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Clonidine Hydrochloride Extended-Release Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-clonidine-hcl-ert-20240830.

DEFINITION

Clonidine Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$).

IDENTIFICATION

• **A. Thin-Layer Chromatographic Identification Test ⟨201⟩**

Standard solution: 10 mg/mL of USP Clonidine Hydrochloride RS in methanol. Sonicate to dissolve, if needed.

Sample solution: Powder NLT 20 Tablets and transfer a portion of the powder equivalent to 1 mg of clonidine hydrochloride to a separator containing 20 mL of water and 1 mL of 1 N sodium hydroxide . Swirl gently to dissolve the sample, and extract with 40 mL of chloroform. Allow the layers to separate for 15 min, and pass the chloroform layer through a suitable filter paper into a glass beaker. Repeat the extraction step and collect the filtrate in the same beaker. Evaporate the filtrate to dryness in a water bath, and dissolve the residue with 0.1 mL of methanol.

Chromatographic system

(See *Chromatography ⟨621⟩, General Procedures, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 5 µL

Developing solvent system: Methanol and ammonium hydroxide (200:3)

Analysis

Samples: *Standard solution* and *Sample solution*

Position the plate in a chromatographic chamber, and develop in *Developing solvent system* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate for 2 min at 70°. Examine the plate under UV light at 254 nm.

Acceptance criteria: The R_F value of the principal spot from the *Sample solution* corresponds to that from the *Standard solution*.

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Buffer: Dissolve 2.2 g of octanesulfonic acid sodium salt in 1000 mL of water.

Solution A: Methanol, *Buffer*, and phosphoric acid (50: 50: 0.1). Adjust with 1 N sodium hydroxide to a pH of 3.0.

Solution B: Acetonitrile, methanol, and water (80:10:10)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
15	100	0
17	10	90
22	100	0
30	100	0

Standard solution: 1 µg/mL of USP Clonidine Hydrochloride RS in *Solution A*

Sample solution: Nominally 1 µg/mL of clonidine hydrochloride prepared as follows. Weigh and transfer 10 Tablets equivalent to 1 mg of clonidine hydrochloride to a 1000-mL volumetric flask. Add 50 mL of methanol and stir for 30 min. Add 700 mL of *Solution A* and stir for 15 min. Sonicate for 30 min with intermittent shaking every 5 min. Dilute with *Solution A* to volume. Pass through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1.5 mL/min

Injection volume: 50 µL

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 percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the portion of Tablets taken:

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of clonidine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution ⟨711⟩**

Test 1

Acid stage medium: 0.01 N hydrochloric acid; 500 mL

Buffer stage medium: pH 7.0 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate and 1.16 g of sodium hydroxide in 1000 mL of water. Adjust with 0.1 N sodium hydroxide to a pH of 7.0.); 500 mL

Apparatus 2: 50 rpm with a suitable sinker

Times

Acid stage: 2 h

Buffer stage: 1, 6, and 16 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Buffer: 2.2 g/L of octanesulfonic acid sodium salt in water

Mobile phase: Methanol, *Buffer*, and phosphoric acid (50: 50: 0.1). Adjust with 1 N sodium hydroxide to a pH of 3.0.

Standard stock solution: 0.105 mg/mL of USP Clonidine Hydrochloride RS in the respective medium. Sonicate to dissolve, if needed.

Standard solution: 0.21 µg/mL of USP Clonidine Hydrochloride RS in the respective medium from the *Standard stock solution*

Sample solution: After 2 h in the *Acid stage medium*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Carefully transfer the Tablet with sinker to a dissolution vessel containing the *Buffer stage medium*. At the times specified for the *Buffer stage*, withdraw an aliquot of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Buffer stage medium*. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1.5 mL/min

Injection volume: 100 µL

Run time: NLT 2.5 times the retention time of clonidine

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 percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in the *Acid stage medium* (Q_A):

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Acid stage medium*; 500 mL

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the sample withdrawn at each *Buffer stage* time point (i):

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

r_U = peak response of clonidine from the *Sample solution* at each time point, i

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) 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 clonidine hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of clonidine hydrochloride dissolved in the *Acid stage medium* (%)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances

Acid stage: 30%–50% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 2 h.

Buffer stage: See *Table 2*.

Table 2

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
1	1	40–60
2	6	65–85
3	16	NLT 85

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 2

Acid stage medium: 0.01 N hydrochloric acid; 500 mL

Buffer stage medium: pH 7.0 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate and 1.1 g of sodium hydroxide in 1000 mL of water. Adjust with 1% hydrochloric acid or 1% sodium hydroxide to a pH of 7.0.); 500 mL

Apparatus 2: 50 rpm with a suitable sinker

Times

Acid stage: 2 h

Buffer stage: 2, 6, and 10 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Buffer: 2.2 g/L of octanesulfonic acid sodium salt in water

Mobile phase: Methanol, *Buffer*, and phosphoric acid (50: 50: 0.1). Adjust with triethylamine to a pH of 3.0.

Standard solution acid stage: 0.2 µg/mL of USP Clonidine Hydrochloride RS in *Acid stage medium*

Standard solution buffer stage: 0.2 µg/mL of USP Clonidine Hydrochloride RS in *Buffer stage medium*

Sample solution: At the time specified for the *Acid stage*, withdraw an aliquot of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Acid stage medium*. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Carefully transfer the Tablet to a dissolution vessel containing the *Buffer stage medium*. At the times specified for the *Buffer stage*, withdraw an aliquot of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Buffer stage medium*. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

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: 10°

Column: 30°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: NLT 2 times the retention time of clonidine

System suitability

Samples: *Standard solution acid stage* and *Standard solution buffer stage*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution acid stage* and *Standard solution buffer stage*

Relative standard deviation: NMT 5.0%, *Standard solution acid stage* and *Standard solution buffer stage*

Analysis

Samples: *Standard solution acid stage*, *Standard solution buffer stage*, and *Sample solution*

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in the *Acid stage medium* (Q_A):

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution acid stage*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution acid stage* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Acid stage medium*; 500 mL

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the sample withdrawn at each *Buffer stage* time point (i):

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

r_U = peak response of clonidine from the *Sample solution* at each time point, i

r_S = peak response of clonidine from the *Standard solution buffer stage*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution buffer stage* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) 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 clonidine hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of clonidine hydrochloride dissolved in the *Acid stage medium* (%)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances

Acid stage: NMT 37% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 2 h.

Buffer stage: See *Table 3*.

Table 3

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
1	2	42–62
2	6	68–88
3	10	NLT 80

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 3

Acid stage medium: 0.01 N hydrochloric acid; 500 mL

Buffer stage medium: pH 7.0 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate and 1.16 g of sodium hydroxide in 1000 mL of water. Adjust with 1 N phosphoric acid TS or 1 N sodium hydroxide to a pH of 7.0.); 500 mL

Apparatus 2: 50 rpm

Times

Acid stage: 2 h

Buffer stage: 2, 6, and 14 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Buffer: 1.8 g/L of octanesulfonic acid sodium salt in water

Mobile phase: Methanol and *Buffer* (40:60). Add 1 mL of phosphoric acid into each liter of the mixture. Adjust with 1 N sodium hydroxide to a pH of 3.0.

Standard solution: 0.2 µg/mL of USP Clonidine Hydrochloride RS in *Acid stage medium*

Sample solution: After 2 h in the *Acid stage medium*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Carefully, replace the *Acid stage medium* with *Buffer stage medium* pre-equilibrated to the appropriate temperature. At the times specified for the *Buffer stage*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Flow rate: 1.5 mL/min

Injection volume: 100 µL

Run time: NLT 3 times the retention time of clonidine

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in the *Acid stage medium* (Q_A):

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Acid stage medium*; 500 mL

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the sample withdrawn at each *Buffer stage* time point (*i*):

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

r_U = peak response of clonidine from the *Sample solution* at each time point, *i*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at each time point (*i*):

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

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

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

C_i = concentration of clonidine hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of clonidine hydrochloride dissolved in the *Acid stage medium* (%)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances

Acid stage: 23%–43% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 2 h.

Buffer stage: See *Table 4*.

Table 4

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
1	2	45–65
2	6	70–90
3	14	NLT 80

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 4

Acid stage medium: 0.01 N hydrochloric acid; 500 mL, deaerated

Buffer stage medium: pH 7.0 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate and 1.16 g of sodium hydroxide in 1000 mL of water. Adjust with 1 N phosphoric acid TS or 1 N sodium hydroxide to a pH of 7.0.); 500 mL

Apparatus 2: 50 rpm with a suitable sinker

Times

Acid stage: 2 h

Buffer stage: 2, 6, and 14 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

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

Standard solution: 0.4 µg/mL of USP Clonidine Hydrochloride RS in *Acid stage medium*

Sample solution: After 2 h in the *Acid stage medium*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Carefully transfer the Tablet with sinker to a dissolution vessel containing the *Buffer stage medium*. At the times specified for the *Buffer stage*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 80 µL

Run time: NLT 2 times the retention time of clonidine

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 percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in the *Acid stage medium* (Q_A):

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Acid stage medium*; 500 mL

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the sample withdrawn at each *Buffer stage* time point (*i*):

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

r_U = peak response of clonidine from the *Sample solution* at each time point, *i*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at each time point (*i*):

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

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

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

C_i = concentration of clonidine hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of clonidine hydrochloride dissolved in the *Acid stage medium* (%)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances

Acid stage: 18%–38% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 2 h.

Buffer stage: See *Table 5*.

Table 5

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
1	2	39–59
2	6	62–82

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
3	14	NLT 80

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 5

Acid stage medium: 0.01 N hydrochloric acid; 500 mL

Buffer stage medium: pH 7.0 phosphate buffer (dissolve 6.8 g of monobasic potassium phosphate in water and add 7.0 mL of 5 N sodium hydroxide. Dilute to 1000 mL with water. Adjust with dilute phosphoric acid or dilute sodium hydroxide to a pH of 7.0.); 500 mL

Apparatus 2: 50 rpm with a suitable sinker

Times

Acid stage: 2 h

Buffer stage: 2, 6, and 16 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Buffer: 6.9 g/L of monobasic sodium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (60:40)

Standard solution: 0.4 µg/mL of USP Clonidine Hydrochloride RS in *Buffer stage medium*

Sample solution: After 2 h in the *Acid stage medium*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 0.45-µm pore size and discard the first few milliliters of the filtrate. Carefully transfer the Tablet with sinker to a dissolution vessel containing the *Buffer stage medium*. At the times specified for the *Buffer stage*, withdraw an aliquot of the solution under test. Pass the solution through a suitable filter of 2.7-µm pore size and discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 10-cm; 5-µm packing L9

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: NLT 1.5 times the retention time of clonidine

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 percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in the *Acid stage medium* (Q_A):

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

r_U = peak response of clonidine from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Acid stage medium*; 500 mL

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the sample withdrawn at each *Buffer stage* time point (*i*):

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

r_U = peak response of clonidine from the *Sample solution* at each time point, *i*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at each time point (*i*):

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

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

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

C_i = concentration of clonidine hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)

V = volume of *Buffer stage medium*, 500 mL

L = label claim (mg/Tablet)

Q_A = percentage of the labeled amount of clonidine hydrochloride dissolved in the *Acid stage medium* (%)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances

Acid stage: 8%–28% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 2 h.

Buffer stage: See *Table 6*.

Table 6

Time Point (*i*)	Time (*h*)	Amount Dissolved (%)
1	2	28–48
2	6	51–71
3	16	NLT 80

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) 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*.

Acid stage medium: 0.01 N hydrochloric acid; 500 mL

Buffer stage stock solution: Dissolve 13.61 g of monobasic potassium phosphate in 400 mL of 0.19 N sodium hydroxide. Adjust the concentration of 0.19 N sodium hydroxide, if necessary, so that a mixture of 10 mL of the solution with 40 mL of *Acid stage medium* has a pH of 7.0.

Buffer stage medium: pH 7.0 phosphate buffer (To 400 mL of *Acid stage medium* add 100 mL of pre-warmed *Buffer stage stock solution*.); 500 mL

Apparatus 2: 50 rpm with wire sinker

Times

Acid stage: 1 and 2 h

[NOTE—The result calculated in *Acid stage* for 2 h is only used for cummulative calculation and not reported.]

Buffer stage: 2, 6, and 14 h. The time in the *Buffer stage medium* does not include the time in the *Acid stage medium*.

Solution A: Transfer 1 mL of triethylamine to 1 L of water. Adjust with phosphoric acid to a pH of 6.9.

Mobile phase: Acetonitrile and *Solution A* (16:84)

Standard stock solution: 4 µg/mL of USP Clonidine Hydrochloride RS in methanol. Sonicate to dissolve, if necessary.

Acid stage standard solution: 0.08 µg/mL of USP Clonidine Hydrochloride RS from *Standard stock solution* in *Acid stage medium*

Buffer stage standard solution: 0.2 µg/mL of USP Clonidine Hydrochloride RS from *Standard stock solution* in *Buffer stage medium*

Acid stage sample solution: At the times specified, withdraw 10 mL of the solution under test. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained. After 2 h, withdraw 90 mL of the solution under test and proceed to *Buffer stage*.

Buffer stage sample solution: At the times specified, withdraw 10 mL of the solution under test and replace with same volume of the *Buffer stage medium* maintained at 37°. Pass through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

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: 35°

Flow rate: 1 mL/min

Injection volume: 100 µL

Run time: NLT 1.4 times the retention time of clonidine

System suitability

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

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

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

Acid stage

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the portion of sample withdrawn in *Acid stage* from the vessel at each time point (i):

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

r_i = peak response of clonidine from the *Acid stage sample solution* at time point *i*

r_S = peak response of clonidine from the *Acid stage standard solution*

C_{SA} = concentration of USP Clonidine Hydrochloride RS in the *Acid stage standard solution* (mg/mL)

[NOTE—The result calculated in *Acid stage* for 2 h is only used for cummulative calculation and not reported.]

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at 1 h in the *Acid stage*:

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

C = concentration of clonidine hydrochloride in the portion of the sample withdrawn at 1 h in the *Acid stage* (mg/mL)

V = volume of *Acid stage medium* (500 mL)

L = label claim (mg/Tablet)

Buffer stage

Calculate the concentration (C_i) of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) in the portion of sample withdrawn in *Buffer stage* from the vessel at each time point (i):

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

r_i = peak response of clonidine from the *Buffer stage sample solution* at time point *i*

r_S = peak response of clonidine from the *Buffer stage standard solution*

C_{SB} = concentration of USP Clonidine Hydrochloride RS in the *Buffer stage standard solution* (mg/mL)

Calculate the percentage of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved in *Buffer stage* at each time point (i):

$$\text{Result}_1 = [(C_1 \times V) + (C_{A2} \times V_{A2}) + (C_{A1} \times V_{A1})] \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S) + (C_{A2} \times V_{A2}) + (C_{A1} \times V_{A1})] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S] + (C_{A2} \times V_{A2}) + (C_{A1} \times V_{A1})\} \times (1/L) \times 100$$

C_i = concentration of clonidine hydrochloride in the portion of the sample withdrawn in *Buffer stage* at time point *i* (mg/mL)

V = volume of *Buffer stage medium* (500 mL)

C_{A2} = concentration of clonidine hydrochloride in the portion of the sample withdrawn in *Acid stage* at 2 h (mg/mL)

V_{A2} = volume of *Acid stage sample solution* withdrawn at 2 h (90 mL)

C_{A1} = concentration of clonidine hydrochloride in the portion of the sample withdrawn in *Acid stage* at 1 h (mg/mL)

V_{A1} = volume of *Acid stage sample solution* withdrawn at 1 h (10 mL)

L = label claim (mg/Tablet)

V_S = volume of *Buffer stage sample solution* withdrawn (10 mL)

Tolerances

Acid stage: NMT 20% of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) is dissolved in 1 h.

Buffer stage: See *Table 7*.

Table 7

Time Point (*i*)	Time (h)	Amount Dissolved (%)
1	2	33–53
2	6	56–76
3	14	NLT 80

The percentages of the labeled amount of clonidine hydrochloride ($C_9H_9Cl_2N_3 \cdot HCl$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.▲ (RB 1-Sep-2024)

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

IMPURITIES

Change to read:

- **Organic Impurities**

Buffer: Dissolve 4 g of octanesulfonic acid sodium salt in 1000 mL of water.

Solution A: Methanol, *Buffer*, and phosphoric acid (45: 55: 0.1). Adjust with phosphoric acid to a pH of 2.5.

Solution B: Acetonitrile, methanol, and water (65:5:30)

Mobile phase: See ▲*Table 8*.

Table 8▲ (RB 1-Sep-2024)

Time (min)	Solution A (%)	Solution B (%)
0	100	0
60	100	0
65	15	85
85	15	85
90	100	0
110	100	0

Diluent 1: 4 g of octanesulfonic acid sodium salt in 1 L of water. Add 1 mL of phosphoric acid. Adjust with triethylamine to a pH of 2.5.

Diluent 2: Methanol and *Diluent 1* (50:50)

Standard stock solution: 0.25 mg/mL of USP Clonidine Hydrochloride RS in methanol. Sonicate to dissolve, if needed.

Standard solution: 0.125 µg/mL of USP Clonidine Hydrochloride RS in *Diluent 2* from the *Standard stock solution*

Sensitivity solution: 0.025 µg/mL of USP Clonidine Hydrochloride RS in *Diluent 2* from the *Standard solution*

Sample stock solution: Nominally 0.05 mg/mL of clonidine hydrochloride prepared as follows. Weigh and finely powder NLT 20 Tablets. Transfer a portion of the powder equivalent to 1 mg of clonidine hydrochloride to a 20-mL volumetric flask. Add 15 mL of methanol. Sonicate for 15 min with intermittent shaking every 2 min at 10°. Dilute with methanol to volume. Centrifuge for 10 min and use the supernatant.

Sample solution: Nominally 25 µg/mL of clonidine hydrochloride in *Diluent 1* from the *Sample stock solution*. Pass through a suitable filter of 0.45-µm pore size. Discard the first few milliliters of the filtrate.

Chromatographic system

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

Mode: LC

Detector: 220 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Autosampler temperature: 10°

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Samples: *Standard solution* and *Sensitivity solution*

Suitability requirements

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response of any unspecified degradation product from the *Sample solution*

r_S = peak response of clonidine from the *Standard solution*

C_S = concentration of USP Clonidine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of clonidine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria

Any unspecified degradation product: NMT 1.0%

Total degradation products: NMT 3.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant 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 Clonidine Hydrochloride RS

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

Topic/Question	Contact	Expert Committee
CLONIDINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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