

1 Valsartan and Hydrochlorothiazide Tablets

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3 Valsartan and Hydrochlorothiazide Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$; 4 435.52) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$; 5 297.74).

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

7 **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 <2.03>. Spot 5 μ 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.

8 (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 <2.03>. Spot 5 μ 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.

9 **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.

10 To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is dis-

11 integrated. 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 ($C_{24}H_{29}N_5O_3$), and use this solution as the sample solution. Proceed as directed in the Assay (1).

$$12 \quad \text{Amount (mg) of valsartan (C}_{24}\text{H}_{29}\text{N}_5\text{O}_3\text{)} \\ 13 \quad = M_S \times A_T / A_S \times V' / V \times 1 / 2$$

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

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

16 To 1 tablet of Valsartan and Hydrochlorothiazide Tablets add 10 mL of water, and shake until the tablet is disintegrated. 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 μ g of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$), and use this solution as the sample solution. Proceed as directed in the Assay (2).

$$17 \quad \text{Amount (mg) of hydrochlorothiazide (C}_{7}\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2\text{)} \\ 18 \quad = M_S \times A_T / A_S \times V' / V \times 1 / 8$$

19 *M_S*: Amount (mg) of Hydrochlorothiazide RS taken

20 **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%.

21 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 μ 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 μ g of valsartan ($C_{24}H_{29}N_5O_3$). 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 <2.48> 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 ex-

99 actly 200 mL, and use this solution as the standard solu-
 100 tion. Perform the test with exactly 10 μL each of the sam-
 101 ple solution and standard solution as directed under Liq-
 102 uid Chromatography <2.01> according to the following
 103 conditions, and determine the peak areas, A_T and A_S , of
 104 valsartan in each solution.

105 Dissolution rate (%) with respect to the labeled amount of
 106 valsartan ($\text{C}_{24}\text{H}_{29}\text{N}_5\text{O}_3$)

$$107 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 180$$

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

110 C : Labeled amount (mg) of valsartan ($\text{C}_{24}\text{H}_{29}\text{N}_5\text{O}_3$) in 1
 111 tablet

112 *Operating conditions—*

113 Detector: An ultraviolet absorption photometer (wave-
 114 length: 225 nm).

115 Column: A stainless steel column 3 mm in inside diam-
 116 eter and 12.5 cm in length, packed with octadecylsilanized
 117 silica gel for liquid chromatography (5 μm in particle di-
 118 ameter).

119 Column temperature: A constant temperature of about
 120 25°C.

121 Mobile phase: Dissolve 14.68 g of disodium hydrogen
 122 phosphate dodecahydrate and 3.81 g of potassium dihy-
 123 drogen phosphate in 1000 mL of water. To 4 volumes of
 124 this solution add 1 volume of acetonitrile.

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

127 *System suitability—*

128 System performance: When the procedure is run with
 129 10 μL of the standard solution under the above operating
 130 conditions, the number of theoretical plates and the sym-
 131 metry factor of the peak of valsartan are not less than 500,
 132 and not less than 0.7 and not more than 1.5, respectively.

133 System repeatability: When the test is repeated 6 times
 134 with 10 μL of the standard solution under the above oper-
 135 ating conditions, the relative standard deviation of the
 136 peak area of valsartan is not more than 1.0%.

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

143 Start the test with 1 tablet of Valsartan and Hydrochlo-
 144 rothiazide Tablets, withdraw not less than 20 mL of the
 145 medium at the specified minute after starting the test, and
 146 filter through a membrane filter with a pore size not ex-
 147 ceeding 0.45 μm . Discard the first 5 mL of the filtrate,
 148 pipet V mL of the subsequent filtrate, add water to make
 149 exactly V' mL so that each mL contains about 6.9 μg of

150 hydrochlorothiazide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$), and use this solu-
 151 tion as the sample solution. Separately, weigh accurately
 152 about 14 mg of Hydrochlorothiazide RS, previously dried
 153 at 105°C for 2 hours, and dissolve in methanol to make
 154 exactly 100 mL. Pipet 5 mL of this solution, add water to
 155 make exactly 100 mL, and use this solution as the stand-
 156 ard solution. Perform the test with exactly 10 μL each of
 157 the sample solution and standard solution as directed un-
 158 der Liquid Chromatography <2.01> according to the fol-
 159 lowing conditions, and determine the peak areas, A_T and
 160 A_S , of hydrochlorothiazide in each solution.

161 Dissolution rate (%) with respect to the labeled amount of
 162 hydrochlorothiazide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$)

$$163 = M_S \times A_T / A_S \times V' / V \times 1 / C \times 45$$

164 M_S : Amount (mg) of Hydrochlorothiazide RS taken

165 C : Labeled amount (mg) of hydrochlorothiazide
 166 ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$) in 1 tablet

167 *Operating conditions—*

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

169 *System suitability—*

170 System performance: When the procedure is run with
 171 10 μL of the standard solution under the above operating
 172 conditions, the number of theoretical plates and the sym-
 173 metry factor of the peak of hydrochlorothiazide are not
 174 less than 3000 and not more than 2.0, respectively.

175 System repeatability: When the test is repeated 6 times
 176 with 10 μL of the standard solution under the above oper-
 177 ating conditions, the relative standard deviation of the
 178 peak area of hydrochlorothiazide is not more than 1.0%.

179 **Assay (1) Valsartan—**Weigh accurately the mass of
 180 not less than 20 tablets of Valsartan and Hydrochlorothia-
 181 zide Tablets, and powder. Weigh accurately a portion of
 182 the powder, equivalent to about 80 mg of valsartan
 183 ($\text{C}_{24}\text{H}_{29}\text{N}_5\text{O}_3$), add 10 mL of water, and shake. Add 10 mL
 184 of acetonitrile, shake thoroughly, add a mixture of water
 185 and acetonitrile (1:1) to make exactly 50 mL, and centri-
 186 fuge. Pipet 5 mL of the supernatant liquid, add a mixture
 187 of water and acetonitrile (1:1) to make exactly 20 mL, and
 188 use this solution as the sample solution. Separately, weigh
 189 accurately about 40 mg of Valsartan RS (separately de-
 190 termine the water <2.48> and the residual solvent in the
 191 same manner as Valsartan), dissolve in a mixture of water
 192 and acetonitrile (1:1) to make exactly 25 mL, and use this
 193 solution as the valsartan standard stock solution. Pipet 5
 194 mL of the valsartan standard stock solution, add a mixture
 195 of water and acetonitrile (1:1) to make exactly 20 mL, and
 196 use this solution as the standard solution. Perform the test
 197 with exactly 10 μL each of the sample solution and stand-
 198 ard solution as directed under Liquid Chromatography
 199 <2.01> according to the following conditions, and deter-

mine the peak areas, A_T and A_S , of valsartan in each solution.

$$\text{Amount (mg) of valsartan (C}_{24}\text{H}_{29}\text{N}_5\text{O}_5\text{)} \\ = M_S \times A_T / A_S \times 2$$

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

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 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.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 25	90 → 10	10 → 90

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

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 and 5 mL of the hydrochlorothiazide standard stock solution in (2) add a mixture of water and acetonitrile (1:1) 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 valsartan is not more than 1.0%.

(2) Hydrochlorothiazide—Weigh accurately the mass of not less than 20 tablets of Valsartan and Hydrochloro-

thiazide Tablets, and powder. Weigh accurately a portion of the powder, equivalent to about 6.25 mg of hydrochlorothiazide ($\text{C}_7\text{H}_8\text{ClN}_3\text{O}_4\text{S}_2$), 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 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.

$$\text{Amount (mg) of hydrochlorothiazide (C}_{7}\text{H}_{8}\text{ClN}_{3}\text{O}_{4}\text{S}_{2}\text{)} \\ = M_S \times A_T / A_S \times 1/2$$

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 add a mixture of water and acetonitrile (1:1) 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%.

294 **Add the following to 9.41 Reagents, Test**
295 **Solutions:**

296 **4-Amino-6-chlorobenzene-1,3-disulfonamide**

297 $C_6H_8ClN_3O_4S_2$ White, crystals or crystalline powder.

298 *Identification*—Determine the infrared absorption spec-
299 trum of 4-amino-6-chlorobenzene-1,3-disulfonamide as
300 directed in the potassium bromide disk method under In-
301 frared Spectrophotometry <2.25>: it exhibits absorption at
302 the wave numbers of about 3380 cm^{-1} , 3250 cm^{-1} , 1638
303 cm^{-1} , 1597 cm^{-1} , 1544 cm^{-1} and 1324 cm^{-1} .

304 *Storage*—Preserve in tight containers.

305 **Valsartan** $C_{24}H_{29}N_5O_3$ [Same as the namesake
306 monograph]