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Clonidine Hydrochloride Extended-Release Tablets

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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 mLCalculate 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, i , in min