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*.

ASSAY

• **PROCEDURE**

Buffer: 0.5 g of citric acid monohydrate and 0.4 g of dibasic sodium phosphate in 1 L of water

Mobile phase: Methanol and *Buffer* (11:9). Adjust with 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: Transfer an amount of powder (from NLT 20 Tablets) to a suitable volumetric flask to obtain a nominal concentration of 2.5 mg/mL of valproic acid. Dissolve in 50% of the flask volume of methanol by shaking for 1 h. Dilute with methanol to volume, and pass through a suitable filter.

Sample solution: 1.0 mg/mL of valproic acid from the filtrate of the *Sample stock solution* in *Diluent*

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: 0.7 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 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 of sodium dodecyl sulfate, 6.9 g of sodium dihydrogen phosphate monohydrate, and 0.12 g of sodium hydroxide in 1 L of water. Adjust with diluted sodium hydroxide or 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,• (RB 1-May-2012) 12, and 24 h in the *Buffer stage medium*
Analysis: 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 of dibasic sodium phosphate and 0.5 mL of glacial acetic acid in 1 L of water. Adjust with phosphoric acid to a pH of 2.5.
Mobile phase: Methanol and *Buffer* (13:7)
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 solutions: 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: 6 min
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 solutions* 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*:

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

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)
L = label claim (mg/Tablet)
V_A = volume of the *Acid stage medium*, 500 mL

Calculate the concentration of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the time interval, *t*, in mg/mL:

$$C_t = (r_U/r_S) \times (C_S \times D_U)$$

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)
D_U = dilution factor of the *Sample solution* in the *Buffer stage medium*, 2

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) in the *Buffer stage medium* at the first time interval:

$$\text{Result} = C_1 \times V_B \times (100/L)$$

C_1 = concentration of valproic acid in the *Buffer stage medium* at the first time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the second time interval:

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

C_2 = concentration of valproic acid in the *Buffer stage medium* at the second time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken at each time interval (mL)
C_1 = concentration of valproic acid in the *Buffer stage medium* at the first time interval (mg/mL)
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the n^{th} time interval:

$$\text{Result} = C_n \times [V_B - (n - 1) \times V_S] + [(C_1 + C_2 + ...+ C_{n-1}) \times V_S] \times (100/L)$$

C_n = concentration of valproic acid in the *Buffer stage medium* at the n^{th} time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken (mL)
C_1 = concentration of valproic acid dissolved in the first time interval in the *Buffer stage medium* (mg/mL)
C_2 = concentration of valproic acid dissolved in the second time interval in the *Buffer stage medium* (mg/mL)
C_{n-1} = concentration of valproic acid dissolved in the $(n - 1)^{th}$ time interval in the *Buffer stage medium* (mg/mL)
L = label claim (mg/Tablet)

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 (h)	Amount Dissolved (Tablets labeled to contain 500 mg of valproic acid)	Amount Dissolved (Tablets labeled to contain 250 mg of valproic acid)
3	10%–30%	10%–30%
9	35%–55%	35%–60%
12	45%–70%	45%–75%
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 *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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 monohydrate, 5.45 g/L of sodium hydroxide, and 48.65 g of sodium lauryl sulfate per L 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 the *Buffer stage concentrate* with 1 N hydrochloric acid or 1 N sodium hydroxide to assure 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*. ● (RB 1-May-2012)

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 monohydrate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (1:1)

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* in the concentrations of 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

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*

Relative standard deviation: NMT 2.0%
Correlation coefficient: NLT 0.999, using the five concentrations of the *Standard solution*

Analysis
Samples: *Sample solutions*

From the standard curve, determine the amount of valproic acid ($C_8H_{16}O_2$) dissolved at each time interval using the response of each *Sample solution*.

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the first time interval:

$$\text{Result} = (C_1 \times V_B) \times (100/L)$$

C_1 = concentration of valproic acid in the *Buffer stage medium* at the 3-h time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
L = label claim (mg/Tablet)

Calculate the percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved in the *Buffer stage medium* at the n^{th} time interval:

$$\text{Result} = C_n \times [V_B - (n - 1) \times V_S] + [(C_1 + C_2 + ...+ C_{n-1}) \times V_B] \times (100/L)$$

C_n = concentration of valproic acid in the *Buffer stage medium* at the n^{th} time interval (mg/mL)
V_B = volume of the *Buffer stage medium*, 900 mL
V_S = volume of the sample taken (mL)
C_1 = concentration of valproic acid dissolved in the first time interval in the *Buffer stage medium* (mg/mL)
C_2 = concentration of valproic acid dissolved in the second time interval in the *Buffer stage medium* (mg/mL)
C_{n-1} = concentration of valproic acid dissolved in the $(n - 1)^{th}$ time interval in the *Buffer stage medium* (mg/mL)
L = label claim (mg/Tablet)

Tolerances: The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to the following acceptance table (*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 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 (row 1); 2, 12, and 24 h in buffer stage (rows 2–4). •The times in the *Buffer stage medium* include the time in the *Acid stage medium*.• (RB 1-May-2012)

Buffer: 0.25 g of citric acid monohydrate, 0.2 g of anhydrous dibasic sodium phosphate, 3.4 g of monobasic potassium phosphate, and 0.85 g of sodium hydroxide in 1 L of 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 valproic acid from *Acid stage stock solution* in *Acid stage medium*, where L is the Tablet label claim, in mg

Buffer stage standard solution: (L/700) mg/mL of valproic acid from *Buffer stage 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 at about 3000 rpm for about 20 min. Use the supernatant.

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

System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Acid stage standard solution*, *Buffer stage standard solution*, *Acid stage sample solutions*, and *Buffer stage sample solutions*

Table 2

		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%.

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

$$Q_1 = (r_U/r_S) \times (C_S/L) \times V \times 100$$

$$Q_2 = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_1$$

$$Q_{12} = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_2$$

$$Q_{24} = [(r_U/r_S) \times (C_S/L) \times V \times 100] + Q_{12}$$

r_U = peak response from the *Sample solution* at the *Acid stage* or *Buffer stage* time points
r_S = peak response from the *Acid stage standard solution* or *Buffer stage standard solution*
C_S = concentration of valproic acid in the *Acid stage standard solution* or *Buffer stage standard solution* (mg/mL)
L = label claim (mg/Tablet)
V = volume of the *Acid stage medium* or *Buffer stage medium*, 250 mL

Tolerances: See *Table 3*.

Table 3

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	NMT 10%	NMT 10%
2	5%–25%	5%–25%
12	55%–75%	65%–85%
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 *Acceptance Table 2* in *Dissolution* ⟨711⟩.

•**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 trisodium phosphate dodecahydrate 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

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 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• (RB 1-Feb-2013) 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• (RB 1-Feb-2013) 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

System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%

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 *Acceptance Table 2* in *Dissolution* ⟨711⟩. • (RB 1-May-2012)

•**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* 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 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*
Acid stage standard solution: (L/5000) mg/mL of valproic acid from *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 valproic acid from *Standard stock solution* in *Buffer stage medium*, where L is the Tablet label claim, in mg
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 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 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
System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
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*):

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

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*):

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

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

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

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

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 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 *Acceptance Table 2* in *Dissolution* ⟨711⟩.

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 6 M sodium hydroxide solution 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 85% 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

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

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 *Acceptance Table 2* in *Dissolution* ⟨711⟩. ● (RB 1-Feb-2013)

- **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