Divalproex Sodium Extended-Release Tablets

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Expert Committee	Chemical Medicines Monographs 4
Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Divalproex Sodium Extended-Release Tablets monograph. The purpose for the revision is to add *Dissolution Test 11* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 11* was validated using an Inertsil C8-3 brand of column with L7 packing. The typical retention time for valproic acid is about 4 min.

The Divalproex Sodium Extended-Release Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Heather Joyce, Senior Scientific Liaison–Team Leader (301-998-6792 or hrj@usp.org).

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

r_i = peak response from the *Sample solution* at time point *i*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)
D = dilution factor of the *Sample solution* in the *Buffer stage medium*, 2

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

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

C_i = concentration of valproic acid in the *Sample solution* withdrawn at time point *i* (mg/mL)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V_S = volume of the *Sample solution* withdrawn at each time point *i* during the *Buffer stage* (mL)

Tolerances

Acid stage: NMT 10% of the labeled amount of valproic acid ($C_8H_{16}O_2$) is dissolved.

Buffer stage: See *Table 1*.

Table 1

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

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

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Acid stage medium: 0.1 N hydrochloric acid; 500 mL

Buffer stage concentrate: 15.53 g/L of monobasic sodium phosphate, 5.45 g/L of sodium hydroxide, and 48.7 g/L of sodium lauryl sulfate in water (final pH approximately 11); 400 mL

Buffer stage medium: Mix 400 mL of *Buffer stage concentrate* with 500 mL of *Acid stage medium* to a pH of 5.5 ± 0.05. [NOTE—If necessary, adjust the pH of *Buffer stage concentrate* with 1 N hydrochloric acid or 1 N sodium hydroxide to ensure that the final pH of the mixture of media is 5.5.] Retain this solution to dilute the solutions prepared later.

Apparatus 2: 100 rpm, with wire helix sinkers

Times: 45 min in the *Acid stage medium*; 3, 9, 12, and 21 h in the *Buffer stage medium*. The times in the *Buffer stage medium* include the time in the *Acid stage medium*.

Procedure: After 45 min in the *Acid stage medium*, stop and lift the paddles from the vessels. Do not perform an analysis of the *Acid stage medium*. Transfer 400 mL of *Buffer stage concentrate* to the vessels containing the *Acid stage medium*, and run the test for the times specified.

Buffer: 3.5 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Mobile phase: Acetonitrile and *Buffer* (50:50)

Standard stock solution: 28 mg/mL of USP Valproic Acid RS in a suitable volumetric flask. Dissolve with 20% of the flask volume of 1 N sodium hydroxide, and dilute with water to volume. Dilute this solution with *Buffer stage medium* to obtain a final concentration of about 2.8 mg/mL.

Standard solutions: Prepare a series of dilutions in *Buffer stage medium* from the *Standard stock solution* at 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL.

Sample solution: Withdraw 10 mL of the solution under test, and pass through a suitable filter of 35-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 50 µL

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

System suitability

Samples: 0.028, 0.11, 0.22, 0.50, and 0.70 mg/mL of the *Standard solutions*

Suitability requirements

Tailing factor: NMT 2.0, using the 0.50-mg/mL *Standard solution*

Correlation coefficient: NLT 0.999, using the five concentrations of the *Standard solution*

Relative standard deviation: NMT 2.0%, using the 0.50-mg/mL *Standard solution*

Analysis

Sample: *Sample solution*

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

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

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

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

Tolerances: The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Table 2*.

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Acid stage medium: 0.1 N hydrochloric acid; 250 mL (row 1)

Buffer stage medium: pH 6.8 buffer (6.8 g of monobasic potassium phosphate and 0.92 g of sodium hydroxide in

Table 2 (Divalproex Sodium Extended-Release Tablets)

	Time Points (*i*)	1	2	3	4
	Times	**3 h**	**9 h**	**12 h**	**21 h**
L1	Individual Tablets	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L2	Individual Tablets	0%–37%	25%–80%	34%–102%	NLT 77%
L3	Average	10%–27%	35%–70%	44%–92%	NLT 87%
L3	Individual Tablets	NMT 2 Tablets are outside the range of 0%–37%, and no individual Tablet is outside the range of 0%–47%.	NMT 2 Tablets are outside the range of 25%–80%, and no individual Tablet is outside the range of 15%–90%.	NMT 2 Tablets are outside the range of 34%–102%, and no individual Tablet is outside the range of 24%–112%.	NMT 2 Tablets release less than 77%, and no individual Tablet releases less than 67%.

1 L of water. Adjust with phosphoric acid or sodium hydroxide to a pH of 6.8 ± 0.05); 250 mL (rows 2–4)

Apparatus 3: 30 dips/min, 20-mesh polypropylene screen on top and bottom; 30-s drip time

Times: 1 h in *Acid stage medium* (row 1); 2, 12, and 24 h in *Buffer stage medium* (rows 2–4). The times in the *Buffer stage medium* include the time in the *Acid stage medium*.

Buffer: 0.25 g/L of citric acid, 0.2 g/L of anhydrous dibasic sodium phosphate, 3.4 g/L of monobasic potassium phosphate, and 0.85 g/L of sodium hydroxide in water. Adjust with phosphoric acid to a pH of 3.0 ± 0.05.

Mobile phase: Acetonitrile and *Buffer* (30:70)

Acid stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in *Acid stage medium*. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize the valproic acid. Dilute with *Acid stage medium* to volume.

Buffer stage standard stock solution: 1 mg/mL of USP Valproic Acid RS in *Buffer stage medium*. Dissolve a suitable amount of USP Valproic Acid RS in a suitable volumetric flask in 10% of the flask volume of methanol to solubilize the valproic acid. Dilute with *Buffer stage medium* to volume.

Acid stage standard solution: (*L*/2500) mg/mL of USP Valproic Acid RS from *Acid stage standard stock solution* in *Acid stage medium*, where *L* is the Tablet label claim in mg

Buffer stage standard solution: (*L*/700) mg/mL of USP Valproic Acid RS from *Buffer stage standard stock solution* in *Buffer stage medium*, where *L* is the Tablet label claim in mg

Sample solutions: Centrifuge a portion of the solution under test. Use the supernatant. [NOTE—The use of a centrifuge speed of 3000 rpm for 20 min may be suitable.]

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 3.9-mm × 15-cm; 5-µm packing L11

Flow rate: 2 mL/min

Injection volume: 100 µL for Tablets labeled to contain 250 mg; 50 µL for Tablets labeled to contain 500 mg

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

System suitability

Samples: *Acid stage standard solution* and *Buffer stage standard solution*

Suitability requirements

Tailing factor: NMT 2.0 each for the *Acid stage standard solution* and the *Buffer stage standard solution*

Relative standard deviation: NMT 2.0% each for the *Acid stage standard solution* and the *Buffer stage standard solution*

Analysis

Samples: *Acid stage standard solution*, *Buffer stage standard solution*, and *Sample solutions*

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

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

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

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

C_S = concentration of USP Valproic Acid RS in the *Acid stage standard solution* or *Buffer stage standard solution* (mg/mL)

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

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

C_i = concentration of valproic acid in the *Acid stage standard solution* or *Buffer stage standard solution* withdrawn at time point *i* (mg/mL)

V = volume of the *Acid stage medium* or *Buffer stage medium*, 250 mL

L = label claim (mg/Tablet)

Tolerances: See *Table 3*.

Table 3

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

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

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Acid stage medium: 0.1 N hydrochloric acid; 500 mL
Buffer stage stock medium: 19.0 g/L of tribasic sodium phosphate in water, adjusted with hydrochloric acid to a pH of 5.5
Buffer stage medium: 21.6 g/L of sodium lauryl sulfate in *Buffer stage stock medium*; 900 mL
Apparatus 2: 100 rpm, with sinkers for 250- and 500-mg Tablets
Times: 45 min in *Acid stage medium*; 3, 9, 12, and 18 h in *Buffer stage medium*. The times in the *Buffer stage medium* include the time in the *Acid stage medium*.
Buffer: 1.36 g/L of monobasic potassium phosphate and triethylamine (99.5: 0.5). Adjust with phosphoric acid to a pH of 2.75.
Solution A: 1.0 g/L of sodium lauryl sulfate in *Buffer*
Mobile phase: Acetonitrile and *Solution A* (50:50), degassed
Acid stage standard stock solution: 1 mg/mL of USP Valproic Acid RS prepared as follows. Transfer a suitable amount of USP Valproic Acid RS to a volumetric flask, and dissolve in 20% of the flask volume of acetonitrile to solubilize valproic acid. Dilute with *Acid stage medium* to volume.
Acid stage standard solution: (*L*/5000) mg/mL of valproic acid from *Acid stage standard stock solution* in *Acid stage medium*, where *L* is the Tablet label claim, in mg
Buffer stage standard solution: (*L*/900) mg/mL of USP Valproic Acid RS, prepared as follows. Transfer a suitable amount of USP Valproic Acid RS to a volumetric flask, and dissolve in (*L*/50)% of the flask volume of acetonitrile. Dilute with *Buffer stage medium* to volume. *L* is the Tablet label claim in mg.
Acid stage sample solution: Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
Buffer stage sample solution: Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 50 µL
Run time: NLT 2.5 times the retention time of valproic acid
System suitability
Samples: *Acid stage standard solution* and *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0 each for the *Acid stage standard solution* and the *Buffer stage standard solution*
Relative standard deviation: NMT 2.0% each for the *Acid stage standard solution* and the *Buffer stage standard solution*
Analysis
Samples: *Acid stage standard solution*, *Buffer stage standard solution*, *Acid stage sample solution*, and *Buffer stage sample solutions*
Calculate the percentage of the labeled amount (Q_A) of valproic acid ($C_8H_{16}O_2$) dissolved in the *Acid stage*:

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

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

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

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

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

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

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

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

Tolerances: See *Table 4*.

Table 4

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

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.
Acid stage medium: 0.1 N hydrochloric acid; 500 mL
Buffer stage stock medium: 7.8 g/L of monobasic sodium phosphate dihydrate in water, adjusted with 2 N sodium hydroxide solution to a pH of 5.5
Buffer stage medium: 21.6 g/L of sodium dodecyl sulfate in *Buffer stage stock medium*; 900 mL
Apparatus 2: 100 rpm, with three-prong sinkers

Times: 45 min in *Acid stage medium*; 3, 9, 12, and 24 h in *Buffer stage medium*. The times in the *Buffer stage medium* do not include the time in the *Acid stage medium*.
Procedure: After 45 min in *Acid stage medium*, discard the remainder of the *Acid stage medium* and add the *Buffer stage medium*.
Solution A: Dilute 5 mL of phosphoric acid with water to 25 mL.
Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with *Solution A* to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (40:60), degassed
Standard stock solution: 1.4 mg/mL of USP Valproic Acid RS in *Mobile phase*
Buffer stage standard solution: (*L*/900) mg/mL of valproic acid from *Standard stock solution* in *Buffer stage medium*, where *L* is the Tablet label claim in mg
Buffer stage sample solution: Withdraw a 10.0-mL aliquot at each time point, and pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the 10.0-mL aliquot withdrawn for analysis with a 10.0-mL aliquot of *Buffer stage medium*.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Column temperature: 50°
Flow rate: 1 mL/min
Injection volume: 50 µL
Run time: NLT 1.5 times the retention time of valproic acid
System suitability
Sample: *Buffer stage standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Buffer stage standard solution* and *Buffer stage sample solutions*
Calculate the concentration (C_i) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each *Buffer stage* time point *i*:

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

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

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

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

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

Tolerances: See *Table 5*.

Table 5

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

The percentage of the labeled amount of valproic acid ($C_8H_{16}O_2$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
Medium: pH 6.8 phosphate buffer (6.0 g/L of anhydrous monobasic sodium phosphate in water, adjusted with 240 g/L of sodium hydroxide in water to a pH of 6.8); 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, 8, and 24 h in *Medium*
Buffer: 6.0 g/L of anhydrous monobasic sodium phosphate in water
Mobile phase: Acetonitrile and *Buffer* (50:50). Adjust with phosphoric acid to a pH of 3.0.
Standard solution: (*L*/900) mg/mL of USP Valproic Acid RS, where *L* is the label claim in mg/Tablet, prepared as follows. Transfer USP Valproic Acid RS to an appropriate volumetric flask. Add 5% of the flask volume of methanol to dissolve the valproic acid. Dilute with *Medium* to volume.
Sample solutions: Withdraw an aliquot at each time point, and pass a portion of the solution under test through a suitable filter.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Column temperature: 30°
Flow rate: 1 mL/min
Injection volume: 100 µL
Run time: NLT 2.5 times the retention time of valproic acid
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solutions*
Calculate the concentration (C_i) of valproic acid ($C_8H_{16}O_2$) in the sample withdrawn from the vessel at each time point *i*:

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

r_i = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Valproic Acid RS in the *Standard solution* (mg/mL)

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

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