Divalproex Sodium Delayed-Release Capsules

Type of Posting	Revision Bulletin
Posting Date	29–July–2016
Official Date	01–Aug–2016
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 Delayed-Release Capsules monograph. The purpose for the revision is to add *Dissolution Test 4* to support a drug product that has been approved by the FDA and to clarify the acceptance criteria for *Dissolution Test 1*.

- *Dissolution Test 4* was validated using a Novapak Phenyl brand of L11 column manufactured by Waters Corp. The typical retention time for valproic acid is about 5.8 min.
- Additionally, minor editorial changes have been made to update the monograph to current *USP* style.

The Divalproex Sodium Delayed-Release Capsules Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the *First Supplement to USP 40–NF 35*.

Should you have any questions, please contact Heather Joyce, Ph.D., Senior Scientific Liaison (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 ($C_8H_{16}O_2$).

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 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• (RB 1-Aug-2016) 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°.
  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):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

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

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)● (RB 1-Aug-2016)

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*.● (RB 1-Aug-2016)

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 ($C_8H_{16}O_2$) 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% ●(*Q*)● (RB 1-Aug-2016) of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved in 15 min (*Sample solution A*); NLT 80% (*Q*) 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 ($C_8H_{16}O_2$) 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;● (RB 1-Aug-2016) 900 mL

Buffer stage medium: ●Phosphate buffer, pH 7.5● (RB 1-Aug-2016) (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 ($C_8H_{16}O_2$) dissolved at each time point:
● (RB 1-Apr-2015)

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

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.● (RB 1-Aug-2016)
Acid stage: NMT 30% (Q) of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved in 2 h (*Acid stage sample solution*). The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at 2 h conforms to *Table 2*.

Table 2

Level	Number Tested	Criteria
A_1	6	No individual value exceeds Q dissolved.
A_2	6	Average of the 12 units ($A_1 + A_2$) is NMT Q dissolved; and no individual unit is greater than Q + 15% dissolved.
A_3	12	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.

Buffer stage: NLT 80% (Q) of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved in 4 h (*Buffer stage sample solution*). The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at 4 h conforms to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
● (RB 1-Aug-2016)

●**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):

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

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):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

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

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

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 (mL)

Tolerances: See *Table 3*.

Table 3

Time Point (i)	Time (h)	Amount Dissolved (NLT %)
1	2	60
2	4	70
3	8	80

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*.● (RB 1-Aug-2016)

- **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