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Estradiol Transdermal System

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click

<https://www.uspnf.com/rb-estradiol-transdermal-system-20191122>.

DEFINITION

Estradiol Transdermal System contains NLT 85.0% and NMT 120.0% of the labeled amount of estradiol ($C_{18}H_{24}O_2$).

IDENTIFICATION

- **A.** 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

Diluent: [Acetonitrile](#) and [water](#) (1:1)

Mobile phase: [Acetonitrile](#) and [water](#) (55:45)

Standard solution: 0.1 mg/mL of [USP Estradiol RS](#) in *Diluent*

Sample solutions: Equivalent to 0.1 mg/mL of estradiol in *Diluent*, prepared as follows. Cut 10 Transdermal Systems into pieces, and keep the pieces from each system separate. Remove and discard the protective liners, if present, from the strips. Transfer the pieces of each system into separate stoppered flasks of suitable size, and add a measured volume of *Diluent* to each flask to provide the target estradiol concentration. Shake by mechanical means for about 3 h, and sonicate for 15 min.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; packing [L1](#)

Column temperature: 35°

Flow rate: 1 mL/min

Injection size: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: 0.9–1.6

Relative standard deviation: NMT 2.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of estradiol ($C_{18}H_{24}O_2$) in each Transdermal System taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of [USP Estradiol RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of estradiol in the *Sample solution* (mg/mL)

Use the individual assays to determine *Uniformity of Dosage Units*.

Acceptance criteria: 85.0%–120.0%

OTHER COMPONENTS

- **ALCOHOL CONTENT** (if present)

Diluent: [Acetonitrile](#) and [water](#) (1:1)

Internal standard solution: Prepare by diluting 4.0 mL of [dehydrated methanol](#) with [water](#) to 100 mL.

Standard stock solution: 5.0 mg/mL of [ethanol](#) in *Diluent*. Prepare by weighing by difference 1.6 mL of [dehydrated alcohol](#) into a tared 50-mL volumetric flask containing 15 mL of [water](#), and dilute with *Diluent* to volume. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Standard solution: 2.5 mg/mL of [ethanol](#). Prepare by pipeting 25.0 mL of the *Standard stock solution* into a 50-mL volumetric flask. Add 5.0 mL of the *Internal standard solution*, and dilute with water to volume.

Sample solutions: Prepare as directed for the *Sample solutions* in the Assay, with the following changes. Pipet 25.0 mL of each solution into individual 50-mL volumetric flasks. Add 5.0 mL of the *Internal standard solution*, and dilute with [water](#) to volume.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: GC

Detector: Flame ionization

Column: 2-mm × 2-m glass; support [S2](#)

Temperature

Column: 100°

Injection port: 200°

Detector: 200°

Carrier gas: Helium

Flow rate: 30 mL/min

Injection size: 2 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for the methanol and alcohol peaks are 0.4 and 1.0, respectively.]

Suitability requirements

Relative standard deviation: NMT 1.5% from the peak response ratio of alcohol to methanol

Analysis

Samples: *Standard solution* and *Sample solutions*

Calculate the percentage of alcohol (C₂H₅OH) in each Transdermal System taken:

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

R_U = peak response ratio of alcohol to methanol from the *Sample solution*

R_S = peak response ratio of alcohol to methanol from the *Standard solution*

C_S = concentration of dehydrated alcohol in the *Standard solution* (mg/mL)

C_U = nominal concentration of alcohol in the *Sample solution* (mg/mL)

Average the percentage of alcohol found in the Transdermal Systems analyzed.

Acceptance criteria: 80%–120% of the labeled amount of C₂H₅OH

PERFORMANCE TESTS

Change to read:

• [DRUG RELEASE \(724\)](#).

Test 1: For products labeled for dosing every 84 h

Medium: [Water](#); 900 mL, deaerated

Apparatus 5: 50 rpm

Times: 24, 48, and 96 h

Mobile phase: [Water](#) and [acetonitrile](#) (3:2)

Standard solution: 9 µg/mL of [USP Estradiol RS](#) in [dehydrated alcohol](#). Dilute this solution with *Medium* to obtain solutions having concentrations of about 0.9, 0.45, and 0.045 µg/mL.

Sample solution: At each sampling time interval, withdraw a 10-mL aliquot of the solution under test.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: Fluorimetric, with excitation at 220 nm and emission at 270 nm

Column: 4.6-mm × 3-cm; packing [L1](#)

Temperature: 40°

Flow rate: 1.0 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Tailing factor: 0.9–2.5

Relative standard deviation: NMT 3.0%, using 0.45 µg/mL of the *Standard solution*

Analysis: Plot the peak responses of the *Standard solutions* versus concentration, in µg/mL, of estradiol. From the graph determine the amount, in µg/mL, of estradiol released. Calculate the cumulative release rate as percentage of the labeled amount of estradiol:

At 24 h:

$$\text{Result} = \{[900(A_1 - b)] / (1000 \times m \times L)\} \times 100$$

At 48 h:

$$\text{Result} = \{[890(A_2 - b) + 10(A_1 - b)] / (1000 \times m \times L)\} \times 100$$

At 96 h:

$$\text{Result} = \{[880(A_3 - b) + 10(A_2 - b) + 10(A_1 - b)] / (1000 \times m \times L)\} \times 100$$

A_1 = peak area of estradiol in the *Sample solution* at the first time interval

A_n = peak area of estradiol in the *Sample solution* at the release interval n

m = slope of the calibration curve

b = y-intercept of the calibration curve

L = Transdermal System label claim (mg)

Tolerances: See [Table 1](#).

Table 1

Time (h)	Amount Dissolved (release rate)
24	1.2%–6.0%
48	3.0%–11.4%
96	5.0%–16.3%

The percentages of the labeled amount of estradiol ($C_{18}H_{24}O_2$) released at the times specified conform 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: 0.005 M phosphate buffer, pH 5.5, containing 0.3% [sodium lauryl sulfate](#); 500 mL

Apparatus 5: 100 rpm. Use a 76-mm stainless steel disk assembly. Adhere the patch to the disk assembly using transfer tape. [NOTE—A suitable tape is available as 3M adhesive transfer tape 927, [www.mmm.com](#).]

Times: 1, 4, 8, and 24 h

Mobile phase: [Acetonitrile](#) and [water](#) (1:1)

Standard stock solution: 800 µg/mL of [USP Estradiol RS](#) in [acetone](#)

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a solution having a known concentration close to that expected in the solution under test, assuming 100% drug release.

Sample solution: At each sampling time interval, withdraw a known volume aliquot of the solution under test.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 205 nm

Column: 3.9-mm × 30-cm; packing [L1](#)

Flow rate: 1.0 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis: Calculate the amount of estradiol released at each sampling time:

$$M_i = (r_U/r_S) \times C_S \times V_i$$

$$m_i = M_i$$