## Divalproex Sodium Extended-Release Tablets

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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 ($C_8H_{16}O_2$).

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

**Standard solution:** 1.0 mg/mL of USP Valproic Acid RS from the *Standard stock solution* in *Diluent*

**Sample 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 *Sample stock solution* in *Diluent*

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm. For *Identification B*, use a diode array detector in the range of 190–400 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

**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 Tablets 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% 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.

**Mobile phase:** Methanol and *Buffer* (65:35)

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

**Standard solution:** 0.15 mg/mL of USP Valproic Acid RS from the *Standard stock solution* in the *Buffer stage medium*. [NOTE—Add 40% of the flask volume of methanol before diluting with *Buffer stage medium* to volume.]

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 20-µm pore size. Use the *Sample solution* from the *Acid stage medium* as is. Dilute the *Sample solution* from the *Buffer stage medium* with methanol by a factor of 2.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 210 nm

**Column:** 3.9-mm × 15-cm; 10-µm packing L11

**Column temperature:** 30°

**Flow rate:** 1 mL/min

**Injection volume:** 80 µL

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

**System suitability**

**Sample:** *Standard solution*

**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 ($C_8H_{16}O_2$) dissolved in the *Acid stage medium*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

$r_U$ = 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 ($C_i$) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each time point *i* during the *Buffer stage*:

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

$r_i$ = 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 ($C_8H_{16}O_2$) dissolved at each time point *i* during the *Buffer stage*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = 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 ($C_8H_{16}O_2$) is dissolved.

**Buffer stage:** See *Table 1*.

**Table 1**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 3 | 10–30 | 10–30 |
| 2 | 9 | 35–55 | 35–60 |
| 3 | 12 | 45–70 | 45–75 |
| 4 | 24 | NLT 75 | NLT 75 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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:** 15.53 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 ($C_i$) of valproic acid ($C_8H_{16}O_2$) dissolved at each time point (*i*) using the response of each *Sample solution*.

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at each time point *i* during the *Buffer stage*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = 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 ($C_8H_{16}O_2$) 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)**

| | Time Points (*i*) | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| | **Times** | **3 h** | **9 h** | **12 h** | **21 h** |
| L1 | Individual Tablets | 10%–27% | 35%–70% | 44%–92% | NLT 87% |
| L2 | Average | 10%–27% | 35%–70% | 44%–92% | NLT 87% |
| L2 | Individual Tablets | 0%–37% | 25%–80% | 34%–102% | NLT 77% |
| L3 | Average | 10%–27% | 35%–70% | 44%–92% | NLT 87% |
| 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 times 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 × 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 ($C_i$) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each time point (*i*):

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

$r_i$ = peak response from the *Sample solution* at time point *i*

$r_S$ = peak response from the *Acid stage standard solution* or *Buffer stage standard solution*

$C_S$ = 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 ($C_8H_{16}O_2$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = (C_2 + C_1) \times V \times (1/L) \times 100$$
$$\text{Result}_3 = (C_3 + C_2 + C_1) \times V \times (1/L) \times 100$$
$$\text{Result}_4 = (C_4 + C_3 + C_2 + C_1) \times V \times (1/L) \times 100$$

$C_i$ = 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**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 1 | NMT 10 | NMT 10 |
| 2 | 2 | 5–25 | 5–25 |
| 3 | 12 | 55–75 | 65–85 |
| 4 | 24 | NLT 80 | NLT 80 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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 tribasic sodium 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 ($Q_A$) of valproic acid ($C_8H_{16}O_2$) dissolved in the *Acid stage*:

$$\text{Result} = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

$r_U$ = peak response from the *Acid stage sample solution*
$r_S$ = peak response from the *Acid stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Acid stage standard solution* (mg/mL)
$V_A$ = volume of the *Acid stage medium*, 500 mL
$L$ = label claim (mg/Tablet)

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

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

$r_U$ = peak response from the *Buffer stage sample solution*
$r_S$ = peak response from the *Buffer stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount ($Q_i$) of valproic acid ($C_8H_{16}O_2$) dissolved at each *Buffer stage* time point *i*:

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + Q_A$$
$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + Q_A$$
$$\text{Result}_3 = (\{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + Q_A$$
$$\text{Result}_4 = (\{(C_4 \times V_B) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + Q_A$$

$C_i$ = concentration of valproic acid in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
$V_B$ = volume of the *Buffer stage medium*, 900 mL
$L$ = label claim (mg/Tablet)
$Q_A$ = percentage of the labeled amount of valproic acid dissolved in the *Acid stage*
$V_S$ = volume of the *Buffer stage sample solution* withdrawn from the vessel (mL)

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

**Table 4**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 3 | 10–30 | 10–30 |
| 2 | 9 | 40–70 | 35–60 |
| 3 | 12 | 60–90 | 50–80 |
| 4 | 18 | NLT 85 | NLT 85 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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-prong 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:** 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 ($C_i$) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each *Buffer stage* time point *i*:

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

$r_i$ = peak response from the *Buffer stage sample solution*
$r_S$ = peak response from the *Buffer stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount ($Q_i$) of valproic acid ($C_8H_{16}O_2$) dissolved at each *Buffer stage* time point *i*:

$$\text{Result}_1 = C_1 \times V_B \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V_B) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of valproic acid in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
$V_B$ = 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 5**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 3 | 10–30 |
| 2 | 9 | 40–60 |
| 3 | 12 | 45–85 |
| 4 | 24 | NLT 85 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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 ($C_i$) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each time point *i*:

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

$r_i$ = 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)

Calculate the percentage of the labeled amount ($Q_i$) of valproic acid ($C_8H_{16}O_2$) dissolved at each *Buffer stage* time point *i*:

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of valproic acid in the *Sample solution* withdrawn at time point *i* (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn from the vessel (mL)

**Tolerances:** See *Table 6*.

**Table 6**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 1 | 10–30 | 10–30 |
| 2 | 4 | 25–45 | 28–48 |
| 3 | 8 | 40–60 | 40–65 |
| 4 | 24 | NLT 70 | NLT 70 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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
**Acid stage sample solution:** Withdraw a 10.0-mL aliquot at the time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
**Buffer stage sample stock solutions:** Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*.
**Buffer stage sample solutions**
**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.
**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 ($C_8H_{16}O_2$) dissolved in the *Acid stage*:

$$\text{Result} = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

$r_U$ = peak response from the *Acid stage sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
$V_A$ = volume of the *Acid stage medium*, 500 mL
$L$ = label claim (mg/Tablet)

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

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

$r_i$ = peak response from the *Buffer stage sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
$D$ = dilution factor between the *Buffer stage sample solution* and the *Buffer stage sample stock solution*

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

$$\text{Result}_1 = [C_1 \times V_B \times (1/L) \times 100] + Q_A$$
$$\text{Result}_2 = \{[(C_2 \times V_B) + (C_1 \times V_S)] \times (1/L) \times 100\} + Q_A$$
$$\text{Result}_3 = (\{(C_3 \times V_B) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + Q_A$$
$$\text{Result}_4 = (\{(C_4 \times V_B) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100) + Q_A$$

$C_i$ = concentration of valproic acid in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
$V_B$ = volume of the *Buffer stage medium*, 900 mL
$L$ = label claim (mg/Tablet)
$Q_A$ = percentage of the labeled amount of valproic acid dissolved in the *Acid stage*

$V_S$ = volume of the *Buffer stage sample solution* withdrawn at each time point and replaced with the *Buffer stage medium* (mL)

**Tolerances:** See *Table 7*.

**Table 7**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 3 | 10–35 | 18–38 |
| 2 | 9 | 35–55 | 47–72 |
| 3 | 12 | 45–65 | 55–90 |
| 4 | 24 | NLT 80 | NLT 80 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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); 900mL

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

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

$r_i$ = 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)

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

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$
$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$
$$\text{Result}_4 = \{(C_4 \times V) + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

$C_i$ = concentration of valproic acid in the *Sample solution* withdrawn at time point *i* (mg/mL)
$V$ = volume of *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point and replaced with *Medium* (mL)

**Tolerances:** See *Table 8*.

**Table 8**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 2 | 10–35 |
| 2 | 6 | 35–60 |
| 3 | 12 | 55–90 |
| 4 | 24 | NLT 80 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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

**Times:** 2, 8, 12, and 24 h

**Buffer:** 6.8 g/L of monobasic potassium phosphate in water, adjusted with phosphoric acid to a pH of 2.2 and passed through a suitable filter

**Mobile phase:** Methanol, acetonitrile, and *Buffer* (50:10:40)

**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 solution:** 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
**Flow rate:** 1 mL/min
**Injection volume:** 10 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 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*:

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

$r_i$ = 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)

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

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of valproic acid in the *Sample solution* withdrawn at time point *i* (mg/mL)
$V$ = volume of the *Medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Sample solution* withdrawn at each time point *i* (mL)

**Tolerances:** See *Table 9*.

**Table 9**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 2 | 15–40 |
| 2 | 8 | 40–70 |
| 3 | 12 | 50–85 |
| 4 | 24 | NLT 70 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) 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 a pH of 5.5); 900 mL
**Apparatus 2:** 100 rpm
**Times:** 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 ($C_8H_{16}O_2$) dissolved in the *Acid stage*:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

$r_U$ = peak response from the *Acid stage sample solution*
$r_S$ = peak response from the *Acid stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Acid stage standard solution* (mg/mL)
$V$ = volume of *Acid stage medium*, 500 mL
$L$ = label claim (mg/Tablet)

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*:

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

$r_i$ = peak response from the *Buffer stage sample solution*
$r_S$ = peak response from the *Buffer stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Buffer stage 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*:

$$\text{Result}_1 = [C_1 \times V \times (1/L) \times 100] + Q_A$$
$$\text{Result}_2 = \{[(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100\} + Q_A$$

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

$C_i$ = concentration of valproic acid in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
$V$ = volume of *Buffer stage medium*, 900 mL
$L$ = label claim (mg/Tablet)
$Q_A$ = percentage of the labeled amount of valproic acid dissolved in the *Acid stage*
$V_S$ = volume of the *Buffer stage sample solution* withdrawn at each time point and replaced with the *Buffer stage medium* (mL)

**Tolerances**
**Acid stage:** NMT 10%
**Buffer stage:** See *Table 10*.

**Table 10**

| Time Point (*i*) | Time (h) | Amount Dissolved (%) |
|---|---|---|
| 1 | 3 | 15–40 |
| 2 | 9 | 40–70 |
| 3 | 15 | NLT 85 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

▲**Test 11:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11*.
**Acid stage medium:** 0.1 N hydrochloric acid VS; 500 mL, degassed
**Buffer stage medium:** 0.05 M phosphate buffer with 75 mM sodium dodecyl sulfate (6.9 g/L of monobasic sodium phosphate and 21.6 g/L of sodium dodecyl sulfate in water, sonicated for 30 min to promote dissolution, and adjusted with 1 N sodium hydroxide VS to a pH of 5.5); 900 mL
**Apparatus 2:** 100 rpm, with suitable sinkers
**Times:** 45 min in *Acid stage medium*; 1.5, 6, 9, and 21 h in *Buffer stage medium*. The time in the *Buffer stage medium* includes the time in the *Acid stage medium*.
**Procedure:** After 45 min in *Acid stage medium*, discard the *Acid stage medium* and replace with the *Buffer stage medium*.
**Buffer:** 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.
**Mobile phase:** Acetonitrile and *Buffer* (50:50)
**Standard stock solution:** 2.75 mg/mL of USP Valproic Acid RS in methanol
**Acid stage standard solution:** (*L*/9100) mg/mL of valproic acid from *Standard stock solution* in *Acid stage medium*, where *L* is the label claim in mg/Tablet
**Buffer stage standard solution:** (*L*/910) mg/mL of valproic acid from *Standard stock solution* in *Buffer stage medium*, where *L* is the label claim in mg/Tablet
**Acid stage sample solution:** Pass a portion of the solution under test through a suitable filter and use the filtrate after discarding the first 2–3 mL.
**Buffer stage sample solution:** Pass a portion of the solution under test through a suitable filter and use the filtrate after discarding the first 2–3 mL.
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 210 nm
**Column:** 4.6-mm × 15-cm; 5-µm packing L7
**Temperatures**
**Autosampler:** 20°
**Column:** 45°
**Flow rate:** 1.5 mL/min
**Injection volume:** 100 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 of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved during the *Acid stage* ($Q_A$):

$$\text{Result} = (r_U/r_S) \times C_S \times V_A \times (1/L) \times 100$$

$r_U$ = peak response from the *Acid stage sample solution*
$r_S$ = peak response from the *Acid stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Acid stage standard solution* (mg/mL)
$V_A$ = volume of the *Acid stage medium*, 500 mL
$L$ = label claim (mg/Tablet)

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

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

$r_i$ = peak response from the *Buffer stage sample solution*
$r_S$ = peak response from the *Buffer stage standard solution*
$C_S$ = concentration of USP Valproic Acid RS in the *Buffer stage 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* during the *Buffer stage*:

$$\text{Result}_1 = C_1 \times V_B \times (1/L) \times 100$$
$$\text{Result}_2 = \{[C_2 \times (V_B - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$
$$\text{Result}_3 = (\{C_3 \times [V_B - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$
$$\text{Result}_4 = (\{C_4 \times [V_B - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

$C_i$ = concentration of valproic acid in the *Buffer stage sample solution* withdrawn at time point *i* (mg/mL)
$V_B$ = volume of the *Buffer stage medium*, 900 mL
$L$ = label claim (mg/Tablet)
$V_S$ = volume of the *Buffer stage 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 is dissolved in 45 min
**Buffer stage:** See *Table 11*.

**Table 11**

| Time Point (*i*) | Time (h) | Amount Dissolved, Tablets labeled to contain 500 mg of valproic acid (%) | Amount Dissolved, Tablets labeled to contain 250 mg of valproic acid (%) |
|---|---|---|---|
| 1 | 1.5 | NMT 20 | NMT 20 |
| 2 | 6 | 32–52 | 40–60 |
| 3 | 9 | 48–68 | 57–77 |
| 4 | 21 | NLT 80 | NLT 80 |

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*. ▲ (RB 19-Nov-2019)

- **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

## 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