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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*.

Table 2

	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%.

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 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 2*.▲ (ERR 1-Oct-2023)

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*.

Test 12: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12*.

Medium: Phosphate buffer pH 6.8 with 2% sodium dodecyl sulfate (dissolve 6.9 g of sodium phosphate monobasic dihydrate and 20.0 g of sodium dodecyl sulfate in 1000 mL of water, adjust with 10 g/L of sodium hydroxide in water to a pH of 6.8); 900 mL

Apparatus 2: 50 rpm, with suitable sinker

Times: 2, 6, and 24 h

Buffer A: 0.5 g/L of citric acid and 4 g/L of sodium phosphate dibasic, anhydrous in water

Buffer B: 6.8 g/L of monobasic potassium phosphate and 1.7 g/L of sodium hydroxide prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate and 1.7 g of sodium hydroxide in 1000 mL of water, adjust with phosphoric acid to a pH of 7.4.

Solution A: *Buffer A* and *Buffer B* (50:50)

Mobile phase: Acetonitrile and *Solution A* (30:70), adjust with phosphoric acid to a pH of 3.0

Standard solution: (*L*/900) mg/mL of USP Valproic Acid RS in *Medium*. Sonicate to dissolve if necessary.

Sample solution: At the times specified, withdraw 10 mL of aliquot. Replace the volume withdrawn with an equal volume of fresh *Medium*. Pass a portion of the solution under test through a suitable glass fiber 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

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

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 of valproic acid from the *Sample solution*

r_S = peak response of valproic acid 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*:

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

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

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

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 12*.

Table 12

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	20–40
2	6	40–60
3	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 2*.

- **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

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
DIVALPROEX SODIUM EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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