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Valsartan and Hydrochlorothiazide Tablets

DEFINITION

Valsartan and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

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_F 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 1

Time (min)	Solution A (%)	Solution B (%)
0	90	10
25	10	90
27	90	10
40	90	10

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 25.0 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 the nominal equivalent of 62.5 mg of hydrochlorothiazide from a number of Tablets add 5 mL of water, 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 200.0 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%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of the corresponding analyte in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **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 ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by using one of the following procedures.

Spectrophotometric procedure

(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)

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 ($C_{24}H_{29}N_5O_3$) dissolved:

$$\text{Result} = [(AT_2 \times D) - (AT_1 \times E)/(C \times D) - (B \times E)] \times 12{,}500$$

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = [(AT_1 \times C) - (AT_2 \times B)/(D \times C) - (E \times B)] \times 80{,}000$$

AT_1 = absorbance of the *Sample solution* at 272 nm

C = $A1\%V_{250}$, absorptivity (1%, 0.2 cm, 250 nm) of valsartan in *Medium*

AT_2 = absorbance of the *Sample solution* at 250 nm

B = $A1\%V_{272}$, absorptivity (1%, 0.2 cm, 272 nm) of valsartan in *Medium*

D = $A1\%H_{272}$, absorptivity (1%, 0.2 cm, 272 nm) of hydrochlorothiazide in *Medium*

E = $A1\%H_{250}$, absorptivity (1%, 0.2 cm, 250 nm) of hydrochlorothiazide in *Medium*

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 with glacial acetic acid to a pH of 5.6

Solution B: Acetonitrile

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	88	12
4	65	35
7	88	12
8	88	12

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*J* 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 ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times D \times V \times 100$$

r_U = peak response of valsartan or hydrochlorothiazide from the *Sample solution*

r_S = peak response of valsartan or hydrochlorothiazide from the *Standard solution*

C_S = concentration of valsartan or hydrochlorothiazide in the *Standard solution* (mg/mL)

L = label claim for valsartan or hydrochlorothiazide (mg/Tablet)

D = dilution factor of the *Sample solution*, if applicable

V = volume of *Medium*, 1000 mL

Tolerances: NLT 80% (Q) of the labeled amount of both valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) 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 to dissolve, and add *Medium* to fill 25% 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 60% of the total volume. Sonicate for 5 min, and dilute with *Medium* to volume.

Standard solution: Prepare solutions of concentrations listed in *Table 3* from *Valsartan standard stock solution* and *Hydrochlorothiazide standard stock solution* in *Medium*. Pass through a suitable filter of 0.45-µm pore size, and discard the first few mL of the filtrate.

Table 3

Tablet Strength of Valsartan/ Hydrochlorothiazide (mg/mg)	Concentration of Valsartan (mg/mL)	Concentration of Hydrochlorothiazide (mg/mL)
320/25	0.32	0.025
320/12.5	0.32	0.0125
160/25	0.16	0.025
160/12.5	0.16	0.0125
80/12.5	0.08	0.0125

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.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

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 amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

r_U = peak response of valsartan or hydrochlorothiazide from the *Sample solution*

r_S = peak response of valsartan or hydrochlorothiazide from the *Standard solution*

C_S = concentration of valsartan or hydrochlorothiazide in the *Standard solution* (mg/mL)

V = volume of *Medium*, 1000 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of both valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

Change to read:

• **Uniformity of Dosage Units ⟨905⟩:** ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity

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

Sample solution: Transfer 1 Tablet to a 200-mL volumetric flask, add 5 mL of water, and allow to stand for 5 min. Add 100 mL of *Diluent*, and sonicate for 15 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 amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the Tablet taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the appropriate USP Reference Standard in the *Standard solution* (mg/mL)

C_U = nominal concentration of the corresponding analyte in the *Sample solution* (mg/mL)

▲▲ (CN 1-Aug-2023)

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 benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of benzothiadiazine related compound A from the *Sample solution*

r_S = peak response of benzothiadiazine related compound A from the *Standard solution*

C_S = concentration of benzothiadiazine related compound A in the *Standard solution* (mg/mL)

C_U = nominal concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each other impurity from the *Sample solution*

r_S = peak response of valsartan from the *Standard solution*

C_S = concentration of valsartan in the *Standard solution* (mg/mL)

C_U = 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

- **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.
- **USP REFERENCE STANDARDS** ⟨11⟩

USP Benzothiadiazine Related Compound A RS

4-Amino-6-chloro-1,3-benzenedisulfonamide.

$C_6H_8ClN_3O_4S_2$ 285.73

USP Hydrochlorothiazide RS

USP Valsartan RS

USP Valsartan Related Compound B RS

N-Butyryl-*N*-{[2'-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.

$C_{23}H_{27}N_5O_3$ 421.49

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
VALSARTAN AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

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