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: 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 and 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

- **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
(*S*-*N*-Butyryl-*N*-([2′-(1*H*-tetrazole-5-yl)biphen-4-yl] methyl)-valine.
$C_{23}H_{27}N_5O_3$ 421.49

Add the following:

•Venlafaxine Hydrochloride Extended-Release Capsules

DEFINITION

Venlafaxine Hydrochloride Extended-Release Capsules contain an amount of Venlafaxine Hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$).

IDENTIFICATION

- **A. Ultraviolet Absorption** ⟨197U⟩

Wavelength range: 250–310 nm

- **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**

Mobile phase: Acetonitrile, triethylamine, and water (250:4:750). Adjust with phosphoric acid to a pH of 3.5.

Standard solution: 0.25 mg/mL of USP Venlafaxine Hydrochloride RS in *Mobile phase*

Sample stock solution: Nominally 1.0 mg/mL of venlafaxine (from the contents of NLT 10 Capsules) prepared as follows. Transfer a weighed quantity of Capsule contents to a suitable volumetric flask. Add 8% of the flask volume of acetonitrile, and shake for 40 min. Add 50% of flask volume of *Mobile phase*, and shake for an additional 20 min. Dilute with *Mobile phase* to volume. Pass a portion through a suitable filter of 0.45-µm pore size.

Sample solution: 0.25 mg/mL of venlafaxine (using the filtrate from the *Sample stock solution*) in *Mobile phase*

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 1.5 times the retention time of venlafaxine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of the *Sample solution*
r_S = peak response of the *Standard solution*
C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of venlafaxine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of venlafaxine, 277.40
M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **DISSOLUTION** ⟨711⟩

Test 1

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Times: 3, 6, 16, and 24 h

Mobile phase: Acetonitrile, triethylamine, and water (450:4:550). Adjust with phosphoric acid to a pH of 3.5.

Standard stock solution: 0.1 mg/mL of USP Venlafaxine Hydrochloride RS in water

Standard solution: 0.05 mg/mL of USP Venlafaxine Hydrochloride RS in acetonitrile, from the *Standard stock solution*

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 274 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 60 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

Relative standard deviation: NMT 2.0%

Calculate the concentration, C_i, of venlafaxine ($C_{17}H_{27}NO_2$) in the *Medium* (mg/mL) after time point *i*:

$$C_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response of the *Sample solution*
r_S = peak response of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
M_{r1} = molecular weight of venlafaxine, 277.40
M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$\text{Result}_4 = \{[C_4 \times (V - (3 \times V_S))] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)
L = label claim (mg/Capsule)

Tolerances: See *Table 1*.

Table 1

Time Point, *i*	Time (h)	Amount Dissolved
1	3	NMT 40%
2	6	35%–60%
3	16	60%–85%
4	24	NLT 75%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Time: 2, 4, 8, 12, and 20 h

Capsule correction solution: Dissolve 6 empty Capsule shells in 900 mL of water.

Blank: Dilute 150 mL of *Capsule correction solution* with water to 900 mL.

Standard solution: (*L*/900) mg/mL of USP Venlafaxine Hydrochloride RS, where *L* is the label claim, in mg/Capsule, prepared as follows. To a weighed amount of the standard equivalent to the sample claim, add *Capsule correction solution* to fill 17% of final flask volume. Dilute with water to volume.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Instrumental conditions

Mode: UV

Detector: 274 nm

Analysis

Samples: *Standard solution* and *Sample solution*

[NOTE—If necessary, the volume of *Medium* may be corrected for volumes removed from any previous sample time points.]

Calculate the concentration, C_i, of venlafaxine ($C_{17}H_{27}NO_2$) in *Medium* (mg/mL) after time point *i*:

$$C_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
M_{r1} = molecular weight of venlafaxine, 277.40
M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

$$Result_1 = C_1 \times V \times (1/L) \times 100$$

$$Result_2 = \{[C_2 \times (V - V_S)] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$Result_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$$Result_i = \{[C_i \times (V - ([i-1] \times V_S))] + [(C_{i-1} + C_{i-2} + ... + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)
L = label claim (mg/Capsule)

Tolerances: See *Table 2*.

Table 2

Time Point, *i*	Time (h)	Amount Dissolved
1	2	10%–30%
2	4	33%–53%
3	8	58%–78%
4	12	68%–88%
5	20	NLT 80%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 4, 8, and 16 h

Buffer: Dissolve 1.4 g of potassium dihydrogen phosphate in 1 L of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (35:65)

Standard stock solution: 0.9 mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*

Standard solution: (*L*/750) mg/mL of USP Venlafaxine Hydrochloride RS in *Medium* from the *Standard stock solution*, where *L* is the label claim, in mg/Capsule. Pass a portion through a suitable filter of 0.45-µm pore size.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 225 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Column temperature: 30°

Injection volume: 10 µL

Run time: 2 times the retention time of venlafaxine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration, C_i, of venlafaxine ($C_{17}H_{27}NO_2$) in *Medium* (mg/mL) after time point *i*:

$$C_i = (r_U/r_S) \times C_S \times (M_{r1}/M_{r2})$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
M_{r1} = molecular weight of venlafaxine, 277.40
M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount (Q_i) of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

$$Result_1 = C_1 \times V \times (1/L) \times 100$$

$$Result_2 = \{[C_2 \times V] + [C_1 \times V_S]\} \times (1/L) \times 100$$

$$Result_3 = \{[C_3 \times V] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at time point *i* (mg/mL)
V = volume of *Medium*, 900 mL
V_S = volume of the *Sample solution* withdrawn from the vessel and replaced with *Medium* (mL)
L = label claim (mg/Capsule)

Tolerances: See *Table 3*.

Table 3

Time Point, *i*	Time (h)	Amount Dissolved
1	4	35%–55%
2	8	65%–90%
3	16	NLT 85%

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Acceptance Table 2* in *Dissolution* ⟨711⟩.

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Mobile phase, Standard solution, and **Sample solution:** Proceed as directed in the *Assay*.

System suitability solution: 0.25 µg/mL of USP Venlafaxine Related Compound A RS in *Standard solution*

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 4 times the retention time of venlafaxine

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for venlafaxine related compound A and venlafaxine are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between venlafaxine related compound A and venlafaxine

Tailing factor: NMT 2.0 for venlafaxine

Relative standard deviation: NMT 5.0% for venlafaxine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$Result = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*
r_S = peak response of venlafaxine from the *Standard solution*
C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of venlafaxine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of venlafaxine, 277.40
M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Acceptance criteria

Individual impurities: NMT 0.2%

Total impurities: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

- **USP Reference Standards** ⟨11⟩
  USP Venlafaxine Hydrochloride RS
  USP Venlafaxine Related Compound A RS
    1-(1-(4-Methoxyphenyl)-2-(methylamino)ethyl)cyclohexanol.
    $C_{16}H_{25}NO_2$ 263.38• (RB 1-Jul-2012)

Vitamin E

DEFINITION

Vitamin E is a form of alpha tocopherol ($C_{29}H_{50}O_2$). It includes the following: *d*- or *dl*-alpha tocopherol ($C_{29}H_{50}O_2$); *d*- or *dl*-alpha tocopheryl acetate ($C_{31}H_{52}O_3$); *d*- or *dl*-alpha tocopheryl acid succinate ($C_{33}H_{54}O_5$). It contains NLT 96.0% and NMT 102.0% of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$, respectively.

IDENTIFICATION

- **A.**
  [Note—Use low-actinic glassware.]
  Sample solutions
  Alpha tocopherol: 1 mg/mL in dehydrated alcohol
  Alpha tocopheryl acetate: Transfer 220 mg of *d*- or *dl*-alpha tocopheryl acetate to a round-bottom, glass-stoppered, 150-mL flask, and dissolve in 25 mL of dehydrated alcohol. Add 20 mL of dilute sulfuric acid in alcohol (1 in 7), and reflux in an all-glass apparatus for 3 h, protected from sunlight. Cool, transfer to a 200-mL volumetric flask, and add dilute sulfuric acid in alcohol (1 in 72) to volume.
  Alpha tocopheryl acid succinate: Transfer an amount of the sample, equivalent to 200 mg of alpha tocopherol, to a round-bottom, glass-stoppered, 250-mL flask, dissolve in 50 mL of dehydrated alcohol, and reflux for 1 min. While the solution is boiling, add, through the condenser, 1 g of potassium hydroxide pellets, one at a time to avoid overheating.
  [**Caution—**Wear safety goggles.]
  Continue refluxing for 20 min and, without cooling, add 2 mL of hydrochloric acid dropwise through the condenser.
  [Note—This technique is essential to prevent oxidative action by air while the sample is in an alkaline medium.]
  Cool, and transfer the contents of the flask to a 500-mL separator, rinsing the flask with 100 mL each of water and of ether, and adding the rinsings to the separator. Shake vigorously, allow the layers to separate, and collect each of the two layers in individual separators. Extract the aqueous layer with two 50-mL portions of ether, and add these extracts to the main ether extract. Wash the combined ether extracts with four 100-mL portions of water, then evaporate the ether solution on a water bath under reduced pressure or in an atmosphere of nitrogen until about 7 or 8 mL remain. Complete the evaporation, removing the last traces of ether without the application of heat. Immediately dissolve the residue in dilute sulfuric acid in alcohol (1 in 72), transfer to a 200-mL volumetric flask, and dilute with the alcoholic sulfuric acid to volume.
  Analysis
  Sample: Use the appropriate *Sample solution.*
  Add 2 mL of nitric acid with swirling to 10 mL of *Sample solution*, and heat at about 75° for 15 min.
  Acceptance criteria: A bright red or orange color develops.
- **B. Optical Rotation** ⟨781⟩
  Sample solutions
  Alpha tocopherol: Dissolve 100 mg of alpha tocopherol in 50 mL of ether.
  Alpha tocopheryl acetate: Transfer a volume of sample solution for *Alpha tocopheryl acetate* from *Identification* test *A*, equivalent to 100 mg of the test article, to a separator, and add 200 mL of water. Extract first with 75 mL, then with 25 mL, of ether, and combine the ether extracts in another separator.
  Alpha tocopheryl acid succinate: Transfer a volume of sample solution for *Alpha tocopheryl acid succinate* from *Identification* test *A*, equivalent to 100 mg of the test article, to a separator, and add 200 mL of water. Extract first with 75 mL, then with 25 mL, of ether, and combine the ether extracts in another separator.
  Analysis
  Sample: Use the appropriate *Sample solution*.
  To the entire volume of a *Sample solution*, as prepared above, add 20 mL of a solution (1 in 10) of potassium ferricyanide in sodium hydroxide solution (1 in 125), and shake for 3 min. Wash the ether solution with four 50-mL portions of water, discard the washings, and dry over anhydrous sodium sulfate. Evaporate the dried ether solution on a water bath under reduced pressure or in an atmosphere of nitrogen until 7–8 mL remain, then complete the evaporation, removing the last traces of ether without the application of heat. Immediately dissolve the residue in 5.0 mL of isooctane, and determine the optical rotation using as *c* the number of g of total tocopherols, determined in the *Assay*, in each 100 mL of solution employed for the test.
  Acceptance criteria
  d-**Isomers:** NLT +24°
  dl-**Forms:** Show no optical rotation activity
- **C.** The retention time of the major peak for alpha tocopherol of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Delete the following:

■• **Alpha Tocopherol**
  [Note—Use low-actinic glassware.]
  Internal standard solution: 1 mg/mL of hexadecyl hexadecanoate in *n*-hexane
  Standard solution: 1 mg/mL of the USP Alpha Tocopherol RS in the *Internal standard solution*
  Sample solution: 1 mg/mL of Vitamin E (*d*- or *dl*-alpha tocopherol) in the *Internal standard solution*
  Interference check solution: 1 mg/mL of Vitamin E (*d*- or *dl*-alpha tocopherol) in *n*-hexane
  System suitability solution: 1 mg/mL each of USP Alpha Tocopherol RS and USP Alpha Tocopheryl Acetate RS in *n*-hexane
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability.*)
  Mode: GC
  Detector: Flame ionization
  Column: 4-mm × 2-m borosilicate glass column packed with 2% to 5% liquid phase G2 on 80- to 100-mesh support S1AB utilizing either a glass-lined sample introduction system or on-column injection
  Temperature
    Column: Between 245° and 265°, isothermal
    Injection port: 10° higher than the column temperature
    Detector: 10° higher than the column temperature
  Flow rate: The flow rate of dry carrier gas is adjusted to obtain a hexadecyl hexadecanoate peak approximately 18–20 min after sample introduction when a 2% liquid phase column is used, or 30–32 min when a 5% liquid phase column is used.
  Injection size: 2–5 µL
  [Note—Chromatograms obtained exhibit relative retention times for alpha tocopherol, alpha tocopherol acetate, and hexadecyl hexadecanoate of approximately 0.53, 0.62, and 1.0 respectively]