Valsartan and Hydrochlorothiazide Tablets

**DEFINITION**

Valsartan and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of valsartan (C₂₄H₂₉N₅O₃) and hydrochlorothiazide (C₇H₈ClN₃O₄S₂).

**IDENTIFICATION**

**A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST (201)**

**Sample solution:** To an amount of ground Tablets, equivalent in weight to a single Tablet, add 2.0 mL of acetone, sonicate for 15 min, and centrifuge.

**Application volume:** 2 µL

**Developing solvent system:** Ethyl acetate, dehydrated alcohol, and 3.6 M of ammonium hydroxide (8:2:1)

**Analysis:** Proceed as directed in the chapter, except develop the plate in a paper-lined chromatographic chamber equilibrated with Developing solvent system for 15 min before use. Allow the chromatogram to develop until the solvent front has moved at least 7 cm. After removing the plate and marking the solvent front, dry the plate under a current of warm air.

**Acceptance criteria:** The R values of the principal spots from the Sample solution correspond to those from the Standard solution.

**B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

**ASSAY**

**PROCEDURE**

**Diluent:** Acetonitrile and water (1:1)

**Solution A:** Acetonitrile, water, and trifluoroacetic acid (10: 90: 0.1)

**Solution B:** Acetonitrile, water, and trifluoroacetic acid (90: 10: 0.1)

**Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>25</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>27</td>
<td>90</td>
<td>10</td>
</tr>
<tr>
<td>40</td>
<td>90</td>
<td>10</td>
</tr>
</tbody>
</table>

**Standard solution:** Transfer 12.5 mg of USP Hydrochlorothiazide RS to a 200-mL volumetric flask, and add 12.5 J mg of USP Valsartan RS, J being the ratio of the labeled amount, in mg, of valsartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Add 100 mL of Diluent, sonicate for 15 min, dilute with Diluent to volume, and mix. Transfer 50.0 mL of this solution to a 50-mL volumetric flask, dilute with Diluent to volume, and mix. Dilute with Diluent to obtain a solution having a concentration of 0.2 mg/mL of USP Valsartan RS in Diluent.

**Sample stock solution:** To a portion of Tablets obtained in the Assay, add 12.5 mL of Diluent, sonicate for 15 min, and allow to stand for 5 min. Then add 100 mL of Diluent, sonicate for 15 min, and shake for 30 min. Dilute with Diluent to 250 mL, and centrifuge a portion of this solution at 3000 rpm. Dilute 25.0 mL of the clear supernatant with Diluent to 200 mL.

**Sample solution:** Nominally 0.2 mg/mL of valsartan from Sample stock solution in Diluent

**Chromatographic system**

*See Chromatography (621), System Suitability.*

**Mode:** LC

**Detector:** UV 265 nm

**Column:** 3.0-mm × 12.5-cm; 5-µm packing L1

**Flow rate:** 0.4 mL/min

**Injection volume:** 10 µL

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Relative standard deviation:** NMT 2.0%

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

**Dissolution (711)**

**Test 1**

**Medium:** pH 6.8 phosphate buffer; 1000 mL

**Apparatus 2:** 50 rpm

**Time:** 30 min

Determine the percentage of the labeled amounts of valsartan (C₂₄H₂₉N₅O₃) and hydrochlorothiazide (C₇H₈ClN₃O₄S₂) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_2}{r_1} \right) \times \left( \frac{C_i}{C_0} \right) \times 100
\]

\[r_1 = \text{peak response from the Sample solution}
\]

\[r_2 = \text{peak response from the Standard solution}
\]

\[C_i = \text{concentration of the appropriate USP Reference Standard in the Standard solution (mg/mL)}
\]

\[C_0 = \text{nominal concentration of the corresponding analyte in the Sample solution (mg/mL)}
\]

**Acceptance criteria:** 90.0%–110.0%

**Spectrophotometric procedure**

*See Spectrophotometry and Light-Scattering (851).*

**Analytical wavelength:** 250 nm for valsartan and 272 nm for hydrochlorothiazide

**Cell path length:** 0.2-cm quartz

**Standard solution:** USP Hydrochlorothiazide RS and USP Valsartan RS in Medium

**Sample solution:** Pass a portion of the solution under test through a suitable glass fiber filter of 1-µm pore size. Dilute with Medium, if necessary, to a concentration similar to that of the Standard solution.

**Analysis**

Calculate the percentage of the labeled amount of valsartan (C₂₄H₂₉N₅O₃) dissolved:

\[
\text{Result} = \left[ \left( \frac{AT_2 \times D}{AT_1 \times D} \right) \left( \frac{C \times D}{B \times E} \right) \right] \times 12500
\]

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

\[
\text{Result} = \left[ \left( \frac{AT_2 \times C}{AT_1 \times B} \right) \left( \frac{D \times C}{E \times B} \right) \right] \times 80000
\]

\[AT_1 = \text{absorbance of the Sample solution at 272 nm}
\]

\[AT_2 = \text{absorbance of the Sample solution at 250 nm}
\]

\[C = \text{A%V}_{250}, \text{absorbivity (1%, 0.2 cm, 250 nm)}
\]

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2 Valsartan

\[ B = A1 % V_{272}, \text{ absorptivity (1%, 0.2 cm, 272 nm)} \]
\[ D = A1 % H_{272}, \text{ absorptivity (1%, 0.2 cm, 272 nm)} \]
\[ E = A1 % H_{350}, \text{ absorptivity (1%, 0.2 cm, 250 nm)} \]

Chromatographic procedure

Diluent: Water and acetonitrile (1:1)

Solution A: 0.2 M ammonium acetate (15.4 g/L of ammonium acetate in water), adjusted to a pH of 5.6

Solution B: Acetonitrile

Mobile phase: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>88</td>
<td>12</td>
</tr>
</tbody>
</table>

System suitability solution: 80 µg/mL of USP Valsartan RS, 60 µg/mL of USP Hydrochlorothiazide RS, 30 µg/mL of USP Benzothiadiazine Related Compound A RS, and 200 µg/mL of USP Valsartan Related Compound B RS in Diluent. Transfer 25 mL of this solution to a 100-mL volumetric flask, and dilute with Medium to volume.

Standard solution: Transfer about 12.5 mg of USP Hydrochlorothiazide RS to a 200-mL volumetric flask. Add about 12.5 mg of USP Valsartan RS, with J being the ratio of the labeled amount (mg) of valsartan to the labeled amount (mg) of hydrochlorothiazide per Tablet. Dilute with Diluent to volume. Transfer 10 mL of this solution to a 50-mL volumetric flask, and dilute with Medium to volume.

Sample solution: For Tablets labeled to contain 12.5 mg of hydrochlorothiazide, pass a portion of the solution under test through a suitable filter. For Tablets labeled to contain 25 mg of hydrochlorothiazide, pass a portion of the solution under test through a suitable filter, and dilute with Medium (1:1).

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 265 nm

Column: 4.6-mm × 25-cm; 5-µm packing L11

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

Samples: System suitability solution and Standard solution

Suitability requirements

Resolution: NLT 2.0 between valsartan and valsartan related compound B; NLT 2.0 between hydrochlorothiazide and benzothiadiazine related compound A, System suitability solution

Relative standard deviation: NMT 2.0% for both valsartan and hydrochlorothiazide, Standard solution

Analysis

Calculate the percentage of the labeled amounts of valsartan (C_{7H8ClN3O4S2}) and hydrochlorothiazide (C_{12H9N2O4S2}) dissolved:

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

\[ r_U = \text{peak response of valsartan or hydrochlorothiazide from the Sample solution} \]

\[ r_S = \text{peak response of valsartan or hydrochlorothiazide from the Standard solution} \]

\[ C_l = \text{concentration of valsartan or hydrochlorothiazide in the Standard solution (mg/mL)} \]

\[ L = \text{label claim for valsartan or hydrochlorothiazide (mg/Tablet)} \]

\[ D = \text{dilution factor of the Sample solution, if applicable} \]

\[ V = \text{volume of Medium, 1000 mL} \]

Tolerances: NLT 80% (Q) of the labeled amount of valsartan (C_{24H29N5O3}) and hydrochlorothiazide (C_{7H8ClN3O4S2}) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.

Medium: pH 6.8 phosphate buffer; 1000 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: Mix 1 mL of trifluoroacetic acid and 1 L of water.

Mobile phase: Acetonitrile and Buffer (450:550)

Valsartan standard stock solution: 3.2 mg/mL of USP Valsartan RS in Medium prepared as follows. To a suitable amount of the USP Valsartan RS in a suitable volumetric flask add methanol to fill 20% of the total volume. Sonicate for 5 min and dilute with Medium to volume.

Hydrochlorothiazide standard stock solution: 0.5 mg/mL of USP Hydrochlorothiazide RS prepared as follows. To a suitable amount of the USP Hydrochlorothiazide RS in a suitable volumetric flask add methanol to fill 10% of the total volume. Sonicate to dissolve, and add Medium to fill 25% of the total volume. Sonicate for 5 min and dilute with Medium to volume.

Table 3

<table>
<thead>
<tr>
<th>Tablet Strength of Valsartan/ Hydrochlorothiazide (mg/mg)</th>
<th>Concentration of Valsartan (mg/mL)</th>
<th>Concentration of Hydrochlorothiazide (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>320/25</td>
<td>0.32</td>
<td>0.025</td>
</tr>
<tr>
<td>320/12.5</td>
<td>0.32</td>
<td>0.0125</td>
</tr>
<tr>
<td>160/25</td>
<td>0.16</td>
<td>0.025</td>
</tr>
<tr>
<td>160/12.5</td>
<td>0.16</td>
<td>0.0125</td>
</tr>
<tr>
<td>80/12.5</td>
<td>0.08</td>
<td>0.0125</td>
</tr>
</tbody>
</table>

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, and discard the first few mL of the filtrate.
Mode: LC
Detector: UV 265 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1
Sample cooler temperature: 20°
Flow rate: 1 mL/min
Injection volume: 10 μL
System suitability
Sample: Standard solution

[NOTE—The relative retention times of valsartan and hydrochlorothiazide are 1.0 and 0.25, respectively.]
Suitability requirements
Tailing factor: NMT 2.0 for both valsartan and hydrochlorothiazide peaks
Relative standard deviation: NMT 2.0% for both valsartan and hydrochlorothiazide peaks

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of valsartan (C24H29N5O3) and hydrochlorothiazide (C7H8ClN3O4S2) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_0'} \right) \times C_s \times V \times \left( \frac{1}{L} \right) \times 100
\]

\[r_0 = \text{peak response of valsartan or hydrochlorothiazide from the Sample solution}\]
\[r_0' = \text{peak response of valsartan or hydrochlorothiazide from the Standard solution}\]
\[C_s = \text{concentration of valsartan or hydrochlorothiazide in the Standard solution (mg/mL)}\]
\[V = \text{volume of Medium, 1000 mL}\]
\[L = \text{label claim (mg/Tablet)}\]

Tolerances: NLT 80% (Q) of the labeled amount of both valsartan (C24H29N5O3) and hydrochlorothiazide (C7H8ClN3O4S2) dissolved.

**UNIFORMITY OF DOSAGE UNITS (905)**
Procedure for content uniformity
Sample solution: Transfer 1 Tablet to a 200-mL volumetric flask, add 5 mL of water, and allow to stand for 5 min. Dilute with Diluent to volume, mix, and centrifuge a portion of this solution at 3000 rpm. Dilute a volume of the clear supernatant with Diluent to obtain a solution having a nominal concentration of 0.2 mg/mL of valsartan.

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of valsartan (C24H29N5O3) and hydrochlorothiazide (C7H8ClN3O4S2) in the Tablet taken:

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

\[r_0 = \text{peak response from the Sample solution}\]
\[r_0' = \text{peak response from the Standard solution}\]
\[C_s = \text{concentration of the appropriate USP Reference Standard in the Standard solution (mg/mL)}\]
\[C_U = \text{nominal concentration of the corresponding analyte in the Sample solution (mg/mL)}\]

Acceptance criteria: Meet the requirements

**IMPURITIES**
• ORGANIC IMPURITIES
Diluent, Solution A, Solution B, Mobile phase, Sample solution, and Chromatographic system: Proceed as directed in the Assay.

**Standard stock solution:** 0.03 mg/mL of USP Benzothiadiazine Related Compound A RS, 0.06 mg/mL of USP Hydrochlorothiazide RS, 0.08 mg/mL of USP Valsartan RS, and 0.2 mg/mL of USP Valsartan Related Compound B RS in Diluent

**System suitability solution:** Dilute 5.0 mL of the Standard stock solution with Diluent to 100 mL.

**Standard solution:** Dilute 10.0 mL of the System suitability solution in 100.0 mL of Diluent.

**System suitability**
Samples: System suitability solution and Standard solution

**Suitability requirements**
Resolution: NLT 1.4 between valsartan related compound B and valsartan; NLT 1.4 between benzothiadiazine related compound A and hydrochlorothiazide.
System suitability solution
Relative standard deviation: NMT 10.0% for the valsartan and hydrochlorothiazide peaks, Standard solution

Analysis
Samples: Standard solution and Sample solution
Disregard the peak, if any, with a retention time of 22 min.
Calculate the percentage of valsartan related compound A from the portion of Tablets taken:

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

\[r_0 = \text{peak response of benzothiadiazine related compound A from the Sample solution}\]
\[r_0' = \text{peak response of benzothiadiazine related compound A from the Standard solution}\]
\[C_s = \text{concentration of benzothiadiazine related compound A in the Standard solution (mg/mL)}\]
\[C_U = \text{nominal concentration of hydrochlorothiazide in the Sample solution (mg/mL)}\]

Calculate the percentage of each other impurity in the portion of Tablets taken:

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

\[r_0 = \text{peak response of each other impurity from the Sample solution}\]
\[r_0' = \text{peak response of valsartan from the Standard solution}\]
\[C_s = \text{concentration of valsartan in the Standard solution (mg/mL)}\]
\[C_U = \text{nominal concentration of valsartan (for calculating other impurities) in the Sample solution (mg/mL)}\]

Acceptance criteria: NMT 1.0% of benzothiadiazine related compound A; NMT 0.2% of any other impurity, excluding valsartan related compound A; NMT 1.3% of total impurities, excluding valsartan related compound A. [NOTE—Valsartan related compound A is the enantiomer of valsartan and coelutes with valsartan in this test.]

**ADDITIONAL REQUIREMENTS**

Add the following:

• LABELING: When more than one Dissolution test is given, the labeling states the Dissolution test used only when Test 1 is not used.

• PACKAGING AND STORAGE: Preserve in tight containers, and protect from moisture and heat. Store at controlled room temperature.

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Valsartan

- **USP Reference Standards** (11)

  - USP Benzothiadiazine Related Compound A RS
  4-Amino-6-chloro-1,3-benzenedisulfonamide.
  C$_7$H$_6$ClN$_3$O$_4$S$_2$  285.73
  - USP Hydrochlorothiazide RS
  - USP Valsartan RS
  - USP Valsartan Related Compound B RS
  ($S$-N-Butyryl-$N$-[(2′-(1H-tetrazole-5-yl)biphen-4-yl)methyl]-valine.

C$_{23}$H$_{27}$N$_5$O$_3$  421.49