Divalproex Sodium Extended-Release Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	19-Nov-2021
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Divalproex Sodium Extended-Release Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 12* to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s).

- *Dissolution Test 12* was validated using a NovaPak Phenyl brand of column with L11 packing. The typical retention time for valproic acid is about 5.5 min.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Josan Thomas, Scientific Liaison +91(404-448-8948 or josan.thomas@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.

Notice of Intent to Revise
Official: To Be Determined

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 (%)

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%

	Time Points (*i*)	1	2	3	4
	Times	**3 h**	**9 h**	**12 h**	**21 h**
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

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 (%)
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*.

▲**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*. ▲ (TBD)

- **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

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