Valsartan and Hydrochlorothiazide Tablets

Valsartan and Hydrochlorothiazide Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of valsartan \((C_{24}H_{29}N_{5}O_{3})\) (343.52) and hydrochlorothiazide \((C_{12}H_{16}ClN_{2}O_{3}S_{2})\) 297.74.

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

Identification (1) To a quantity of powdered Valsartan and Hydrochlorothiazide Tablets, equivalent to 80 mg of valsartan, add 5 mL of acetone, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 16 mg of valsartan in 1 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.3.3>. Spot 5 \(\mu\)L each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and acetic acid (100) (15:5:2) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); one of the two spots obtained from the sample solution and the spot from the standard solution show the same \(R_f\) value.

(2) To a quantity of powdered Valsartan and Hydrochlorothiazide Tablets, equivalent to 6.25 mg of hydrochlorothiazide, add 5 mL of acetone, shake, centrifuge, and use the supernatant liquid as the sample solution. Separately, dissolve 12.5 mg of hydrochlorothiazide in 10 mL of acetone, and use this solution as the standard solution. Perform the test with these solutions as directed under Thin-layer Chromatography <2.3.3>. Spot 5 \(\mu\)L each of the sample solution and standard solution on a plate of silica gel with fluorescent indicator for thin-layer chromatography. Develop the plate with a mixture of ethyl acetate, hexane and acetic acid (100) (15:5:2) to a distance of about 10 cm, and air-dry the plate. Examine under ultraviolet light (main wavelength: 254 nm); one of the two spots obtained from the sample solution and the spot from the standard solution show the same \(R_f\) value.

Uniformity of dosage units <6.02> (1) Valsartan — Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is dissolved. Add 10 mL of acetonitrile, shake thoroughly, and add a mixture of water and acetonitrile (1:1) to make exactly 50 mL. Centrifuge this solution, pipet V mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly V’ mL so that each mL contains about 0.4 mg of valsartan \((C_{24}H_{29}N_{5}O_{3})\) and use this solution as the sample solution. Proceed as directed in the Assay (1).

\[
\text{Amount (mg) of valsartan} = M_S \times \frac{A_T}{A_S} \times \frac{V}{V'} \times \frac{1}{2}
\]

\(M_S\): Amount (mg) of Valsartan RS taken, calculated on the anhydrous and residual solvent-free basis.

(2) Hydrochlorothiazide — Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is dissolved. Add 10 mL of acetonitrile, shake thoroughly, and add a mixture of water and acetonitrile (1:1) to make exactly 50 mL. Centrifuge this solution, pipet V mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly V’ mL so that each mL contains about 31 \(\mu\)g of hydrochlorothiazide \((C_{12}H_{16}ClN_{2}O_{3}S_{2})\), and use this solution as the sample solution. Proceed as directed in the Assay (2).

\[
\text{Amount (mg) of hydrochlorothiazide} = M_S \times \frac{A_T}{A_S} \times \frac{V}{V'} \times \frac{1}{8}
\]

\(M_S\): Amount (mg) of Hydrochlorothiazide RS taken

Dissolution <6.10> (1) Valsartan — When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 30 minutes of valsartan of Valsartan and Hydrochlorothiazide Tablets is not less than 75%.

Start the test with 1 tablet of Valsartan 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 5 mL or more of the filtrate, pipet V mL of the subsequent filtrate, and add water to make exactly V’ mL so that each mL contains about 89 \(\mu\)g of valsartan \((C_{24}H_{29}N_{5}O_{3})\). Pipet 5 mL of this solution, add methanol to make exactly 10 mL, and use this solution as the sample solution. Separately, weigh accurately about 45 mg of Valsartan RS (separately determine the water <2.4>) and the residual solvent in the same manner as Valsartan, and dissolve in methanol to make exactly 50 mL. Pipet 10 mL of this solution, add exactly 100 mL of water, then add methanol to make exactly 250 mL. Centrifuge this solution, pipet 25 mL of this solution, add 25 mL of 10% methanol, and shake thoroughly. Filtrate this solution, pipet 5 mL of the filtrate, then add dilute hydrochloric acid, and add water to make exactly 50 mL. Centrifuge this solution, and use this solution as the sample solution.

Proceed as directed in the Assay (1).
acty 200 mL, and use this solution as the standard solution. Perform the test with exactly 10 µL of the sample solution and standard solution as directed under Liquid Chromatography <2.07> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of valsartan in each solution.

Dissolution rate (%) with respect to the labeled amount of valsartan ($C_{\text{H}_2\text{H}_5\text{N}_3\text{O}_3}$) 

$$M_S = \frac{A_T}{A_S} \times V' \times 1/C \times 100$$

$C$: Labeled amount (mg) of valsartan ($C_{\text{H}_2\text{H}_5\text{N}_3\text{O}_3}$) in 1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 3 mm in inside diameter and 12.5 cm in length, packed with octadecysilanized silica gel for liquid chromatography (5 µm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase: Dissolve 14.68 g of disodium hydrogen phosphate dodecahydrate and 3.81 g of potassium dihydrogen phosphate in 1000 mL of water. To 4 volumes of this solution add 1 volume of acetonitrile.

Flow rate: Adjust so that the retention time of valsartan is about 6 minutes.

System suitability—

System performance: When the procedure is run with 10 µL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of valsartan are less than 500, and not less than 0.7 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 10 µL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valsartan is not more than 1.0%.

(2) Hydrochlorothiazide—When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of water as the dissolution medium, the dissolution rate in 15 minutes of hydrochlorothiazide of Valsartan and Hydrochlorothiazide Tablets is not less than 85%.

Start the test with 1 tablet of Valsartan 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 5 mL of the filtrate, pipet $V$ mL of the subsequent filtrate, add water to make exactly $V'$ mL so that each mL contains about 6.9 µg of hydrochlorothiazide ($C_{\text{H}_2\text{CIN}_5\text{O}_3}\text{S}_2$), 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 dissolve in methanol to make exactly 100 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 10 µL of each of the sample solution and standard solution as directed under Liquid Chromatography <2.07> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of hydrochlorothiazide in each solution.

Dissolution rate (%) with respect to the labeled amount of hydrochlorothiazide ($C_{\text{H}_2\text{CIN}_5\text{O}_3}\text{S}_2$) 

$$M_S = \frac{A_T}{A_S} \times V' \times 1/C \times 45$$

$C$: Labeled amount (mg) of hydrochlorothiazide ($C_{\text{H}_2\text{CIN}_5\text{O}_3}\text{S}_2$) in 1 tablet

Operating conditions—

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

System suitability—

System performance: When the procedure is run with 10 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 3000 and not more than 2.0, respectively.

System repeatability: When the test is repeated 6 times with 10 µL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 1.0%.

Assay (1) Valsartan—Weigh accurately the mass of not less than 20 tablets of Valsartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 80 mg of valsartan ($C_{\text{H}_2\text{H}_5\text{N}_3\text{O}_3}$), add 10 mL of water, and shake. Add 10 mL of acetonitrile, shake thoroughly, add a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and centrifuge. Pipet 5 mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 40 mg of Valsartan RS (separately determine the water <2.48> and the residual solvent in the same manner as Valsartan), dissolve in a mixture of water and acetonitrile (1:1) to make exactly 25 mL, and use this solution as the standard solution. Perform the test with exactly 10 µL of each of the sample solution and standard solution as directed under Liquid Chromatography <2.07> according to the following conditions, and deter-
mine the peak areas, $A_T$ and $A_S$, of valsartan in each solution.

$$\text{Amount (mg) of valsartan} (\text{C}_9\text{H}_{13}\text{N}_2\text{O}_3) = M_S \times \frac{A_T}{A_S} \times 2$$

$M_S$: Amount (mg) of Valsartan RS taken, calculated on the anhydrous and residual solvent-free basis.

Operating conditions—

Detector: An ultraviolet absorption photometer (wave-length: 271 nm).

Column: A stainless steel column 3 mm in inside diameter and 12.5 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 25°C.

Mobile phase A: A mixture of water, acetonitrile and trifluoroacetic acid (900:100:1).

Mobile phase B: A mixture of acetonitrile, water and trifluoroacetic acid (900:100:1).

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></td>
<td>0 → 25</td>
<td>90 → 10</td>
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</tbody>
</table>

Flow rate: Adjust so that the retention time of valsartan is about 16 minutes.

System performance: Dissolve 1 mg of 4-amino-6-chlorobenzene-1,3-disulfonamide in a mixture of water and acetonitrile (1:1) to make 200 mL. To 1 mL of this solution, 5 mL of the valsartan standard stock solution and 5 mL of the hydrochlorothiazide standard stock solution in (2) are added. The mixture of water and acetonitrile (1:1) is used to make 20 mL. When the procedure is run with 10 μL of this solution in the above operating conditions, 4-amino-6-chlorobenzene-1,3-disulfonamide, hydrochlorothiazide and valsartan are eluted in this order with the resolution between the peaks of 4-amino-6-chlorobenzene-1,3-disulfonamide and hydrochlorothiazide being not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of valsartan is not more than 1.0%.

(2) Hydrochlorothiazide—Weigh accurately the mass of not less than 20 tablets of Valsartan and Hydrochlorothiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 6.25 mg of hydrochlorothiazide (C$_7$H$_6$ClN$_3$O$_3$S$_2$), add 10 mL of water, and shake. Add 10 mL of acetonitrile, shake thoroughly, add a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and centrifuge. Pipet 5 mL of the supernatant liquid, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the sample solution. Separately, weigh accurately about 12.5 mg of Hydrochlorothiazide RS, previously dried at 105°C for 2 hours, and dissolve in a mixture of water and acetonitrile (1:1) to make exactly 50 mL, and use this solution as the hydrochlorothiazide standard stock solution. Pipet 2.5 mL of the hydrochlorothiazide standard stock solution, add a mixture of water and acetonitrile (1:1) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 10 μL of 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 $A_S$, of hydrochlorothiazide in each solution.

$$\text{Amount (mg) of hydrochlorothiazide} (\text{C}_7\text{H}_6\text{ClN}_3\text{O}_3\text{S}_2) = M_S \times \frac{A_T}{A_S} \times 1/2$$

$M_S$: Amount (mg) of Hydrochlorothiazide RS taken.

Operating conditions—

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

System suitability—

System performance: Dissolve 1 mg of 4-amino-6-chlorobenzene-1,3-disulfonamide in a mixture of water and acetonitrile (1:1) to make 200 mL. To 1 mL of this solution, 5 mL of the valsartan standard stock solution in (1) and 5 mL of the hydrochlorothiazide standard stock solution are added. The mixture of water and acetonitrile (1:1) is used to make 20 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, 4-amino-6-chlorobenzene-1,3-disulfonamide, hydrochlorothiazide and valsartan are eluted in this order with the resolution between the peaks of 4-amino-6-chlorobenzene-1,3-disulfonamide and hydrochlorothiazide being not less than 1.5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of hydrochlorothiazide is not more than 1.0%.
Add the following to 9.41 Reagents, Test Solutions:

**4-Amino-6-chlorobenzene-1,3-disulfonamide**

C₆H₇ClN₃O₄S₂  White, crystals or crystalline powder.

**Identification** — Determine the infrared absorption spectrum of 4-amino-6-chlorobenzene-1,3-disulfonamide as directed in the potassium bromide disk method under Infrared Spectrophotometry <2.25>: it exhibits absorption at the wave numbers of about 3380 cm⁻¹, 3250 cm⁻¹, 1638 cm⁻¹, 1597 cm⁻¹, 1544 cm⁻¹ and 1324 cm⁻¹.

**Storage** — Preserve in tight containers.

**Valsartan**  C₂₄H₂₉N₅O₃  [Same as the namesake monograph]