolving solution: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 1.8 with phosphoric acid. Dissolving so.

Detector: An ultraviolet absorption photometer (wavelength: 270 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 7.5 cm in length, packed with octylsylanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 40°C.

Mobile phase A: Dissolve 2 g of ammonium dihydrogen phosphate in 1000 mL of water, and adjust to pH 3.5 with phosphoric acid.

Mobile phase B: Acetonitrile.

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Flow rate: 0.8 mL per minute.
System repeatability: When the test is repeated 6 times
with 5 μL of the standard solution under the above oper-
ating conditions, the relative standard deviation of the
peak area of telmisartan is not more than 1.0%.

(2) Hydrochlorothiazide—Weigh accurately the mass
of not less than 20 Telmisartan and Hydrochlorothiazide
Tablets, and powder. Weigh accurately a portion of the
powder, equivalent to about 12.5 mg of hydrochlorothia-
zide (C₇H₈ClN₃O₄S₂), add 40 mL of the dissolving solu-
tion, sonicate, and add the dissolving solution to make
exactly 50 mL. Centrifuge this solution, pipet 5 mL of the
supernatant liquid, add the buffer solution to make exactly
25 mL, and use this solution as the sample solution. Sep-
arately, weigh accurately about 12.5 mg of Hydrochloro-
thiazide RS, previously dried at 105°C for 2 hours, and
add the dissolving solution to make exactly 50 mL. Pipet
5 mL of this solution, add the buffer solution to make
exactly 25 mL, and use this solution as the standard solu-
tion. Perform the test with exactly 5 μL each of the sam-
ple solution and standard solution as directed under Liq-
uid Chromatography <2.01> according to the following
conditions, and determine the peak areas, A_T and A_S, of
hydrochlorothiazide in each solution.

\[ M_s \times A_T / A_S \]

M_s: Amount (mg) of Hydrochlorothiazide RS taken

Dissolving solution: Dissolve 2 g of ammonium dihy-
drogen phosphate in 1000 mL of water, and adjust to pH
1.8 with phosphoric acid. To 1000 mL of this solution add
1000 mL of acetonitrile.

Buffer solution: Dissolve 2 g of ammonium dihydrogen
phosphate in 1000 mL of water, and adjust to pH 1.8 with
phosphoric acid.

Operating conditions—

- Proceed as directed in the operating conditions in (1).

System suitability—

- System performance: When the procedure is run with 5
  μL of the standard solution under the above operating
  conditions, the number of theoretical plates and the sym-
  metry factor of the peak of hydrochlorothiazide are not
  less than 15,000 and not more than 2.0, respectively.

- System repeatability: When the test is repeated 6 times
  with 5 μL of the standard solution under the above oper-
  ating conditions, the relative standard deviation of the
  peak area of hydrochlorothiazide is not more than 1.0%.

Containers and storage—Containers—Tight containers.