

Clonidine Transdermal System

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Reason for Revision	Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Clonidine Transdermal System monograph. The purpose for the revision is to revise the acceptance criterion for the lower limit of the release rate at the 8 h time point from 6.5 $\mu\text{g}/\text{h}/\text{cm}^2$ to 5.5 $\mu\text{g}/\text{h}/\text{cm}^2$ in *Drug Release Test 3* to accommodate FDA-approved drug products.

The Clonidine Transdermal System Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Edith Chang, Senior Scientific Liaison (301-816-8392 or yec@usp.org).

Clonidine Transdermal System

DEFINITION

Clonidine Transdermal System contains NLT 80.0% and NMT 120.0% of the labeled amount of clonidine ($C_9H_9Cl_2N_3$).

[NOTE—Throughout the following procedures, avoid the use of tetrahydrofuran stabilized with butylated hydroxytoluene (BHT). In the presence of peroxides, BHT may react with clonidine, producing impurity peaks.]

IDENTIFICATION

A. INFRARED ABSORPTION (197K)

Buffer solution: 242.28 g/L of tris(hydroxymethyl) aminomethane in water. Adjust with dilute hydrochloric acid to a pH of 9.2.

Sample: Carefully peel the release liner from each Transdermal System, and place a number of Transdermal Systems equivalent to 25 mg of clonidine into a 50-mL screw-capped centrifuge tube. Add 5 mL of chloroform, and mix on a vortex mixer for 5 min. Allow to stand for 30 min, and mix intermittently on a vortex mixer. Transfer the chloroform solution to another 50-mL centrifuge tube, and wash the residue with an additional 3 mL of chloroform, combining the extracts. Add 2 mL of 0.5 N hydrochloric acid to the extract, mix on a vortex mixer for 1 min, and centrifuge at about 1000 rpm for 4 min. Remove and discard the bottom chloroform layer. Extract the aqueous layer with 4 mL of chloroform. Centrifuge at 1000 rpm for an additional 5 min, and again discard the bottom chloroform layer. Add 5 mL of *Buffer solution* and 3 mL of methylene chloride. Mix on a vortex mixer for 1 min. Centrifuge at 1000 rpm for 4 min. Transfer the bottom methylene chloride layer into a 100-mL beaker, and dry the methylene chloride with anhydrous sodium sulfate (about 1/4 liquid height). Decant, and evaporate to dryness with a stream of nitrogen. Dry at 105° for 30 min, and allow to cool in a desiccator.

Analysis: Determine the IR spectrum of the *Sample solution* and USP Clonidine RS in the wavelength region of 3500–600 cm^{-1} .

Acceptance criteria: Meets the requirements

- 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 solution: 2.5 mL of triethylamine in 1 L of water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer solution* (60:40). [NOTE—Stir the solution for 30 min.]

Diluent: Tetrahydrofuran and methanol (1:1)

System suitability solution: 250 $\mu g/mL$ of USP Clonidine RS and 10 $\mu g/mL$ of USP Clonidine Related Compound B RS in *Diluent*

Standard stock solution: 1 mg/mL of USP Clonidine RS in tetrahydrofuran

Standard solutions: Prepare a minimum of four *Standard solutions* from the *Standard stock solution* in *Diluent* that bracket the expected clonidine concentration in the sample. The standard concentrations should be within the range of 50–300 $\mu g/mL$. [NOTE—The *Standard solutions* are stable for up to 2 days if stored at 4°.]

Sample solution: 357 $\mu g/mL$ of clonidine prepared as follows. Remove each Transdermal System from its package, discard the release liner from each system, and transfer into a 50-mL centrifuge tube with a Teflon-lined

screw cap. Add the appropriate volume of tetrahydrofuran as listed in *Table 1*.

Table 1

For systems containing about 2.5 mg of clonidine	7.0 mL
For systems containing about 5.0 mg of clonidine	14.0 mL
For systems containing about 7.5 mg of clonidine	21.0 mL

Mix vigorously on a vortex mixer until the systems are washed down and fully submerged in the tetrahydrofuran. Let the systems soak in tetrahydrofuran for about 5 min, and mix on a vortex mixer until the systems are completely delaminated. Allow the systems to remain submerged for an additional 60 min, mixing on a vortex mixer every 30 min. Add methanol in a volume equal to the volume of tetrahydrofuran, and mix vigorously on a vortex mixer. The solution turns milky. Centrifuge for 10 min at 2000 rpm. Use the supernatant as the *Sample solution*.

Chromatographic system

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

Mode: LC

Detector: UV 210 and 242 nm

[NOTE—The detector is programmed initially to 242 nm and switched to 210 nm after the elution of the clonidine peak but before the elution of the clonidine related compound B peak.]

Column: 4.6-mm \times 15-cm; packing L10

Flow rate: 1 mL/min

Injection size: 25 μL

System suitability

Sample: *System suitability solution*

[NOTE—The relative retention times for clonidine and clonidine related compound B are 1.0 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 2.0 between clonidine and clonidine related compound B

Capacity factor (*k'*): NLT 0.6 for clonidine

Tailing factor: NMT 3.0 for both clonidine and clonidine related compound B

Relative standard deviation: NMT 2.0% for the clonidine peak area

Analysis

Samples: At least three *Standard solutions* that will bracket the expected sample concentration range and the *Sample solution*

Calculate the peak response ratios of the analyte, and plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient: it should be NLT 0.995.

Calculate the percentage of the labeled amount of clonidine ($C_9H_9Cl_2N_3$) in the Transdermal System taken:

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

C_S = concentration of clonidine from the linear regression analysis ($\mu g/mL$)

C_U = nominal concentration of clonidine in the *Sample solution* ($\mu g/mL$)

Acceptance criteria: 80.0%–120.0%

PERFORMANCE TESTS**Change to read:****• DRUG RELEASE (724)****Test 1**

Medium: 0.001 M phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; 200 mL for systems containing more than 5 mg of clonidine

Times: 8, 24, 96, and 168 h

Apparatus 7: Proceed as directed in the chapter, using the transdermal system holder-angled disk (see *Drug Release* (724), *Figure 5a*). The appropriate size of the holder, 1.42 or 1.98 inches, should be chosen based on the size of the system to prevent overhang. Use 100-mL beakers for *Medium* volumes of 80 mL and 300-mL beakers for *Medium* volumes of 200 mL. Gently press the Transdermal System to a dry, smooth, square piece of cellulose membrane, or equivalent, with the adhesive side against the membrane. Attach the membrane/system to a suitable inert sample holder with a Viton O-ring, or equivalent, so that the backing of the system is adjacent to and centered on the bottom of the sample holder. Trim the excess cellulose membrane with scissors. Suspend each sample holder from the arm of a reciprocating shaker so that each system is continuously immersed in a beaker containing the specified volume of *Medium*. The filled beakers are weighed and pre-equilibrated to $32.0 \pm 0.3^\circ$ before immersing the test sample. Agitate the sample in an up-down motion at a frequency of 30 cycles/min with an amplitude of 2.0 ± 0.1 cm. The *Medium* must be added daily to the beakers during each interval to maintain sample immersion. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of *Medium*, weighed and pre-equilibrated to $32.0 \pm 0.3^\circ$.

Mobile phase: 0.1% solution of triethylamine in a mixture of methanol and water (30:70). Adjust with phosphoric acid to a pH of 6.0 ± 0.2 .

System suitability solution: 10 µg/mL of USP Clonidine RS in 0.001 M phosphoric acid

Standard solutions: Prepare a minimum of four *Standard solutions* of USP Clonidine RS in 0.001 M phosphoric acid having known concentrations of clonidine similar to those of the *Sample solutions*.

Sample solutions: At the end of each release interval, allow the beakers to cool to room temperature, and make up for evaporative *Medium* losses by adding *Medium* to obtain the original weight, then mix.

Chromatographic system
(See *Chromatography* (621), *System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; packing L1

Flow rate: 1.5 mL/min

Injection size: 25 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Capacity factor (*k'*): NLT 0.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solutions* and *Sample solutions*
Construct a standard curve of concentration (µg/mL) of clonidine in the *Standard solutions* versus peak area by

linear regression analysis. The correlation coefficient is NLT 0.995.

Calculate the release rate of clonidine:

$$\text{Result} = CV/TA$$

C = concentration of clonidine in the sample of the standard curve (µg/mL)

V = volume of the *Medium* (mL)

T = time (h)

A = area of the Transdermal System (cm²)

Tolerances: See *Table 2*.

Table 2

Time (h)	Time for Sampling (h)	Release Rate (µg/h/cm ²)
0–8	8	7.5–16.0
8–24	24	1.5–4.6
24–96	96	1.5–4.6
96–168	168	1.5–3.3

The release rate of clonidine (C₉H₉Cl₂N₃) from the Transdermal System, expressed as µg/h/cm² at the times specified, conforms to *Drug Release* (724), *Acceptance Table 1*.

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

Medium: 0.01 N hydrochloric acid; 500 mL for systems labeled as 0.1 mg/day, 900 mL for systems labeled as 0.2 or 0.3 mg/day

Apparatus 6: 100 rpm. Apply double-sided tape around the lower-most circumference of the cylinder, overlapping the ends to prevent peeling of the tape end from the cylinder. Remove the outer layer of the tape. Attach the Transdermal System to the cylinder with the backing side against the double-sided tape and the longitudinal axis parallel to the bottom of the cylinder. Carefully smooth the system to remove any air bubbles, and remove the release liner from the system. For systems requiring 500 mL of *Medium*, apply the double-sided tape to the system such that the bottom edge of each is NMT 2 mm from the bottom of the cylinder to prevent evaporation during the test from exposure to air. After setting the cylinder in the vessel, cover the vessel to minimize evaporation.

Times: 6, 48, 96, and 168 h

Buffer: 0.3% triethylamine in 0.025 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 6.20 ± 0.10 .

Mobile phase: *Buffer* and tetrahydrofuran (94:6)

Standard solutions: Solutions containing 0.7, 3.0, 5.3, 7.5, and 9.8 µg/mL of USP Clonidine RS in *Medium*. A small amount of methanol (not exceeding 10% of the final volume) can be used to solubilize clonidine.

Sample solution: 1.5 mL aliquots of the solution under test. After sampling the last time point, measure the volume of *Medium* remaining in the vessel.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Columns

Guard: 3.0-mm × 4-mm; packing L1

Analytical: 4.6-mm × 15-cm; packing L1

Flow rate: 1.0 mL/min

Injection size: 50 µL

System suitability

Sample: 5.3 µg/mL of the *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solutions* and *Sample solution*

Construct a standard curve of concentration (µg/mL) of clonidine in the *Standard solutions* versus peak area by linear regression analysis. The correlation coefficient is NLT 0.997. Calculate the release rate of clonidine.

Calculate the volume loss rate in mL/h (L):

$$L = [V - F + (N \times 1.5)]/T$$

- V = initial volume of *Medium* (mL)
- F = final volume of *Medium* (mL)
- N = number of sampling time points
- T = total elapsed time between start of run and final volume measurement (h)

Calculate the volume (mL) at each sampling time adjusted for evaporation (V_{adj}):

$$V_{adj} = V - (L \times t_c) - [(n - 1) \times 1.5]$$

- t_c = cumulative time for the sample withdrawal (6, 48, 96, or 168 h)
- n = sampling number (1, 2, 3, or 4 for the 6-, 48-, 96-, and 168-h sampling times, respectively)

Calculate the release rate of clonidine (µg/h/cm²):

$$\text{Result} = [(r_U - b) \times V_{adj}]/(m \times A \times t_i)$$

- r_U = peak response from the *Sample solution*
- b = y-intercept of the standard curve
- m = slope of the standard curve
- A = area of the system (cm²)
- t_i = interval time (h)

Tolerances: See *Table 3*.

Table 3

Time (h)	Time for Sampling (h)	Interval Time (h)	Release Rate (µg/h/cm ²)
0-6	6	6	7.6-12.0
6-48	48	42	1.7-2.5
48-96	96	48	2.0-2.9
96-168	168	72	1.7-2.6

The release rate of clonidine (C₉H₉Cl₂N₃) from the Transdermal System, expressed as µg/h/cm² at the times specified, conforms to *Drug Release (724)*, *Acceptance Table 1*.

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

Medium: 100 mM acetate buffer, pH 5.0, with 0.01% of cetyltrimethylammonium bromide (13.6 g/L of sodium acetate monohydrate in water, adjust with glacial acetic acid to a pH of 5.0, and add 0.1 g/L of cetyltrimethylammonium bromide); 900 mL

Apparatus 5: 100 rpm, with the 76-mm disk

Times: 8, 24, 96, and 168 h

Solution A: 2.4 g/L of octanesulfonic acid sodium salt and 2 mL/L of phosphoric acid in water

Mobile phase: Methanol and *Solution A* (45:55). Adjust with 10 N sodium hydroxide to a pH of 3.0.

Standard stock solution: 1 mg/mL of USP Clonidine RS in methanol

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration similar to the expected concentration in the *Sample solution*, considering complete drug release.

Sample solution: Apply double-sided adhesive tape to the stainless steel disk to cover enough of the disk area so that the entire patch is secured by the tape. Apply a Transdermal System with the release liner intact to the adhesive layer on the stainless steel disk. Press the backing film of the patch to the adhesive tape with the clear release liner film of the system facing up. Peel the release liner from the affixed system on the disk assembly, and place the disk assembly flat on the bottom of the vessel with the exposed transdermal adhesive side up and parallel to the bottom edge of the paddle blade. Lower the paddle, and start the equipment. At each sampling time withdraw an appropriate volume of the solution under test.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection size: 30 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.8

Relative standard deviation: NMT 2.0%

Analysis:

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of clonidine (C₉H₉Cl₂N₃) in the *Medium* (mg/mL) at each time point:

$$C_i = (r_U/r_S) \times C_S$$

- r_U = peak response from the *Sample solution*
- r_S = peak response from the *Standard solution*
- C_S = concentration of the *Standard solution* (mg/mL)
- i = interval, where i = 1 at 8 h, i = 2 at 24 h, i = 3 at 96 h, i = 4 at 168 h

Calculate the rate of clonidine (C₉H₉Cl₂N₃) released in µg/h/cm² at each time point:

$$\text{Result} = [(C_i - C_{i-1}) \times V_i \times 1000]/[S \times (T_i - T_{i-1})]$$

$$V_i = V_0 - [(i - 1) \times V_A]$$

- V_i = volume of *Medium* at a given time point
- V_0 = initial volume of *Medium*, 900 mL
- V_A = volume of *Medium* withdrawn at each time point
- 1000 = conversion factor from mg to µg
- S = system size in cm²
- T_i = current time point
- T_{i-1} = previous time point

Tolerances: See *Table 4*.

Table 4

Time (h)	Release Rate ($\mu\text{g}/\text{h}/\text{cm}^2$)
8	$\blacktriangle 5.5 \blacktriangle$ (RB 1-Jun-2019)–11.0
24	2.5–5.5
96	2.5–5.0
168	2.0–3.8

The release rate of clonidine ($\text{C}_9\text{H}_9\text{Cl}_2\text{N}_3$) from the Transdermal System, expressed as $\mu\text{g}/\text{h}/\text{cm}^2$ at the times specified, conforms to *Drug Release* (724), *Acceptance Table 1*.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meets the requirements

IMPURITIES• **ORGANIC IMPURITIES**

Mobile phase, Diluent, System suitability solution, Sample solution, and Chromatographic system:

Proceed as directed in the *Assay*.

Standard stock solution: 1 mg/mL of USP Clonidine Related Compound B RS in tetrahydrofuran

Standard solutions: Prepare a minimum of four *Standard solutions* in *Diluent* that bracket the expected clonidine related compound B concentration in the sample. The standard concentrations should be within the range of 0.2–10.0 $\mu\text{g}/\text{mL}$.

[NOTE—The *Standard solutions* are stable for up to 2 days if stored at 4°.]

Analysis

Samples: At least three *Standard solutions* that will bracket the expected sample concentration range and the *Sample solution*

Measure the responses for clonidine related compound B. Calculate the peak response ratios of the analyte, and

plot the results. Determine the linear regression equation of the standards by the mean-square method, and record the linear regression equation and the correlation coefficient: it should be NLT 0.995. Determine the concentration of clonidine related compound B.

Calculate the amount, in $\mu\text{g}/\text{cm}^2$, of clonidine related compound B in the portion of the Transdermal System taken:

$$\text{Result} = CV/A$$

- C = concentration of clonidine related compound B from the linear regression analysis ($\mu\text{g}/\text{mL}$)
 V = volume of the *Sample solution* (mL)
 A = area of the sample system (cm^2)

Acceptance criteria: NMT 10.0 $\mu\text{g}/\text{cm}^2$

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in sealed, single-dose containers at a temperature not exceeding 30°.
- **LABELING:** The label states the total amount of clonidine in the Transdermal System and the release rate, in mg/day, for the duration of the application of one system. When more than one *Drug Release* test is given, the labeling states the *Drug Release* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS** (11)
 - USP Clonidine RS
 - USP Clonidine Related Compound B RS
 - 2-[(E)-2,6-Dichlorophenylimino]-1-(1-{2-[(E)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl)imidazolidine.
 - $\text{C}_{20}\text{H}_{20}\text{Cl}_4\text{N}_6$ 486.23