

Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-Aug-2024
Document Type: USP Monographs
DocId: GUID-3B7951FE-ECF9-4B2E-9080-687FECFEA59D_8_en-US
DOI: https://doi.org/10.31003/USPNF_M18610_08_01
DOI Ref: 36je5

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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 (C₉H₉Cl₂N₃).
[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
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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 (C₉H₉Cl₂N₃) 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 (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.