In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 4 Expert Committee has revised the Divalproex Sodium Delayed-Release Capsules monograph. The purpose for the revision is to add Dissolution Test 5 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

- Dissolution Test 5 was validated using a Novapak Phenyl brand of L11 column. The typical retention time for valproic acid is about 6 min.

The Divalproex Sodium Delayed-Release Capsules Revision Bulletin supersedes the currently official monograph.

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

DEFINITION
Divalproex Sodium Delayed-Release Capsules contain an amount of divalproex sodium equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of valproic acid (C₈H₁₆O₂).

IDENTIFICATION

• A. Spectroscopic Identification Tests (197), Infrared Spectroscopy: 197K
  Diluent: Acetonitrile and water (1:1)
  Standard: Prepare as directed in 197F using USP Valproic Acid RS.
  Sample: Dissolve the contents of 20 Capsules in 30 mL of Diluent in a 50-mL volumetric flask. Sonicate for 30 min to dissolve. Dilute with Diluent to volume. Centrifuge the solution at 3000 rpm for about 20 min. Pipet 20 mL of the supernatant into a separatory funnel. Extract with 50 mL of n-hexane. Collect the n-hexane layer and evaporate the solvent. Cast 1 mg of the liquid obtained after evaporation to sodium chloride (NaCl) windows.

• 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
  Buffer: 6.8 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.0.
  Mobile phase: Acetonitrile and Buffer (2:3)
  Diluent: Acetonitrile and water (1:1)
  Standard solution: Transfer a suitable amount of USP Valproic Acid RS to a suitable volumetric flask to obtain a solution having a final concentration of 2.5 mg/mL of valproic acid. Add 40% of the flask volume of Diluent. Sonicate for 5 min and add 20% of the flask volume of 0.1 N hydrochloric acid. Dilute with Diluent to volume.
  Sample solution: Transfer an amount of contents (from NLT 20 Capsules) to a suitable volumetric flask to obtain a nominal concentration of 2.5 mg/mL of valproic acid. Dissolve in 20% of the flask volume of 0.1 N hydrochloric acid and sonicate for 5 min. Add 60% of the flask volume of Diluent and sonicate for an additional 25 min. Dilute with Diluent to volume. Centrifuge at 4000 rpm for 10 min and use the clear supernatant.

Chromatographic system
(See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 215 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Flow rate: 1.8 mL/min
  Injection volume: 20 µL

System suitability
  Sample: Standard solution
  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 (C$_8$H$_{16}$O$_2$) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- $r_U$ = 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)
- $C_U$ = nominal concentration of valproic acid in the Sample solution (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** (711)

Test 1

Medium: Phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate and 1.64 g/L of sodium hydroxide in water; adjusted with 0.08 N hydrochloric acid TS to a pH of 7.5); 500 mL, degassed

Apparatus 2: 50 rpm, with sinkers

Times: 2, 4, and 6 h

Buffer and Mobile phase: Prepare as directed in the Assay.

Standard stock solution: 1.6 mg/mL of USP Valproic Acid RS in Mobile phase

Standard solution: 0.26 mg/mL of valproic acid from the Standard stock solution and Medium

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the volume withdrawn with an equal volume of Medium previously heated at 37.0 ± 0.5°C.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 210 nm

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

Flow rate: 1.8 mL/min

Injection volume: 40 µL

System suitability

Sample: Standard solution

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 concentration ($C_i$) of valproic acid (C$_8$H$_{16}$O$_2$) in the sample withdrawn from the vessel at each time point ($i$):
Result_1 = (r_U / r_S) \times C_S \\
\quad r_U = \text{peak response from the Sample solution} \\
\quad r_S = \text{peak response from the Standard solution} \\
\quad C_S = \text{concentration of the Standard solution (mg/mL)} \\
Calculate the percentage of the labeled amount of valproic acid (C_{8H_{16}O_{2}}) dissolved at each time point (i):

Result_1 = C_1 \times V \times (1/L) \times 100 \\
Result_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100 \\
Result_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100 \\
\quad C_i = \text{concentration of valproic acid in the portion of sample withdrawn at the specified time point (mg/mL)} \\
\quad V = \text{volume of Medium, 500 mL} \\
\quad L = \text{label claim (mg/Capsule)} \\
\quad V_S = \text{volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)} \\

Tolerances: See Table 1.

Table 1

<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>15–40</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>70–90</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid (C_{8H_{16}O_{2}}) dissolved at each time point conforms to Dissolution (711), Acceptance Table 2.

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

Procedure A

Medium: 0.05 M phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate and 1.64 g/L of sodium hydroxide in water; adjusted with 2 N sodium hydroxide to a pH of 7.5); 500 mL

Apparatus 2: 50 rpm, contents of the Capsule

Time: 15 min

Standard solution A: 0.036 mg/mL of USP Valproic Acid RS in Medium. A volume of acetonitrile not exceeding 10% of the total volume may be used to dissolve the valproic acid.

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

Procedure B

Medium: 0.05 M phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate and 1.64 g/L of sodium hydroxide in water; adjusted with 2 N sodium hydroxide to a pH of 7.5); 900 mL
Apparatus 2: 50 rpm, with wire helix sinkers
Time: 4 h
Buffer A: 0.5 g/L of citric acid and 0.4 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
Mobile phase: Acetonitrile, Buffer A, and Buffer B (30:35:35); adjusted with phosphoric acid to a pH of 3.0
Standard solution B: 0.13 mg/mL of USP Valproic Acid RS in Medium. A volume of acetonitrile not exceeding 10% of the total volume may be used to dissolve the valproic acid.
Sample solution B: 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 210 nm
Column: 3.9-mm × 15-cm; 4-µm packing L11
Flow rate: 1.2 mL/min
Injection volume: 200 µL for Standard solution A and Sample solution A; 50 µL for Standard solution B and Sample solution B

System suitability
Sample: Standard solution B
Suitability requirements
Tailing factor: NMT 2.0 for valproic acid
Relative standard deviation: NMT 2.0% for valproic acid

Analysis
Samples: Standard solution A, Sample solution A, Standard solution B, and Sample solution B

Calculate the percentage of the labeled amount of valproic acid (C₈H₁₆O₂) dissolved at each time point:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times 100
\]

\( r_U \) = peak response from Sample solution A or Sample solution B
\( r_S \) = peak response from Standard solution A or Standard solution B
\( C_S \) = concentration of Standard solution A or Standard solution B (mg/mL)
\( L \) = label claim (mg/Capsule)
\( V \) = volume of Medium; 500 mL for Sample solution A, 900 mL for Sample solution B

Tolerances: NMT 20% of the labeled amount of valproic acid (C₈H₁₆O₂) is dissolved in 15 min (Sample solution A); NLT 80% (Q) of the labeled amount of valproic acid (C₈H₁₆O₂) is dissolved in 4 h (Sample solution B). The percentage of the labeled amount of valproic acid (C₈H₁₆O₂) dissolved at 4 h conforms to Dissolution (711), Acceptance Table 1.

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

Medium
Acid stage medium: 0.08 N hydrochloric acid TS; 900 mL
**Buffer stage medium:** Phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate and 1.6 g/L of sodium hydroxide in water, prepared as follows. Transfer suitable quantities of monobasic potassium phosphate and sodium hydroxide to a suitable volumetric flask. Dissolve in 83% of the flask volume of water and adjust with 0.1 N hydrochloric acid, if necessary, to a pH of 7.5. Dilute the resulting solution with water to volume.); 900 mL

**Times**
- **Acid stage:** 2 h
- **Buffer stage:** 4 h

**Apparatus 2:** 50 rpm, with sinkers

**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

**Mobile phase:** Acetonitrile and Buffer (45:55); mixed, degassed, and adjusted with phosphoric acid to a pH of 2.5

**Standard solution:** 0.14 mg/mL of USP Valproic Acid RS prepared as follows. Transfer a portion of USP Valproic Acid RS to a suitable volumetric flask. Dissolve in methanol using 5.0% of the final volume. Dilute with Buffer stage medium to final volume and mix.

**Sample solutions**
- **Acid stage sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate.
- **Buffer stage sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate.

**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:** 1 mL/min
- **Injection volume:** 50 µL

**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 solution

  Calculate the percentage of the labeled amount of valproic acid (C8H16O2) dissolved at each time point:

\[
\text{Result} = \frac{r_U}{r_S} \times \frac{C_S}{L} \times V \times 100
\]

- \(r_U\) = peak response from the Acid stage sample solution or the Buffer stage sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of the Standard solution (mg/mL)
- \(L\) = label claim (mg/Capsule)
- \(V\) = volume of the Acid stage medium or the Buffer stage medium, 900 mL
Tolerances: The requirements for the Acid stage and the Buffer stage must be met. 

**Acid stage:** NMT 30% \((Q)\) of the labeled amount of valproic acid \((\text{C}_8\text{H}_{16}\text{O}_2)\) is dissolved in 2 h (**Acid stage sample solution**). The percentage of the labeled amount of valproic acid \((\text{C}_8\text{H}_{16}\text{O}_2)\) dissolved at 2 h conforms to **Table 2**.

<table>
<thead>
<tr>
<th>Level</th>
<th>Number Tested</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A_1)</td>
<td>6</td>
<td>No individual value exceeds (Q) dissolved.</td>
</tr>
<tr>
<td>(A_2)</td>
<td>6</td>
<td>Average of the 12 units ((A_1 + A_2)) is NMT (Q) dissolved; and no individual unit is greater than (Q + 15%) dissolved.</td>
</tr>
<tr>
<td>(A_3)</td>
<td>12</td>
<td>Average of the 24 units ((A_1 + A_2 + A_3)) is NMT (Q) dissolved; and no individual unit is greater than (Q + 15%) dissolved.</td>
</tr>
</tbody>
</table>

**Buffer stage:** NLT 80% \((Q)\) of the labeled amount of valproic acid \((\text{C}_8\text{H}_{16}\text{O}_2)\) is dissolved in 4 h (**Buffer stage sample solution**). The percentage of the labeled amount of valproic acid \((\text{C}_8\text{H}_{16}\text{O}_2)\) dissolved at 4 h conforms to **Dissolution (711), Acceptance Table 2**.

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

**Medium:** 0.05 M phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate in water; adjusted with 2 N sodium hydroxide to a pH of 7.5); 500 mL

**Apparatus 2:** 50 rpm

**Times:** 2, 4, and 8 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

**Mobile phase:** Acetonitrile, Buffer A, and Buffer B \((30:35:35)\); adjusted with phosphoric acid to a pH of 3.0

**Standard solution:** 0.25 mg/mL of USP Valproic Acid RS in Medium

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

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 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 1.5 times the retention time of valproic acid

**System suitability**
**Sample: Standard solution**

**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 concentration \((C_i)\) of valproic acid \((C_8H_{16}O_2)\) in the sample withdrawn from the vessel at each time point \((i)\):

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

- \(r_U\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of the Standard solution \((\text{mg/mL})\)

Calculate the percentage of the labeled amount of valproic acid \((C_8H_{16}O_2)\) dissolved at each time point \((i)\):

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

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

\[
\text{Result}_3 = \left\{ \left[ C_2 \times (V - (2 \times V_S)) \right] + \left[ (C_2 + C_i) \times V_S \right] \right\} \times \left( \frac{1}{L} \right) \times 100
\]

- \(C_i\) = concentration of valproic acid in the portion of sample withdrawn at the specified time point \((\text{mg/mL})\)
- \(V\) = volume of Medium, 500 mL
- \(L\) = label claim \((\text{mg/Capsule})\)
- \(V_S\) = volume of the Sample solution withdrawn at each time point \((\text{mL})\)

**Tolerances:** See Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((\text{NLT %}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>80</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid \((C_8H_{16}O_2)\) dissolved at each time point conforms to Dissolution (711), Acceptance Table 4.

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

**Medium:** 0.05 M phosphate buffer, pH 7.5 (6.8 g/L of monobasic potassium phosphate and 1.64 g/L of sodium hydroxide in water; adjusted with 2 N sodium hydroxide to a pH of 7.5); 900 mL, deaerated

**Apparatus 2:** 50 rpm with suitable sinkers
**Times:** 1 and 4 h

**Buffer A:** 0.5 g/L of citric acid and 0.4 g/L of dibasic sodium phosphate in water; adjusted with phosphoric acid to a pH of 7.4

**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 3.0

**Mobile phase:** Acetonitrile, Buffer A, and Buffer B (30:35:35); adjusted with phosphoric acid to a pH of 3.0

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

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 2–3 mL of the filtrate.

**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:** 1.2 mL/min

**Injection volume:** 50 µL

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

**System suitability**

**Sample:** Standard solution

**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 concentration \((C_i)\) of valproic acid \((C_8H_{16}O_2)\) in the sample withdrawn from the vessel at each time point \((i)\):

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

- \(r_U\) = peak response from the Sample solution
- \(r_S\) = peak response from the Standard solution
- \(C_S\) = concentration of the Standard solution (mg/mL)

Calculate the percentage of the labeled amount of valproic acid \((C_8H_{16}O_2)\) dissolved at each time point \((i)\):

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

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

- \(C_i\) = concentration of valproic acid in the portion of sample withdrawn at the specified time point (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 (mL)

**Tolerances:** See *Table 4*.  

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**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>1</td>
<td>NMT 25</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentage of the labeled amount of valproic acid ($\text{C}_8\text{H}_{16}\text{O}_2$) dissolved at each time point conforms to *Dissolution (711), Acceptance Table 2*.\(^\text{▲}(\text{RB 1-Apr-2021})\)

- **Uniformity of Dosage Units (905)**: Meet the requirements

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage**: Preserve in tight, light-resistant containers at controlled room temperature.
- **Labeling**: Divalproex Sodium Delayed-Release Capsules may be swallowed whole or may be administered by carefully opening the Capsule and sprinkling the entire contents on a small amount of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. 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