Venlafaxine Hydrochloride Extended-Release Capsules

Type of Posting	Revision Bulletin
Posting Date	26-Feb-2021
Official Date	1-Mar-2021
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Venlafaxine Hydrochloride Extended-Release Capsules monograph. The purpose for the revision is to add *Dissolution Tests 10* and *11* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 10* was validated using the Zorbax SB-C18 brand of column with L1 packing. The typical retention time for venlafaxine is about 5 min.

- *Dissolution Test 11* was validated using the Zorbax SB-C18 brand of column with L1 packing. The typical retention time for venlafaxine is about 3 min.

The Venlafaxine Hydrochloride Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Nicholas Garito Jr., Sr. Scientific Liaison (301-816-8321 or njg@usp.org).

Revision Bulletin
Official: March 1, 2021

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. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U
  Wavelength range: 250–310 nm
  Acceptance criteria: Meet the requirements
- **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 from the *Sample solution*

r_S = peak response 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: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **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 stock solution: Pass a portion of the solution under test through a suitable filter.

Sample solution: *Sample stock solution* and acetonitrile (50:50)

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%

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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of the USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*, 2

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount 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 *Dissolution ⟨711⟩, Acceptance Table 2*.

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

Times: 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*:

$$\text{Result}_i = ({}^{\blacktriangle}A_U/A_{S\blacktriangle\ \text{(ERR 1-Mar-2021)}}) \times C_S \times (M_{r1}/M_{r2})$$

${}^{\blacktriangle}A_U$ = absorbance$_{\blacktriangle\ \text{(ERR 1-Mar-2021)}}$ from the *Sample solution*

${}^{\blacktriangle}A_S$ = absorbance$_{\blacktriangle\ \text{(ERR 1-Mar-2021)}}$ from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

$$\text{Result}_i = \{[C_i \times (V - ([i - 1] \times V_S))] + [(C_{i-1} + C_{i-2} + \ldots + C_1) \times V_S]\} \times (1/L) \times 100$$

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 *Dissolution ⟨711⟩, Acceptance Table 2*.

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

Times: 4, 8, and 16 h

Buffer: Dissolve 1.4 g of monobasic potassium 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: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. 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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

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 *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

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

Solution A: Dilute 10 mL of phosphoric acid with water to 100 mL.

Buffer: 11.4 g/L of ammonium dihydrogen phosphate in water

Mobile phase: Acetonitrile and *Buffer* (35:65). Adjust with *Solution A* to a pH of 4.4.

Standard stock solution: 0.24 mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*. Sonication may be used to aid in dissolution.

Standard solution: See *Table 4* for the concentration of USP Venlafaxine Hydrochloride RS in *Medium* from the *Standard stock solution*. Using a glass syringe, pass a portion through a suitable filter of 0.45-µm pore size.

Table 4

Label Claim (*L*)	Standard Solution (mg/mL)
37.5	0.05
75	0.1
150	0.1

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. For Capsules that are labeled to contain 150 mg of venlafaxine, dilute this solution with an equal volume of *Medium*. Using a glass syringe, 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 L7

Flow rate: 1.2 mL/min

Injection volume: 20 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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in the *Standard solution* (mg/mL)

D = dilution factor for the *Sample solution*, 2 for Capsules labeled to contain 150 mg of venlafaxine; 1 for Capsules labeled to contain 37.5 or 75 mg of venlafaxine

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

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

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

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

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

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

$$\text{Result}_5 = \{[C_5 \times V] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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 vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See *Table 5*.

Table 5

Time Point, *i*	Time (h)	Amount Dissolved
1	2	10%–30%
2	4	35%–55%
3	8	60%–80%
4	12	NLT 70%
5	20	NLT 85%

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

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Times: 2, 5, 8, and 20 h

Buffer: 11.4 g/L of monobasic ammonium phosphate in water. Adjust with dilute phosphoric acid (1 in 10) or dilute ammonia solution (1 in 10) to a pH of 4.4.

Mobile phase: Acetonitrile and *Buffer* (25.5: 74.5)

Standard solution: (*L*/900) mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*, where *L* is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample 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 × 15-cm; 5-µm packing L7

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 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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

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

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 vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See *Table 6*.

Table 6

Time Point, *i*	Time (h)	Amount Dissolved
1	2	NMT 20%
2	5	35%–55%
3	8	60%–80%
4	20	NLT 80%

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

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: Water; 900 mL, deaerated
Apparatus 1: 100 rpm
Times: 2, 4, 8, 12, and 24 h
Buffer: 10 mL/L of triethylamine in water adjusted with phosphoric acid to a pH of 3.0
Mobile phase: Acetonitrile and *Buffer* (20:80)
Standard solution: (*L*/900) mg/mL of venlafaxine from USP Venlafaxine Hydrochloride RS in *Medium,* where *L* is the label claim, in mg/Capsule
Sample solution: Centrifuge a portion of the solution under test.
Chromatographic system
(See *Chromatography ⟨621⟩, System Suitability*.)
Mode: LC
Detector: UV 226 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Flow rate: 2.5 mL/min
Injection volume: 20 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 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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

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

$$\text{Result}_5 = \{[C_5 \times (V - (4 \times V_S))] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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 7*.

Table 7

Time Point, *i*	Time (h)	Amount Dissolved
1	2	NMT 30%
2	4	40%–60%
3	8	60%–80%
4	12	70%–90%
5	24	NLT 85%

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

Test 7: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

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

Buffer: 1.7 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid (1 in 10) to a pH of 7.0.

Mobile phase: Acetonitrile and *Buffer* (80:20)

Standard solution: (*L*/900) mg/mL of USP Venlafaxine Hydrochloride RS in *Medium*, where *L* is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 227 nm

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

Column temperature: 45°

Flow rate: 1.5 mL/min

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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

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

$$\text{Result}_5 = \{[C_5 \times V] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

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 vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See *Table 8*.

Table 8

Time Point, *i*	Time (h)	Amount Dissolved
1	2	NMT 10%
2	4	NMT 30%
3	8	40%–70%
4	12	60%–90%
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 *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 8: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 8*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Times: 1, 6, 16, and 24 h

Diluent: Acetonitrile and water (30:70)

Buffer: Dissolve 8.9 g of dibasic sodium phosphate dihydrate and 2.5 g of sodium 1-octanesulfonate in 1 L of water. Adjust with 10% phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (32:68)

Standard stock solution: 0.9 mg/mL of USP Venlafaxine Hydrochloride RS prepared as follows. Dissolve the weighed amount of the Standard first in acetonitrile using 20% of flask volume. Sonicate to dissolve, and dilute with *Diluent* to volume.

Standard solution: (*L*/900) mg/mL of USP Venlafaxine Hydrochloride RS from *Standard stock solution* in *Diluent*, where *L* is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample

through a suitable filter of 0.45-µm pore size.

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: 1.5 mL/min

Injection volume: 20 µL

Run time: 1.7 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*:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *i*:

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

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

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

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

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 vessel and replaced with *Medium* (mL)

L = label claim (mg/Capsule)

Tolerances: See *Table 9*.

Table 9

Time Point, *i*	Time (h)	Amount Dissolved
1	1	NMT 25%
2	6	50%–70%

Time Point, *i*	Time (h)	Amount Dissolved
3	16	70%–95%
4	24	NLT 80%

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

Test 9: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 9*.

Medium: Water; 900 mL, degassed

Apparatus 1: 100 rpm

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

Buffer: Dissolve 3.4 g of monobasic potassium phosphate in 700 mL of water. Add 5 mL of triethylamine. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Standard stock solution: 1.6 mg/mL of USP Venlafaxine Hydrochloride RS prepared as follows. Dissolve a weighed amount of the Standard first in methanol using 20% of flask volume. Sonicate to dissolve, and dilute with water to volume.

Standard solution: (*L*/900) mg/mL of USP Venlafaxine Hydrochloride RS from the *Standard stock solution* in *Medium*, where *L* is the label claim, in mg/Capsule

Sample solution: At the end of the specified time interval, withdraw a known volume of the solution from the dissolution vessel, and replace it with an equal volume of fresh *Medium*. Pass a portion of the withdrawn sample through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 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*):

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Venlafaxine Hydrochloride RS in 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 of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at each time point *(i)*:

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

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

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

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

$$\text{Result}_5 = \{[C_5 \times V] + [(C_4 + C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of venlafaxine in *Medium* in the portion of sample withdrawn at the specified 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 10*.

Table 10

Time Point, *i*	Time (h)	Amount Dissolved
1	2	NMT 25%
2	4	30%–50%
3	8	55%–80%
4	12	65%–90%
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 *Dissolution ⟨711⟩, Acceptance Table 2*.

▲**Test 10:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 10*.

Medium: Water; 900 mL

Apparatus 1: 100 rpm

Times: 2, 4, and 20 h

Buffer: Add 5 mL of triethylamine to 1000 mL of water and mix. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (20:80)

Standard stock solution: 1 mg/mL of USP Venlafaxine Hydrochloride RS in methanol. Sonicate to dissolve, if necessary.

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

Sample solution: At the specified times, withdraw a known volume of the solution from the dissolution vessel. Dilute with *Medium*, if necessary, to a concentration that is simlar to that of the *Standard solution*. Pass a portion of solution through a suitable filter of 0.45-µm pore size, discarding the first 5 mL of filtrate, and use the filtrate. Replace the portion removed with the same volume of *Medium*.

Chromatographic system

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

Mode: LC

Detector: UV 226 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 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 the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of venlafaxine 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)

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

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

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

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

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

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

C_i = concentration of venlafaxine in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See *Table 11*.

Table 11

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 30
2	4	37–57
3	20	NLT 80

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

Test 11: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.

Medium: pH 6.8, 0.05 M phosphate buffer (Dissolve 6.8 g of monobasic potassium phosphate and 0.9 g of sodium hydroxide in 1 L of water. Adjust with dilute phosphoric acid in water or dilute sodium hydroxide in water to a pH of 6.8.); 900 mL

Apparatus 1: 100 rpm

Times: 2, 8, and 24 h

Mobile phase: Acetonitrile and water (45:55). Add 4 mL of triethylamine to each liter of the mixture. Adjust with phosphoric acid to a pH of 3.5.

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

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

Sample solution: At the specified times, withdraw a known volume of the solution from the dissolution vessel. Pass a portion of solution through a suitable filter of 0.45-µm pore size, discarding the first 2 mL of filtrate. Transfer a suitable volume of the filtrate, equal to one-half of the flask volume, to an appropriate volumetric flask. Dilute with acetonitrile to volume.

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

Run time: NLT 2 times the retention time of venlafaxine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.5

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 the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of venlafaxine 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)

D = dilution factor of the *Sample solution*, 2

M_{r1} = molecular weight of venlafaxine, 277.40

M_{r2} = molecular weight of venlafaxine hydrochloride, 313.86

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

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

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

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

C_i = concentration of venlafaxine in the portion of sample withdrawn at time point i (mg/mL)

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

V_S = volume of the *Sample solution* withdrawn at each time point from the *Medium* (mL)

Tolerances: See *Table 12*.

Table 12

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	NMT 25
2	8	50–70
3	24	NLT 80

The percentages of the labeled amount of venlafaxine ($C_{17}H_{27}NO_2$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*. ▲ (RB 1-Mar-2021)

- **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 the *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:

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

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 hydrochloride.

$C_{16}H_{25}NO_2 \cdot HCl$ 299.84

Page Information:

Not Applicable

DocID: