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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
Change to read:

• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Buffer solution: 242.28 g/L of tris(hydroxymethyl)aminomethane in water. Adjust with ▲diluted hydrochloric acid▲ (IRA 1-Aug-2024) 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* 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 solutions*, as obtained in the *Assay*.

ASSAY
Change to read:

• **Procedure**

▲[Note—The *Diluent* and the *Sample solution* preparation listed below are found suitable for transdermal systems that meet the requirements of *Drug Release Test 1*. Formulations labeled as meeting USP *Drug Release* test other than *Test 1* may need a different *Diluent* and different extraction procedures to achieve complete drug extraction from the transdermal systems.]▲ (IRA 1-Aug-2024)

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)

Diluent: Tetrahydrofuran and methanol (50:50)

System suitability solution: 250 µg/mL of USP Clonidine RS and 10 µg/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 at least three *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 µg/mL. [Note—The *Standard solutions* are stable for up to 2 days if stored at 4°.]

Sample solution: Nominally 179 µg/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 × 15-cm; 5-µm packing L10

Flow rate: 1 mL/min

Injection volume: 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

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

Relative standard deviation: NMT 2.0% for clonidine

Analysis

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

Construct a curve of concentration (µg/mL) of clonidine in the *Standard solutions* versus peak response by linear regression analysis. The correlation coefficient is 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 determined from the linear regression analysis (µg/mL)

C_U = nominal concentration of clonidine in the *Sample solution* (µg/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 ± 0.3° 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 ± 0.3°.

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.

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; 5-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 25 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Tailing factor: NMT 2.0

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:

$$\text{Result} = (C \times V)/(T \times A)$$

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 (cm^2)

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 ($C_9H_9Cl_2N_3$) from the Transdermal System, expressed as µg/h/cm^2 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 6.2.

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

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; 5-µm packing L1

Analytical: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.0 mL/min

Injection volume: 50 µL

Run time: NLT 1.4 times the retention time of clonidine

System suitability

Sample: *Standard solution* containing 5.3 µg/mL of USP Clonidine RS in *Medium*

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/cm^2):

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

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

b = y-intercept of the standard curve

m = slope of the standard curve

A = area of the system (cm^2)

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 ($C_9H_9Cl_2N_3$) from the Transdermal System, expressed as µg/h/cm^2 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 (trihydrate)▲ (IRA 1-Aug-2024) 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 clonidine 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; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 30 µL

Run time: NLT 1.4 times the retention time of clonidine

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 ($C_9H_9Cl_2N_3$) in the *Medium* (mg/mL) at each time point (*i*):

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

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 RS in 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 ($C_9H_9Cl_2N_3$) released in µg/h/cm^2 at each time point (i):

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

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

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 cm^2

T_i = current time point

T_{i-1} = previous time point

Tolerances: See *Table 4*.

Table 4

Time (h)	Release Rate (µg/h/cm^2)
8	5.5–11.0
24	2.5–5.5
96	2.5–5.0
168	2.0–3.8

The release rate of clonidine ($C_9H_9Cl_2N_3$) from the Transdermal System, expressed as µg/h/cm^2 at the times specified, conforms to *Drug Release ⟨724⟩, Acceptance Table 1*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 4*.

Medium: 0.1 mM phosphoric acid; 80 mL for Transdermal Systems labeled as 0.1 mg/day and 0.2 mg/day; 200 mL for Transdermal Systems labeled as 0.3 mg/day

Times: 8, 24, 96, and 168 h

Apparatus 7: 30 dips/min with an amplitude of 2.0 ± 0.2 cm. Use the appropriate sample holder: 5.092-cm diameter reciprocating disk sample holder for Transdermal Systems labeled as 0.1 mg/day and 0.2 mg/day (see *Drug Release ⟨724⟩*, *Figure 4*); cylinder sample holder for Transdermal Systems labeled as 0.3 mg/day (see *Drug Release ⟨724⟩*, *Figure 5b*).

Remove the release liner from the Transdermal System. Place the Transdermal System onto a piece of suitable cellulose membrane of sufficient size to fit the sample holder being used so that the contact adhesive side of the system is against the membrane. Ensure no air bubbles or creases exist between the membrane and the Transdermal System. Attach the membrane and system to the appropriate sample holder using O-rings,[1] so that the adhesive side is facing outward. Weigh the empty and dry medium tubes. Fill each medium tube with either 80 mL or 200 mL of *Medium* and equilibrate to 32.0 ± 0.3°. Attach the assembled membrane-system-sample holder onto the reciprocating arms of the drug release station, immerse the test sample into the *Medium*, and start the drug release test. At the specified time point of 8, 24, and 96 h, withdraw the *Sample solution* for analysis and immediately replace with fresh *Medium*. Continue the drug release test. At 168 h, remove each *Medium* tube, dry off the bath water outside the tube, and weigh. Replace calculated *Medium* loss due to evaporation with water.

Buffer: 1.36 g/L of potassium phosphate monobasic in water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (10:90)

Standard stock solution: 0.1 mg/mL of USP Clonidine RS, prepared as follows. Weigh a suitable amount of USP Clonidine RS in a suitable volumetric flask. Add methanol to about 10% of the flask volume. Sonicate if necessary. Dilute with *Medium* to volume.

Standard solutions: Prepare a minimum of 5 *Standard solutions* of USP Clonidine RS in *Medium* with varied concentrations that can bracket those of *Sample solutions* at different time points, from the *Standard stock solution*.

Sample solutions: At each specified time point, withdraw an appropriate amount of the solution under test.

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Columns

Guard: 3.9-mm × 2-cm; 5-µm packing L1

Analytical: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.25 mL/min

Injection volume: 25 µL

Run time: NLT 1.5 times the retention time of clonidine

System suitability

Sample: *Standard solution* with a concentration close to the middle level

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solutions* and *Sample solutions*

Plot a standard curve of concentration (µg/mL) versus peak response from clonidine by linear regression analysis using the *Standard solutions*. The square of the correlation coefficient is NLT 0.995.

Calculate the rate of clonidine ($C_9H_9Cl_2N_3$) released, in µg/h/cm^2, at each time point (i):

$$\text{Result}_i = (C_i \times V)/(T \times A)$$

C_i = concentration of clonidine in the sample withdrawn at each time point (i) as determined from the standard curve (µg/mL)

V = volume of the *Medium*, 80 or 200 mL

T = time at each time point (h)

A = area of the Transdermal System (cm^2)

Tolerances: See *Table 5*.

Table 5

Time Point (*i*)	Time (h)	Release Rate (µg/h/cm^2)
1	8	13.7–22.2
2	24	2.9–6.0
3	96	0.9–2.7
4	168	0.4–1.4

The release rate of clonidine ($C_9H_9Cl_2N_3$) from the Transdermal System, expressed as µg/h/cm^2 at the times specified, conforms to *Drug Release ⟨724⟩, Acceptance Table 1*.

• **Uniformity of Dosage Units ⟨905⟩:** Meets the requirements

Delete the following:

▲IMPURITIES

• **Organic Impurities**▲ (IRA 1-Aug-2024)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in sealed, single-dose containers at controlled room temperature.

• **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.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Clonidine RS

USP Clonidine Related Compound B RS

2-(2,6-Dichlorophenylimino)-1-{1-[2-(2,6-dichlorophenylimino)imidazolidin-1-yl]-ethyl}imidazolidine;

Also known as 2-[(*E*)-2,6-Dichlorophenylimino]-1-(1-{2-[(*E*)-2,6-dichlorophenylimino]-imidazolidin-1-yl}-ethyl) imidazolidine.

$C_{20}H_{20}Cl_4N_6$ ▲486.22▲ (IRA 1-Aug-2024)

[1] Viton O-rings or equivalent.

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

Topic/Question	Contact	Expert Committee
CLONIDINE TRANSDERMAL SYSTEM	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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