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. **INFRARED ABSORPTION** (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 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
- Standard solution: Prepare as directed in Assay. Dilute with Diluent to obtain a nominal concentration of 2.5 mg/mL of USP Valproic Acid RS in the Sample solution.
- Mobile phase: Acetonitrile and water (1:1)
- Buffer: Phosphoric acid, pH 3.0
- Mobile phase: Acetonitrile and Buffer (2:3)
- Diluent: Acetonitrile and water (1:1)

**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
- Absolute amount of valproic acid (C8H16O2) dissolved (D) at each time interval:
  \[ D = (D_1 / V) \times V \times 100 \]
- \( D_1 \) = peak response from the Standard solution
- \( D_2 \) = peak response from the Sample solution
- \( V \) = volume of Medium, 500 mL
- Percentage of valproic acid dissolved at 2 h = \( D_1 \)
- Percentage of valproic acid dissolved at 4 h = \( D_2 + \left( \frac{D_2}{V} \times V \right) \)
- Percentage of valproic acid dissolved at 6 h = \( D_3 + \left( \frac{D_3}{V} \times V \right) \)
- \( V \) = volume of Medium, 500 mL
- \( V_s \) = volume withdrawn at each sampling time (mL)

**Tolerances:** 15%–40% (NLT 1-Apr-2015) (Q) of the labeled amount of valproic acid (C8H16O2) is dissolved in 2 h; 70%–90% (NLT 1-Apr-2015) (Q) of the labeled amount of valproic acid (C8H16O2) is dissolved in 4 h; and NLT 100.0% of the labeled amount of valproic acid (C8H16O2) is dissolved in 6 h.

\[ C_r = \text{concentration of USP Valproic Acid RS in the Standard solution (mg/mL)} \]
\[ C_0 = \text{nominal concentration of valproic acid in the Sample solution (mg/mL)} \]

**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 to a pH of 7.5); 500 mL, degassed
    - Apparatus: 2: 50 rpm, with sinkers
    - Time: 2, 4, and 6 h
  - Buffer and Mobile phase: Prepare as directed in the Assay.
  - Standard 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.

**Acceptance criteria:** NLT 90.0% at 2 h; NLT 95.0% at 4 h; NLT 99.5% at 6 h.
Divalproex

85% (Q) of the labeled amount of valproic acid (C8H16O2) is dissolved in 6 h.

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 monohydrate 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 x 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:

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

\(r_u\) = peak response from Sample solution A or Sample solution B

\(r_s\) = peak response from Standard solution A or Standard solution B

\(C\) = 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; 900 mL

Buffer stage medium: pH 7.5 phosphate buffer (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 85% 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 monohydrate, 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 4 h methanol using 5.0% of the final volume. Dilute with Buffer stage medium to final volume and mix.

Sample solution B

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 x 15-cm; 4-µm packing L11

Flow rate: 1 mL/min

Injection volume: 50 µL

System suitability

Sample: Standard solution B

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:

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

\(r_u\) = peak response from the Acid stage sample solution or the Buffer stage sample solution

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

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\(C_s\) = 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

**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 1.

**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.

**Tolerances:** The requirements for the Acid stage and the Buffer stage must be met.

### Table 1

<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>

**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 R5

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