Divalproex Sodium Extended-Release Tablets

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Expert Committee: Chemical Medicines Monographs 4
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Divalproex Sodium Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 11* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 11* was validated using an Inertsil C8-3 brand of column with L7 packing. The typical retention time for valproic acid is about 4 min.

The Divalproex Sodium Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison–Team Leader (301-998-6792 or hrj@usp.org).
Divalproex Sodium Extended-Release Tablets

**DEFINITION**
Divalproex Sodium Extended-Release Tablets contain an amount of divalproex sodium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid (C₆H₁₂O₂).

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

**ASSAY**

**PROCEDURE**
- **Buffer:** 0.5 g/L of anhydrous citric acid and 0.4 g/L of anhydrous dibasic sodium phosphate in water
- **Mobile phase:** Methanol and Buffer (55:45). Adjust with diluted sodium hydroxide or phosphoric acid to a pH of 5.0.
- **Diluent:** Buffer, adjusted with phosphoric acid to a pH of 2.0
- **Standard stock solution:** Nominally 2.5 mg/mL of valproic acid prepared as follows. Transfer an amount of powder from NLT 20 Tablets to a suitable volumetric flask. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, pass through a suitable filter, and use the filtrate.
- **Sample solution:** Nominally 1.0 mg/mL of valproic acid from the Standard stock solution in Diluent

**Chromatographic system**
(See **Chromatography** (621), **System Suitability**.)
- **Mode:** LC
- **Detector:** UV 210 nm
- **Column:** 3.9-mm × 15-cm; 4-µm packing L11
- **Flow rate:** 0.7 mL/min
- **Injection volume:** 20 µL
- **Run time:** NLT 2 times the retention time of valproic acid

**Suitability requirements**
- **Tailing factor:** NMT 2.0 for valproic acid
- **Relative standard deviation:** NMT 2.0% for valproic acid

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of valproic acid (C₆H₁₂O₂) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_s}{r_u} \right) \times \frac{(C_s/C_U) \times 100}{100}
\]

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_s\) = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)
- \(C_U\) = nominal concentration of valproic acid in the Sample solution (mg/mL)

**Acceptance criteria:** 90.0%–110.0% of valproic acid

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**
  **Test 1**
  - **Acid stage medium:** 0.1 N hydrochloric acid; 500 mL
  - **Buffer stage medium:** 21.6 g/L of sodium dodecyl sulfate, 6.9 g/L of monobasic sodium phosphate, and 0.12 g/L of sodium hydroxide in water. Adjust with diluted sodium hydroxide or diluted phosphoric acid to a pH of 5.5; 900 mL
  - **Apparatus 2:** 100 rpm, with three-prong sinkers only for 250-mg Tablets, if necessary
  - **Times:** 45 min in the Acid stage medium; 3, 9, 12, and 24 h in the Buffer stage medium

  **Procedure:** After 45 min in the Acid stage medium, withdraw a sample from the solution, and immediately filter. Replace the Acid stage medium with the Buffer stage medium, and run the test for the times specified.

  **Buffer:** 1.42 g/L of dibasic sodium phosphate in 0.008 M acetic acid TS. Adjust with phosphoric acid to a pH of 2.5.

  **Standard solution:** 2.5 mg/mL of USP Valproic Acid RS in methanol

  **Chromatographic system**
  (See **Chromatography** (621), **System Suitability**.)
  - **Mode:** LC
  - **Detector:** UV 210 nm
  - **Column:** 3.9-mm × 15-cm; 10-µm packing L11
  - **Flow rate:** 1 mL/min
  - **Injection volume:** 80 µL
  - **Run time:** NLT 1.5 times the retention time of valproic acid

  **Suitability requirements**
  - **Tailing factor:** NMT 2.5
  - **Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution, Sample solution from the Acid stage medium, and Sample solution from the Buffer stage medium

Calculate the percentage of the labeled amount of valproic acid (C₆H₁₂O₂) dissolved in the Acid stage medium:

\[
\text{Result} = \left( \frac{r_s/r_u}{} \right) \times C_s \times V \times (1/L) \times 100
\]

- \(r_u\) = peak response from the Sample solution
- \(r_s\) = peak response from the Standard solution
- \(C_s\) = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)
- \(V\) = volume of the Acid stage medium, 500 mL
- \(L\) = label claim (mg/Tablet)

Calculate the concentration (C) of valproic acid (C₆H₁₂O₂) in the sample withdrawn from the vessel at each time point i during the Buffer stage:

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2 Divalprox

Result_1 = (r_1/r_2) × C_S × D

\( r_i \) = peak response from the Sample solution at time point \( i \)
\( r_S \) = peak response from the Standard solution
\( C_S \) = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)
\( D \) = dilution factor of the Sample solution in the Buffer stage medium, 2

Calculate the percentage of the labeled amount of valproic acid (C_2H_3O_2) dissolved at each time point \( i \) during the Buffer stage:

Result_1 = C_S × V × (1/L) × 100
Result_2 = \{[(C_S × (V − V_j)) + (C_i × V_j)] × (1/L) × 100
Result_3 = \{[(C_S × [V − (2 × V_j)]) + [(C_i + C_j) × V_j)] × (1/L) × 100

\( C_i \) = concentration of valproic acid in the Sample solution withdrawn at time point \( i \) (mg/mL)
\( V \) = volume of the Buffer stage medium, 900 mL
\( L \) = label claim (mg/Tablet)
\( V_S \) = volume of the Sample solution withdrawn at each time point \( i \) during the Buffer stage (mL)

Tolerances

Acid stage: NMT 10% of the labeled amount of valproic acid (C_2H_3O_2) is dissolved.
Buffer stage: See Table 1.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10–30</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>35–55</td>
<td>35–60</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>45–70</td>
<td>45–75</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 75</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C_2H_3O_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.

Acid stage medium: 0.1 N hydrochloric acid; 500 mL
Buffer stage concentrate: 13.53 g/L of monobasic sodium phosphate, 5.45 g/L of sodium hydroxide, and 48.7 g/L of sodium lauryl sulfate in water (final pH approximately 11); 400 mL
Buffer stage medium: Mix 400 mL of Buffer stage concentrate with 500 mL of Acid stage medium to a pH of 5.5 ± 0.05. [Note—If necessary, adjust the pH of Buffer stage concentrate with 1 N hydrochloric acid or 1 N sodium hydroxide to ensure that the final pH of the mixture of media is 5.5.] Retain this solution to dilute the solutions prepared later.
Apparatus 2: 100 rpm, with wire helix sinkers
Times: 45 min in the Acid stage medium; 3, 9, 12, and 21 h in the Buffer stage medium. The times in the Buffer stage medium include the time in the Acid stage medium.
Procedure: After 45 min in the Acid stage medium, stop and lift the paddles from the vessels. Do not perform an analysis of the Acid stage medium. Transfer 400 mL of Buffer stage concentrate to the vessels containing the Acid stage medium, and run the test for the times specified.
Buffer: 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.
Mobile phase: Acetonitrile and Buffer (50:50)
Standard stock solution: 28 mg/mL of USP Valproic Acid RS in a suitable volumetric flask. Dissolve with 20% of the flask volume of 1 N sodium hydroxide, and dilute with water to volume. Dilute this solution with Buffer stage medium to obtain a final concentration of about 2.8 mg/mL.
Standard solutions: Prepare a series of dilutions in Buffer stage medium from the Standard stock solution at 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL.
Sample solution: Withdraw 10 mL of the solution under test, and pass through a suitable filter of 35-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 215 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 50 µL
Run time: NLT 1.5 times the retention time of valproic acid
System suitability
Samples: 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL of the Standard solutions
Suitability requirements:
Tailing factor: NMT 2.0, using the 0.50-mg/mL Standard solution
Correlation coefficient: NLT 0.999, using the five concentrations of the Standard solution
Relative standard deviation: NMT 2.0%, using the 0.50-mg/mL Standard solution

Analysis
Sample: Sample solution
From the standard curve, determine the concentration (C) of valproic acid (C_2H_3O_2) dissolved at each time point (i) using the response of each Sample solution. Calculate the percentage of the labeled amount of valproic acid (C_2H_3O_2) dissolved at each time point i during the Buffer stage:

Result_1 = C_S × V × (1/L) × 100
Result_2 = \{[(C_S × (V − V_j)) + (C_i × V_j)] × (1/L) × 100
Result_3 = \{[(C_S × [V − (2 × V_j)]) + [(C_i + C_j) × V_j)] × (1/L) × 100

\( C_i \) = concentration of valproic acid in the Sample solution withdrawn at time point i (mg/mL)
\( V \) = volume of the Buffer stage medium, 900 mL
\( L \) = label claim (mg/Tablet)
\( V_S \) = volume of the Sample solution withdrawn at each time point i during the Buffer stage (mL)

Tolerances: The percentage of the labeled amount of valproic acid (C_2H_3O_2) dissolved at the times specified conform to Table 2.

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

Acid stage medium: 0.1 N hydrochloric acid; 250 mL (row 1)
Buffer stage medium: pH 6.8 buffer (6.8 g of monobasic potassium phosphate and 0.92 g of sodium hydroxide in
Table 2 (Divalproex Sodium Extended-Release Tablets)

<table>
<thead>
<tr>
<th>Time Points (h)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1 Individual Tablets</td>
<td>10%–27%</td>
<td>35%–70%</td>
<td>44%–92%</td>
<td>NLT 87%</td>
</tr>
<tr>
<td>L2 Average</td>
<td>10%–27%</td>
<td>35%–70%</td>
<td>44%–92%</td>
<td>NLT 87%</td>
</tr>
<tr>
<td>L2 Individual Tablets</td>
<td>0%–37%</td>
<td>25%–80%</td>
<td>34%–102%</td>
<td>NLT 77%</td>
</tr>
<tr>
<td>L3 Average</td>
<td>10%–27%</td>
<td>35%–70%</td>
<td>44%–92%</td>
<td>NLT 87%</td>
</tr>
</tbody>
</table>
| L3 Individual Tablets | NMT 2 Tablets are outside the range of 0%–37%, and no individual Tablet is outside the range of 0%–47%. | NMT 2 Tablets are outside the range of 25%–80%, and no individual Tablet is outside the range of 15%–90%. | NMT 2 Tablets are outside the range of 34%–102%, and no individual Tablet is outside the range of 24%–112%. | NMT 2 Tablets release less than 77%, and no individual Tablet releases less than 67%.

1 L of water. Adjust with phosphoric acid or sodium hydroxide to a pH of 6.8 ± 0.05; 250 mL (rows 2–4).

Apparatus 3: 30 dips/min, 20-mesh polypropylene screen on top and bottom; 30-s drip time.

Times: 1 h in Acid stage medium (row 1); 2, 12, and 24 h in Buffer stage medium (rows 2–4). The time in the Buffer stage medium include the time in the Acid stage medium.

Buffer: 0.25 g/L of citric acid, 0.2 g/L of anhydrous dibasic sodium phosphate, 3.4 g/L of monobasic potassium phosphate, and 0.85 g/L of sodium hydroxide in water. Adjust with phosphoric acid to a pH of 3.0 ± 0.05.

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

Acid stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in Acid stage medium. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize the valproic acid. Dilute with Acid stage medium to volume.

Buffer stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in Buffer stage medium. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize the valproic acid. Dilute with Buffer stage medium to volume.

Acid stage standard solution: (L/2500) mg/mL of USP Valproic Acid RS from Acid stage standard stock solution in Acid stage medium, where L is the Tablet label claim in mg.

Buffer stage standard solution: (L/700) mg/mL of USP Valproic Acid RS from Buffer stage standard stock solution in Buffer stage medium, where L is the Tablet label claim in mg.

Sample solutions: Centrifuge a portion of the solution under test. Use the supernatant. [Note—The use of a centrifuge speed of 3000 rpm for 20 min may be suitable.]

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm x 15-cm; 5-µm packing L11

Flow rate: 2 mL/min

Injection volume: 100 µL for Tablets labeled to contain 250 mg; 50 µL for Tablets labeled to contain 500 mg

Run time: NLT 1.5 times the retention time of valproic acid

System suitability

Samples: Acid stage standard solution and Buffer stage standard solution

Suitability requirements

Tailing factor: NMT 2.0 each for the Acid stage standard solution and the Buffer stage standard solution

Relative standard deviation: NMT 2.0% each for the Acid stage standard solution and the Buffer stage standard solution

Analysis

Samples: Acid stage standard solution, Buffer stage standard solution, and Sample solutions

Calculate the concentration (C) of valproic acid (C₇H₁₄O₂) in the sample withdrawn from the vessel at each time point (i):

Result = (rᵢ/rₛ) × Cₛ

rᵢ = peak response from the Sample solution at time point i

rₛ = peak response from the Acid stage standard solution or Buffer stage standard solution

Cₛ = concentration of USP Valproic Acid RS in the Acid stage standard solution or Buffer stage standard solution (mg/mL)

Calculate the percentage of the labeled amount of valproic acid (C₇H₁₄O₂) dissolved at each time point (i):

Resultᵢ = Cₛ × V × (1/L) × 100

Resultᵢ₁ = Cₛ + Cᵢ × V × (1/L) × 100

Resultᵢ₂ = Cₛ + Cᵢ + Cᵢ₂ × V × (1/L) × 100

Resultᵢ₃ = Cₛ + Cᵢ + Cᵢ₂ + Cᵢ₃ × V × (1/L) × 100

Cᵢ = concentration of valproic acid in the Acid stage standard solution or Buffer stage standard solution withdrawn at time point i (mg/mL)

V = volume of the Acid stage medium or Buffer stage medium, 250 mL

L = label claim (mg/Tablet)

Tolerances: See Table 3.

Table 3

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 10</td>
<td>NMT 10</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5–25</td>
<td>5–25</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>55–75</td>
<td>65–85</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 80</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C₇H₁₄O₂) 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.

Acid stage medium: 0.1 N hydrochloric acid; 500 mL

Buffer stage stock medium: 19.0 g/L of trisodium phosphate in water, adjusted with hydrochloric acid to a pH of 5.5

Buffer stage medium: 21.6 g/L of sodium lauryl sulfate in Buffer stage stock medium; 900 mL

Apparatus 2: 100 rpm, with sinkers for 250- and 500-mg Tablets

Times: 45 min in Acid stage medium; 3, 9, 12, and 18 h in Buffer stage medium. The times in the Buffer stage medium include the time in the Acid stage medium.

Buffer: 1.36 g/L of monobasic potassium phosphate and triethylamine (99.5: 0.5). Adjust with phosphoric acid to a pH of 2.75.

Solution A: 1.0 g/L of sodium lauryl sulfate in Buffer Mobile phase: Acetonitrile and Solution A (50:50), degassed

Acid stage standard stock solution: 1 mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable amount of USP Valproic Acid RS to a volumetric flask, and dissolve in 20% of the flask volume of acetonitrile to solubilize valproic acid. Dilute with Acid stage medium to volume.

Acid stage standard solution: (L/5000) mg/mL of valproic acid from Acid stage standard stock solution in Acid stage medium, where L is the Tablet label claim, in mg

Buffer stage standard solution: (L/900) mg/mL of USP Valproic Acid RS, prepared as follows. Transfer a suitable amount of USP Valproic Acid RS to a volumetric flask, and dissolve in (L/50)% of the flask volume of acetonitrile.

Dilute with Buffer stage medium to volume. L is the Tablet label claim in mg.

Acid stage sample solution: Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Buffer stage sample solution: Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of Buffer stage medium.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 210 nm

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

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

Run time: NLT 2.5 times the retention time of valproic acid

System suitability
Samples: Acid stage standard solution and Buffer stage standard solution

Suitability requirements
Tailing factor: NMT 2.0 each for the Acid stage standard solution and the Buffer stage standard solution

Relative standard deviation: NMT 2.0% each for the Acid stage standard solution and the Buffer stage standard solution

Analysis
Samples: Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, and Buffer stage sample solutions

Calculate the percentage of the labeled amount (Q) of valproic acid (C₇H₁₄O₂) dissolved in the Acid stage:

\[ \text{Result} = (r_i/r_f) \times C \times V \times (1/L) \times 100 \]

\( r_i = \text{peak response from the Acid stage sample solution} \)

\( r_f = \text{peak response from the Acid stage standard solution} \)

\( C = \text{concentration of USP Valproic Acid RS in the Acid stage standard solution (mg/mL)} \)

\( V = \text{volume of the Acid stage medium, 500 mL} \)

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

Calculate the concentration (C) of valproic acid (C₇H₁₄O₂) in the sample withdrawn from the vessel at each Buffer stage time point i:

\[ \text{Result}_i = (r_i/r_f) \times C \times 100 \]

\( r_i = \text{peak response from the Buffer stage sample solution} \)

\( r_f = \text{peak response from the Buffer stage standard solution} \)

\( C = \text{concentration of USP Valproic Acid RS in the Buffer stage standard solution (mg/mL)} \)

Calculate the percentage of the labeled amount (Q) of valproic acid (C₇H₁₄O₂) dissolved at each Buffer stage time point i:

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

\( C_i = \text{concentration of valproic acid in the Buffer stage sample solution withdrawn at time point } i \text{ (mg/mL)} \)

\( V_i = \text{volume of the Buffer stage medium, 900 mL} \)

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

\( Q_i = \text{percentage of the labeled amount of valproic acid dissolved in the Acid stage} \)

\( V_i = \text{volume of the Buffer stage sample solution withdrawn from the vessel (mL)} \)

Tolerances: See Table 4.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10–30</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>40–70</td>
<td>35–60</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>60–90</td>
<td>50–80</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C₇H₁₄O₂) 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.

Acid stage medium: 0.1 N hydrochloric acid; 500 mL

Buffer stage stock medium: 7.8 g/L of monobasic sodium phosphate dihydrate in water, adjusted with 2 N sodium hydroxide solution to a pH of 5.5

Buffer stage medium: 21.6 g/L of sodium dodecyl sulfate in Buffer stage stock medium; 900 mL

Apparatus 2: 100 rpm, with three-pronged sinkers
**Times:** 45 min in Acid stage medium; 3, 9, 12, and 24 h in Buffer stage medium. The times in the Buffer stage medium do not include the time in the Acid stage medium.

**Procedure:** After 45 min in Acid stage medium, discard the remainder of the Acid stage medium and add the Buffer stage medium.

**Solution A:** Dilute 5 mL of phosphoric acid with water to 25 mL.

**Buffer:** 6.8 g/L of monobasic potassium phosphate in water. Adjust with Solution A to a pH of 3.0.

**Mobile phase:** Acetonitrile and Buffer (40:60), degassed

**Standard stock solution:** 1.4 mg/mL of USP Valproic Acid RS in Mobile phase

**Buffer stage standard solution:** (L/900) mg/mL of valproic acid from Standard stock solution in Buffer stage medium, where L is the Tablet label claim in mg

**Buffer stage sample solution:** Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of Buffer stage medium.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 10-cm; 5-µm packing L1

**Column temperature:** 50°

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

**Run time:** 1 mL/min

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 1.5 times the retention time of valproic acid

**System suitability**

**Sample:** Buffer stage standard solution

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Buffer stage standard solution and Buffer stage sample solutions

Calculate the concentration (C) of valproic acid (C₆H₁₄O₂) in the sample withdrawn from the vessel at each Buffer stage time point i:

\[
\text{Result}_i = \left( \frac{r_i}{r_s} \right) \times C_i
\]

where:

- \( r_i \) = peak response from the Buffer stage sample solution
- \( r_s \) = peak response from the Buffer stage standard solution
- \( C_i \) = concentration of USP Valproic Acid RS in the Buffer stage standard solution (mg/mL)

Calculate the percentage of the labeled amount (Q) of valproic acid (C₆H₁₄O₂) dissolved at each Buffer stage time point i:

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

\[
\text{Result}_1 = \left( \frac{(C_1 \times V_s) + (C_2 \times V_s)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_2 = \left( \frac{(C_2 \times V_s) + (C_3 \times V_s)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_3 = \left( \frac{(C_3 \times V_s) + (C_4 \times V_s)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

where:

- \( C_i \) = concentration of valproic acid in the Buffer stage sample solution withdrawn at time point i (mg/mL)
- \( V_s \) = volume of the Buffer stage medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( V_s \) = volume of the Buffer stage sample solution withdrawn from the vessel (mL)

**Tolerances:** See Table 5.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>45–85</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C₆H₁₄O₂) 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:** pH 6.8 phosphate buffer (6.0 g/L of anhydrous monobasic sodium phosphate in water, adjusted with 240 g/L of sodium hydroxide in water to a pH of 6.8); 900 mL

**Apparatus 2:** 100 rpm

**Times:** 1, 4, 8, and 24 h in Medium

**Buffer:** 6.0 g/L of anhydrous monobasic sodium phosphate in water

**Mobile phase:** Acetonitrile and Buffer (50:50). Adjust with phosphoric acid to a pH of 3.0.

**Standard solution:** (L/900) mg/mL of USP Valproic Acid RS, where L is the label claim in mg/Tablet, prepared as follows. Transfer USP Valproic Acid RS to an appropriate volumetric flask. Add 5% of the flask volume of methanol to dissolve the valproic acid. Dilute with Medium to volume.

**Sample solutions:** Withdraw an aliquot at each time point, and pass a portion of the solution under test through a suitable filter.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 100 µL

**Run time:** NLT 2.5 times the retention time of valproic acid

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solutions

Calculate the concentration (C) of valproic acid (C₆H₁₄O₂) in the sample withdrawn from the vessel at each time point i:

\[
\text{Result}_i = \left( \frac{r_i}{r_s} \right) \times C_i
\]

where:

- \( r_i \) = peak response from the Sample solution
- \( r_s \) = peak response from the Standard solution
- \( C_i \) = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)

Calculate the percentage of the labeled amount (Q) of valproic acid (C₆H₁₄O₂) dissolved at each Buffer stage time point i:

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

\[
\text{Result}_1 = \left( \frac{(C_1 \times V) + (C_2 \times V)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_2 = \left( \frac{(C_2 \times V) + (C_3 \times V)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_3 = \left( \frac{(C_3 \times V) + (C_4 \times V)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_4 = \left( \frac{(C_4 \times V) + (C_5 \times V)}{2} \right) \times \left( \frac{1}{L} \right) \times 100
\]

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Result_{1} = \left( \frac{[C_{1} + (V - (2 \times V_{1}))]}{[C_{2} + (C_{1} \times V_{1})]} \times \frac{1}{L} \right) \times 100

Result_{2} = \left( \frac{[C_{1} + (V - (3 \times V_{1}))]}{[C_{2} + (C_{1} + C_{2}) \times V_{1}]} \times \frac{1}{L} \right) \times 100

C_{1} = \text{concentration of valproic acid in the Sample solution withdrawn at time point } i \text{ (mg/mL)}

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

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

V_{i} = \text{volume of the Sample solution withdrawn from the vessel (mL)}

Tolerances: See Table 6.

<table>
<thead>
<tr>
<th>Time Point (t)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>10–30</td>
<td>10–30</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>25–45</td>
<td>28–48</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>40–60</td>
<td>40–65</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 70</td>
<td>NLT 70</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C_{6}H_{10}O_{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.

Acid stage medium: 0.1 N hydrochloric acid; 500 mL

Buffer stage medium: pH 5.5 phosphate buffer with 75 mM sodium dodecyl sulfate (dissolve 78.0 g of monobasic sodium phosphate dihydrate in 10 L of water, adjust with 10 g/L of sodium hydroxide in water to a pH of 5.5, and add 216.3 g of sodium dodecyl sulfate); 900 mL

Apparatus 2: 100 rpm

Times: 45 min in Acid stage medium; 3, 9, 12, and 24 h in the Buffer stage medium. The times in the Buffer stage medium include the time in the Acid stage medium.

Procedure: After 45 min in the Acid stage medium and the collection of the Acid stage sample solution, discard the remainder of the Acid stage medium and add the Buffer stage medium.

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

Buffer: 3.5 g/L of monobasic sodium phosphate dihydrate in water, adjusted with Solution A to a pH of 3.5, and passed through a suitable filter

Mobile phase: Acetonitrile and Buffer (35:65)

Standard stock solution: 0.7 mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable quantity of USP Valproic Acid RS to an appropriate volumetric flask and dissolve in 10% of the final flask volume of methanol. Sonication may be used to promote dissolution. Dilute with Mobile phase to volume.

Standard solution: 0.14 mg/mL of USP Valproic Acid RS from the Standard stock solution in Mobile phase passed through a suitable filter of 0.45-µm pore size

Analysis

For Tablets labeled to contain 500 mg of valproic acid:

Dilute 5 mL of Buffer stage sample stock solutions with Mobile phase to 20 mL and pass through a suitable filter of 0.45-µm pore size.

Buffer stage sample solutions

For Tablets labeled to contain 250 mg of valproic acid:

Dilute 5 mL of Buffer stage sample stock solutions with Mobile phase to 10 mL and pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 2.0 mL/min

Injection volume: 50 µL

Run time: NLT 2.5 times the retention time of valproic acid

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution, Acid stage sample solution, and Buffer stage sample solutions

Calculate the percentage of the labeled amount (Q_{a}) of valproic acid (C_{6}H_{10}O_{2}) dissolved in the Acid stage:

Result = \left( \frac{r_{i}O_{i}}{C_{i}} \right) \times \frac{V_{i}}{L} \times \frac{1}{100}

r_{i} = \text{peak response from the Acid stage sample solution}

O_{i} = \text{peak response from the Standard solution}

C_{i} = \text{concentration of USP Valproic Acid RS in the Standard solution (mg/mL)}

V_{i} = \text{volume of the Acid stage medium, 500 mL}

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

Calculation of the percentage of the labeled amount of valproic acid (C_{6}H_{10}O_{2}) in the sample withdrawn from the vessel at each Buffer stage time point i:

Result = \left( \frac{r_{i}O_{i}}{C_{i}} \right) \times D

r_{i} = \text{peak response from the Buffer stage sample solution}

O_{i} = \text{peak response from the Standard solution}

C_{i} = \text{concentration of USP Valproic Acid RS in the Standard solution (mg/mL)}

D = \text{dilution factor between the Buffer stage sample solution and the Buffer stage sample stock solution}

Calculate the percentage of the labeled amount of valproic acid (C_{6}H_{10}O_{2}) dissolved at each Buffer stage time point i:

Result_{1} = \left( \frac{C_{i} \times V_{b} \times \left( \frac{1}{L} \right) \times 100}{} \right) + Q_{a}

Result_{2} = \left( \frac{\left( \frac{C_{1} \times V_{1}}{[C_{1} + (C_{2} \times V_{2})]} \times \left( \frac{1}{L} \right) \times 100}{} \right) + Q_{a}

Result_{3} = \left( \frac{\left( \frac{C_{1} \times V_{1}}{[C_{2} + (C_{1} \times V_{2})]} \times \left( \frac{1}{L} \right) \times 100}{} \right) + Q_{a}

Result_{4} = \left( \frac{\left( \frac{C_{1} \times V_{1}}{[C_{2} + (C_{1} + C_{2}) \times V_{1}]} \times \left( \frac{1}{L} \right) \times 100}{} \right) + Q_{a}

C_{i} = \text{concentration of valproic acid in the Buffer stage sample solution withdrawn at time point i (mg/mL)}

V_{b} = \text{volume of the Buffer stage medium, 900 mL}

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

Q_{a} = \text{percentage of the labeled amount of valproic acid dissolved in the Acid stage}
If the product complies with this test, the labeling should indicate that it meets USP Dissolution Test 8.

**Medium:** pH 6.8 phosphate buffer with 2% sodium dodecyl sulfate (20.0 g/L of sodium dodecyl sulfate and 6.9 g/L of monobasic sodium phosphate dihydrate in water, adjusted with 10 g/L of sodium hydroxide in water to a pH of 6.8); 900 mL.

**Apparatus:** 2: 50 rpm

**Times:** 2, 6, 12, and 24 h

**Buffer A:** 0.5 g/L of citric acid and 4 g/L of dibasic sodium phosphate in water

**Buffer B:** 6.8 g/L of monobasic potassium phosphate and 1.7 g/L of sodium hydroxide in water, adjusted with phosphoric acid to a pH of 7.4

**Buffer C:** Buffer A and Buffer B (50:50)

**Mobile phase:** Acetonitrile and Buffer C (30:70), adjusted with phosphoric acid to a pH of 3.0

**Standard solution:** (L/900) mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable quantity of USP Valproic Acid RS to an appropriate volumetric flask and dissolve in 50% of the final volume of Medium. Sonication may be used to promote dissolution. Dilute with Medium to volume.

**Sample solutions:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace with the same volume of Medium.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 3.9-mm × 15-cm; 4-µm packing L11

**Column temperature:** 30°

**Flow rate:** 1.2 mL/min

**Injection volume:** 50 µL

**Run time:** NLT 1.1 times the retention time of valproic acid

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- Tailing factor: NMT 2.0
- Relative standard deviation: NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solutions

Calculate the concentration (C) of valproic acid (C6H9O2) in the sample withdrawn from the vessel at each time point i:

\[
C_i = \frac{V_i 	imes (1/L)}{r_i}
\]

where:

- \(C_i\) = concentration of USP Valproic Acid RS in the Standard solution (mg/mL)
- \(V_i\) = volume of the Sample solution withdrawn at time point i (mg/mL)
- \(L\) = label claim (mg/Tablet)
- \(r_i\) = peak response from the Standard solution
- \(r_s\) = peak response from the Sample solution

The percentage of the labeled amount of valproic acid (C6H9O2) 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:** pH 6.8 phosphate buffer with 2% sodium dodecyl sulfate (20.0 g/L of sodium dodecyl sulfate and 6.9 g/L of monobasic sodium phosphate dihydrate in water, adjusted with 10 g/L of sodium hydroxide in water to a pH of 6.8); 900 mL.

**Apparatus:** 2: 50 rpm

**Time points:** 1 3 10–35 18–38 2 6 35–60 55–90 3 12 55–90 4 24 NLT 80

**Times:** 2, 6, 12, and 24 h

**Buffer A:** 0.5 g/L of citric acid and 4 g/L of dibasic sodium phosphate in water

**Buffer B:** 6.8 g/L of monobasic potassium phosphate and 1.7 g/L of sodium hydroxide in water, adjusted with phosphoric acid to a pH of 7.4

**Buffer C:** Buffer A and Buffer B (50:50)

**Mobile phase:** Acetonitrile and Buffer C (30:70), adjusted with phosphoric acid to a pH of 3.0

**Standard solution:** (L/900) mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable quantity of USP Valproic Acid RS to an appropriate volumetric flask and dissolve in 50% of the final volume of Medium. Sonication may be used to promote dissolution. Dilute with Medium to volume.

**Sample solutions:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace with the same volume of Medium.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.1 times the retention time of valproic acid

The percentage of the labeled amount of valproic acid (C6H9O2) dissolved at the times specified conform to Dissolution (711), Acceptance Table 1.

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

**Medium:** pH 6.8 phosphate buffer with 75 mM sodium dodecyl sulfate (130 g/L of sodium dodecyl sulfate in water and pH 6.8 buffer (8.3 g/L of monobasic sodium phosphate in water, adjusted with 5 N hydrochloric acid or 5 N sodium hydroxide to a pH of 6.8 and then degassed (17:83)); 900 mL.

**Apparatus:** 2: 100 rpm, with spiral sinkers

**Time points:** 1 2 10–35 18–38 2 6 35–60 55–90 3 12 55–90 4 24 NLT 80

**Times:** 2, 6, 12, and 24 h

**Buffer:** 6.8 g/L of monobasic potassium phosphate and 1.7 g/L of sodium hydroxide in water, adjusted with phosphoric acid to a pH of 7.4

**Buffer C:** Buffer A and Buffer B (50:50)

**Mobile phase:** Acetonitrile and Buffer C (30:70), adjusted with phosphoric acid to a pH of 3.0

**Standard solution:** (L/900) mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable quantity of USP Valproic Acid RS to an appropriate volumetric flask and dissolve in 10% of the final volume of acetonitrile. Dilute with Medium to volume.

**Sample solutions:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace with the same volume of Medium.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 4.6-mm × 15-cm; 5-µm packing L7

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 1.1 times the retention time of valproic acid

The percentage of the labeled amount of valproic acid (C6H9O2) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Table 7**

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>10–35</td>
<td>18–38</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>35–55</td>
<td>47–72</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>45–65</td>
<td>55–90</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 80</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C6H9O2) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

The percentage of the labeled amount of valproic acid (C6H9O2) dissolved at the times specified conform to Dissolution (711), Acceptance Table 1.
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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) of valproic acid (C_3H_8O_2) in the sample withdrawn from the vessel at each time point i:

$$\text{Result}_i = \frac{r_i}{r_s} \times C_i$$

Calculate the percentage of the labeled amount of valproic acid (C_3H_8O_2) dissolved at each time point i:

$$\frac{\text{Result}_i}{\text{label claim (mg/Tablet)}} \times \frac{V}{L} = \frac{C_i \times V \times (1/L) \times 100}{V_s}$$

Tolerances: See Table 9.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15–40</td>
</tr>
<tr>
<td>2</td>
<td>40–70</td>
</tr>
<tr>
<td>3</td>
<td>50–85</td>
</tr>
<tr>
<td>4</td>
<td>NLT 70</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C_3H_8O_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.

Acid stage medium: 0.1 N hydrochloric acid, degassed; 500 mL
Buffer stage medium: pH 5.5 phosphate buffer with 75 mM sodium dodecyl sulfate (21.6 g/L of sodium dodecyl sulfate, 6.9 g/L of monobasic sodium phosphate, and 0.12 g/L of sodium hydroxide in water, adjusted with diluted phosphoric acid or diluted sodium hydroxide to pH of 5.5); 900 mL
Apparatus 2: 100 rpm
Tubes: 45 min in Acid stage medium; 3, 9, and 15 h in Buffer stage medium. After 45 min in the Acid stage medium, discard the excess Acid stage medium and use the same Tablets in the Buffer stage medium. The time in the Buffer stage medium does not include the time in the Acid stage medium.

Buffer A: 0.5 g/L of citric acid and 0.4 g/L of anhydrous dibasic sodium phosphate in water

Buffer B: 6.8 g/L of monobasic potassium phosphate and 1.7 g/L of sodium hydroxide in water, adjusted with diluted phosphoric acid to a pH of 7.4

Mobile phase: Acetonitrile, Buffer A, and Buffer B (50:25:25). Adjust with diluted phosphoric acid to a pH of 3.0

Acid stage standard solution: (L/5000) mg/mL of USP Valproic Acid RS in Acid stage medium where L is the label claim of valproic acid in mg/Tablet
Buffer stage standard solution: (L/900) mg/mL of USP Valproic Acid RS in Buffer stage medium where L is the label claim of valproic acid in mg/Tablet

Acid stage sample solution: Pass a portion of the solution under test through a suitable filter, discard the first 2 mL, and use the filtrate.
Buffer stage sample solution: Pass a portion of the solution under test through a suitable filter. Replace with the same volume of Buffer stage medium.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Flow rate: 1.8 mL/min
Injection volume: 50 µL
Run time: NLT 2 times the retention time of valproic acid

System suitability
Samples: Acid stage standard solution and Buffer stage standard solution
Suitability requirements
Tailing factor: NMT 2.0, Acid stage standard solution and Buffer stage standard solution
Relative standard deviation: NMT 2.0%, Acid stage standard solution and Buffer stage standard solution

Analysis
Samples: Acid stage standard solution, Buffer stage standard solution, Acid stage sample solution, and Buffer stage sample solution
Calculate the percentage (Q_a) of the labeled amount of valproic acid (C_3H_8O_2) dissolved in the Acid stage:

$$\text{Result} = \frac{R_i}{R_s} \times C_i \times V \times (1/L) \times 100$$

The concentration of USP Valproic Acid RS in the Sample solution withdrawn at each time point i:

$$\text{Result}_i = \frac{(C_i \times (V - V_i)) + (C_i \times V_i) \times (1/L) \times 100}{V_s}$$

Calculate the concentration (C) of valproic acid (C_3H_8O_2) in the sample withdrawn from the vessel at each time point i:

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

Calculate the percentage of the labeled amount of valproic acid (C_3H_8O_2) dissolved at each time point i:

$$\frac{\text{Result}_i}{\text{label claim (mg/Tablet)}} \times \frac{V}{L} = \frac{C_i \times V \times (1/L) \times 100}{V_s}$$
If the product complies with this test, the labeling should indicate that it meets USP Dissolution Test 11, Acceptance Table 2.

### Test 11: Dissolution Test

#### Acid stage: NMT 10%

**Buffer stage:** See Table 10.

<table>
<thead>
<tr>
<th>Time Point (h)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>15–40</td>
</tr>
<tr>
<td>2</td>
<td>9</td>
<td>40–70</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C₇H₁₃O₂) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

#### Analysis

Calculate the percentage of the labeled amount of valproic acid (C₇H₁₃O₂) dissolved during the Acid stage (Qₐ):

$$\text{Result} = \left( \frac{r_o}{r_s} \right) \times C_o \times \left( \frac{1}{L} \right) \times 100$$

$$r_o = \text{peak response from the Acid stage sample solution}$$
$$r_s = \text{peak response from the Acid stage standard solution}$$
$$C_o = \text{concentration of USP Valproic Acid RS in the Acid stage standard solution (mg/mL)}$$
$$V_o = \text{volume of the Acid stage medium, 500 mL}$$
$$L = \text{label claim (mg/Tablet)}$$

Calculate the concentration (Cₐ) of valproic acid (C₇H₁₃O₂) in the sample withdrawn from the vessel at each Buffer stage time point: $r_i = \left( \frac{r_o}{r_s} \right) \times C_o$

Calculate the percentage of the labeled amount of valproic acid (C₇H₁₃O₂) dissolved during the Buffer stage (Qₐ):

$$\text{Result} = \left( \frac{r_o}{r_s} \right) \times C_o \times \left( \frac{1}{L} \right) \times 100$$

$$r_o = \text{peak response from the Acid stage sample solution}$$
$$r_s = \text{peak response from the Acid stage standard solution}$$
$$C_o = \text{concentration of USP Valproic Acid RS in the Buffer stage standard solution (mg/mL)}$$
$$V_o = \text{volume of the Buffer stage medium, 900 mL}$$
$$L = \text{label claim (mg/Tablet)}$$

#### Tolerances

**Acid stage:** NMT 10% of the labeled amount of valproic acid is dissolved in 45 min

**Buffer stage:** See Table 11.
The percentage of the labeled amount of valproic acid \((\text{C}_8\text{H}_{16}\text{O}_2)\) dissolved at the times specified conform to the requirements of **Dissolution (711), Acceptance Table 2.**

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and 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 Valproic Acid RS

### Table 11

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%)</th>
<th>Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>NMT 20</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>32–52</td>
<td>40–60</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>48–68</td>
<td>57–77</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>NLT 80</td>
<td>NLT 80</td>
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</tbody>
</table>