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 (C17H27NO2).

**IDENTIFICATION**
- **A. ULTRAVIOLET ABSORPTION (197U)**
  - Wavelength range: 250–310 nm
  - Acceptance criteria: Meet the requirements

**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 solution**: Nominally 1.0 mg/mL of venlafaxine (from the contents of 10 Capsules) prepared as follows. Transfer a weighed quantity of capsules to a suitable volumetric flask. Add 8% of the flask volume of acetonitrile, and shake for 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 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 2.5
  - **Relative standard deviation**: NMT 1.5%

**Analysis**
- **Samples**: Standard solution and Sample solution
  - Calculate the concentration, Ci, of venlafaxine (C17H27NO2) in Medium (mg/mL) after time point i:
    \[ \text{Result}_i = \left( \frac{r_i}{r_s} \right) \times \left( \frac{C_i}{C_s} \right) \times \left( \frac{M_i}{M_s} \right) \times 100 \]
  - \( r_i \) = peak response from the Sample solution
  - \( r_s \) = peak response from the Standard solution
  - \( C_i \) = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)
  - \( C_s \) = nominal concentration of venlafaxine in the Sample solution (mg/mL)
  - \( M_i \) = molecular weight of venlafaxine, 277.40
  - \( M_s \) = molecular weight of venlafaxine hydrochloride, 313.86
  - \( D \) = dilution factor for the Sample solution, 2
  - \( M_{i1} \) = molecular weight of venlafaxine, 277.40
  - \( M_{i2} \) = molecular weight of venlafaxine hydrochloride, 313.86

Calculate the percentage of the labeled amount of venlafaxine (C17H27NO2) dissolved at each time point i:
\[ \text{Result}_1 = C_1 \times V \times (1/L) \times 100 \]
\[ \text{Result}_2 = \left[ \left( C_1 \times (V - V_3) \right) + \left( C_1 \times V_3 \right) \right] \times (1/L) \times 100 \]
\[ \text{Result}_3 = \left[ \left( C_1 \times (V - (2 \times V_2)) \right) + \left( (C_2 + C_1) \times V_2 \right) \right] \times (1/L) \times 100 \]
\[ \text{Result}_4 = \left[ \left( C_1 \times (V - (3 \times V_2)) \right) + \left( (C_2 + C_1 + C_2 + C_1) \times V_2 \right) \right] \times (1/L) \times 100 \]
- \( C_1 \) = concentration of venlafaxine in Medium in the portion of sample withdrawn at time point i (mg/mL)
- \( V \) = volume of Medium, 900 mL

**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)
Venlafaxine

\[ V_s = \text{volume of the Sample solution withdrawn from the Medium (mL)} \]
\[ L = \text{label claim (mg/Capsule)} \]

**Tolerances:** See Table 1.

**Table 1**

<table>
<thead>
<tr>
<th>Time Point, ( t_i )</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>NMT 40%</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>35%-60%</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>60%-85%</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of venlafaxine \((C_1\text{H}_2\text{H}_2\text{NO}_2)\) 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. In case the product complies with this test, the label indicates that it meets USP Dissolution Test 2.

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

\[ \text{Result}_i = \left( \frac{r_U}{r_S} \right) \times C_i \times \left( \frac{M_1}{M_2} \right) \]

- \(r_U\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_i\) = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)
- \(M_1\) = molecular weight of venlafaxine, 277.40
- \(M_2\) = molecular weight of venlafaxine hydrochloride, 313.86

**Chromatographic system**

- **Mode:** LC
- **Detector:** UV 225 nm
- **Column:** 4.6-mm \(\times\) 25-cm; 5-\(\mu\)m packing L1
- **Flow rate:** 1 mL/min
- **Column temperature:** 30°C
- **Injection volume:** 10 \(\mu\)L
- **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 \((C_1\text{H}_2\text{H}_2\text{NO}_2)\) in Medium (mg/mL) after time point \(t_i\):

\[ \text{Result}_i = \left( \frac{r_U}{r_S} \right) \times \left[ \left( \frac{C_i \times V - \left( \frac{C_i}{2} \times V_i \right) }{1/L} \right) \times 100 \right] \]

**Table 2**

<table>
<thead>
<tr>
<th>Time Point, ( t_i )</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>10%-30%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>33%-53%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>58%-78%</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>68%-88%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of venlafaxine \((C_1\text{H}_2\text{H}_2\text{NO}_2)\) 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:** 0.1N hydrochloric acid; 900 mL
- **Apparatus 1:** 100 rpm
- **Time:** 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-\(\mu\)m 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-\(\mu\)m pore size.

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$M_r = \text{molecular weight of venlafaxine hydrochloride, 313.86}$

Calculate the percentage of the labeled amount of venlafaxine ($C_{i1}\text{H}_{27}\text{NO}_2$) dissolved at each time point $i$:

$$\text{Result}_i = C_i \times V \times (1/l) \times 100$$

$$\text{Result}_i = [(C_i \times V) + (C_i \times V)] \times (1/l) \times 100$$

$$\text{Result}_i = [(C_i \times V) + [(C_i + C_i) \times V]] \times (1/l) \times 100$$

where $C_i = \text{concentration of venlafaxine in Medium in the portion of sample withdrawn at time point } i \text{ (mg/mL)}$

$V = \text{volume of Medium, 900 mL}$

$\text{Vol}_i = \text{volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)}$

$L = \text{label claim (mg/Capsule)}$

Tolerances: See Table 3.

### Table 3

<table>
<thead>
<tr>
<th>Time Point, $i$</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>35%-55%</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>65%-90%</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of venlafaxine ($C_{i1}\text{H}_{27}\text{NO}_2$) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

**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

**Time:** 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>
<thead>
<tr>
<th>Label Claim (mg)</th>
<th>Standard Solution (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>37.5</td>
<td>0.05</td>
</tr>
<tr>
<td>75</td>
<td>0.1</td>
</tr>
<tr>
<td>150</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**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 ($C_{i1}\text{H}_{27}\text{NO}_2$) in Medium (mg/mL) after time point $i$:

$$r_U = \text{peak response from the Sample solution}$$

$$r_S = \text{peak response from the Standard solution}$$

$$C_i = \text{concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)}$$

$D = \text{dilution factor for the Sample solution, 2 for Capsules labeled to contain 37.5 or 75 mg of venlafaxine}$

$M_r = \text{molecular weight of venlafaxine, 313.86}$

$M_r = \text{molecular weight of venlafaxine hydrochloride, 277.40}$

Calculate the percentage of the labeled amount of venlafaxine ($C_{i1}\text{H}_{27}\text{NO}_2$) dissolved at each time point $i$:

$$\text{Result}_i = (r_U/r_S) \times C_i \times D \times (M_r/M_r)$$

$$r_U = \text{peak response from the Sample solution under test}$$

$$r_S = \text{peak response from the Standard solution}$$

$$C_i = \text{concentration of USP Venlafaxine Hydrochloride RS in Medium (mg/mL)}$$

$\text{Vol}_i = \text{volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)}$

$L = \text{label claim (mg/Capsule)}$

Tolerances: See Table 5.

### Table 4

<table>
<thead>
<tr>
<th>Time Point, $i$</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>10%-30%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>35%-55%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>60%-80%</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 70%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>NLT 85%</td>
</tr>
</tbody>
</table>
Venlafaxine

The percentages of the labeled amount of venlafaxine (C₁₇H₂₇NO₂) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711).

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
Time: 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 x 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, Cᵢ, of venlafaxine (C₁₇H₂₇NO₂) in Medium (mg/mL) after time point i:

Resultᵢ = (rᵢ/rₛ) × Cᵢ × (Mᵢ/Mₛ)

rᵢ = peak response from the Sample solution
rₛ = peak response from the Standard solution
Cᵢ = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)
Mᵢ = molecular weight of venlafaxine, 277.40
Mₛ = molecular weight of venlafaxine hydrochloride, 313.86

The percentages of the labeled amount of venlafaxine (C₁₇H₂₇NO₂) dissolved at each time point i:

Resultᵢ = Cᵢ × V × (1/L) × 100

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

Tolerances: See Table 6.

Table 6

<table>
<thead>
<tr>
<th>Time Point, i</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 20%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>35%-55%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>60%-80%</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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Calculate the percentage of the labeled amount of venlafaxine \((C_{17}H_{27}NO_{2})\) dissolved at each time point \(i:\)

\[
\text{Result}_i = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = ([C_i \times (V - V_i)] + [C_i \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_3 = ([C_i \times (V - (2 \times V_i))] + [(C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_4 = ([C_i \times (V - (3 \times V_i))] + [(C_i + C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_5 = ([C_i \times (V - (4 \times V_i))] + [(C_i + C_i + C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

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

\(V\) = volume of Medium, 900 mL

\(V_i\) = volume of the Sample solution withdrawn from the Medium (mL)

\(L\) = label claim (mg/Capsule)

**Tolerances:** See Table 7.

<table>
<thead>
<tr>
<th>Time Point, (i)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
</tr>
</tbody>
</table>

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 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

**Time:** 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

**Temperature:** 45°C

**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 \(i:\)

\[
\text{Result}_1 = (r_1/r_2) \times C \times (M_2/M_1)
\]

\(r_1\) = peak response from the Sample solution

\(r_2\) = peak response from the Standard solution

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

\(M_1\) = molecular weight of venlafaxine, 277.40

\(M_2\) = 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 \(i:\)

\[
\text{Result}_1 = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = ([C_i \times V] + [C_i \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_3 = ([C_i \times (V - (2 \times V_i))] + [(C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_4 = ([C_i \times (V - (3 \times V_i))] + [(C_i + C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

\[
\text{Result}_5 = ([C_i \times (V - (4 \times V_i))] + [(C_i + C_i + C_i + C_i) \times V_i]) \times (1/L) \times 100
\]

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

\(V\) = volume of Medium, 900 mL

\(V_i\) = volume of the Sample solution withdrawn from the Medium (mL)

\(L\) = label claim (mg/Capsule)

**Tolerances:** See Table 8.

<table>
<thead>
<tr>
<th>Time Point, (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 10%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>NMT 30%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>40%-70%</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>60%-90%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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 8:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 8.
from the dissolution vessel, and replace it with an
Analysis
System suitability
Standard 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 stock solution: (621) 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 \( t \):
\[
\text{Result}_i = \left( \frac{r_i}{r_0} \right) \times C_i \times \left( \frac{M_1}{M_2} \right)
\]
\( r_0 \) = peak response from the Sample solution
\( r_i \) = peak response from the Standard solution
\( C_i \) = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)
\( M_1 \) = molecular weight of venlafaxine, 277.40
\( M_2 \) = 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 \( i \):
\[
\text{Result}_i = \left[ \left( C_i \times V \right) + \left[ C_i \times V_i \right] \right] \times (1/L) \times 100
\]
\( V \) = volume of Medium, 900 mL
\( V_i \) = volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)
\( L \) = label claim (mg/Capsule)

**Tolerances:** See Table 9.

<table>
<thead>
<tr>
<th>Time Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

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 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
Time: 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 (32:68)
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: (621) 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 \( i \):
\[
\text{Result}_i = \left( \frac{r_i}{r_0} \right) \times C_i \times \left( \frac{M_1}{M_2} \right)
\]
\( r_0 \) = peak response from the Sample solution
\( r_i \) = peak response from the Standard solution
\( C_i \) = concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)
\( M_1 \) = molecular weight of venlafaxine, 277.40
\( M_2 \) = molecular weight of venlafaxine hydrochloride, 313.86
Calculate the percentage of the labeled amount of venlafaxine (C₁₇H₂₇NO₂) dissolved at each time point (i):

\[ \text{Result}_3 = C_i \times V \times \left( \frac{1}{L} \right) \times 100 \]

\[ \text{Result}_2 = \left[ \left( C_2 \times V \right) + \left( C_1 \times V_0 \right) \right] \times \left( \frac{1}{L} \right) \times 100 \]

\[ \text{Result}_3 = \left[ \left( C_1 \times V \right) + \left( C_2 + C_3 \right) \times V_0 \right] \times \left( \frac{1}{L} \right) \times 100 \]

\[ \text{Result}_4 = \left[ \left( C_1 \times V \right) + \left( C_2 + C_3 + C_4 \right) \times V_0 \right] \times \left( \frac{1}{L} \right) \times 100 \]

\[ C_i = \text{concentration of venlafaxine in Medium in the portion of sample withdrawn at the specified time point } i \text{ (mg/mL)} \]

\[ V = \text{volume of Medium, 900 mL} \]

\[ V_0 = \text{volume of the Sample solution withdrawn from the vessel and replaced with Medium (mL)} \]

\[ L = \text{label claim (mg/Capsule)} \]

**Tolerances:** See Table 10.

**Table 10**

<table>
<thead>
<tr>
<th>Time Point, i</th>
<th>Time (h)</th>
<th>Amount Dissolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 25%</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>30%-50%</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>55%-80%</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>65%-90%</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of venlafaxine (C₁₇H₂₇NO₂) dissolved at the times specified conform to Acceptance Table 2 in Dissolution (711). [RB 1-Feb-2014]

- **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:

\[ \text{Result}_5 = \left[ \left( C_4 \times V \right) + \left( C_3 + C_2 + C_1 \right) \times V_0 \right] \times \left( \frac{1}{L} \right) \times \frac{r_U}{r_S} \times \frac{C_S}{C_U} \times \frac{Mr_1}{Mr_2} \times 100 \]

\[ r_U = \text{peak response of each individual impurity from the Sample solution} \]

\[ r_S = \text{peak response of venlafaxine from the Standard solution} \]

\[ C_S = \text{concentration of USP Venlafaxine Hydrochloride RS in the Standard solution (mg/mL)} \]

\[ C_U = \text{nominal concentration of venlafaxine in the Sample solution (mg/mL)} \]

\[ M_{r1} = \text{molecular weight of venlafaxine, 277.40} \]

\[ M_{r2} = \text{molecular weight of venlafaxine hydrochloride, 313.86} \]

**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**
  - USP Venlafaxine Hydrochloride RS
  - USP Venlafaxine Related Compound A RS

\[ C_{16}H_{25}NO_2 \cdot HCl \; 299.84 \]

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