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Divalproex Sodium Delayed-Release Capsules

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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 ($C_8H_{16}O_2$).

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 ($C_8H_{16}O_2$) in the portion of Capsules taken:

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

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 $37.0 \pm 0.5^\circ$.

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 ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each time point (i):

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

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):

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

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

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

C_i = concentration of valproic acid in the portion of sample withdrawn at the specified time point (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Capsule)

V_S = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

Tolerances: See [Table 1](#).

Table 1

Time Point (i)	Time (h)	Amount Dissolved (%)
1	2	15–40
2	4	70–90
3	6	NLT 85

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- μ m 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- μ m pore size.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm $\times$ 15-cm; 4- μ m packing [L11](#)

Flow rate: 1.2 mL/min

Injection volume: 200 μ L for *Standard solution A* and *Sample solution A*; 50 μ L 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 ($C_8H_{16}O_2$) dissolved at each time point:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

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 ($C_8H_{16}O_2$) is dissolved in 15 min (*Sample solution A*). NLT 80% of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved in 4 h (*Sample solution B*). The percentage of the labeled amount of valproic acid