Estradiol Transdermal System

Type of Posting: Revision Bulletin
Posting Date: 27–Jan–2017
Official Date: 01–Feb–2017
Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Estradiol Transdermal System monograph. The purpose for the revision is to add Drug Release Test 4 to accommodate a drug product that was approved with different drug release test conditions and acceptance criteria.

The liquid chromatographic procedure used in Drug Release Test 4 is based on analyses performed with the Symmetry C18 brand of L1 column manufactured by Waters. The typical retention time for estradiol is about 4.5 minutes.

The Estradiol Transdermal System Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the Second Supplement to USP 40–NF 35.

Should you have any questions, please contact Gerald Hsu, Ph.D., Senior Scientific Liaison (240-221-3097 or gdh@usp.org).
Estradiol Transdermal System

**DEFINITION**
Estradiol Transdermal System contains NLT 85.0% and NMT 120.0% of the labeled amount of estradiol (C₁₈H₂₄O₂).

**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 stopped 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: Flame ionization
Column: 2-mm x 2-m glass; support S2
Temperature: 80°
Injection port: 200°
Detector: 200°
Carrier gas: Helium
Flow rate: 30 mL/min
Injection size: 2 µL

**System suitability**
Sample: Standard solution

- **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:

\[
\text{Result} = \frac{R_u}{R_s} \times \left(\frac{C_u}{C_s}\right) \times 100
\]

- \(R_u\) = 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 alcohol in the Sample solution (mg/mL)

Use the individual assays to determine Uniformity of Dosage Units.

**Acceptance criteria:** 80%–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.

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

**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:

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

At 48 h:

\[
\text{Result} = \frac{([890(A_2 - b) + 10(A_3 - b)]/(1000 \times m \times L) \times 100)
\]

At 96 h:

\[
\text{Result} = \frac{([880(A_3 - b) + 10(A_4 - b) + 10(A_1 - b)]/(1000 \times m \times L) \times 100)
\]

\[A_1 = \text{peak area of estradiol in the Sample solution at the first time interval}
\]

\[A_n = \text{peak area of estradiol in the Sample solution at the release interval } n\]

\[m = \text{slope of the calibration curve}\]

\[b = \text{y-intercept of the calibration curve}\]

\[L = \text{Transdermal System label claim (mg)}\]

Tolerances: *See Table 1.· (RB 1-Feb-2017)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>1.2%–6.0%</td>
</tr>
<tr>
<td>48</td>
<td>3.0%–11.4%</td>
</tr>
<tr>
<td>96</td>
<td>5.0%–16.3%</td>
</tr>
</tbody>
</table>

*The percentages of the labeled amount of estradiol (C18H24O2) released at the times specified conform to Drug Release (724), Acceptance Table 1.· (RB 1-Feb-2017)

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 acetonitrile

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, assuring 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
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:

\[
m_1 = M_1
\]

\[
m_2 = M_2 + M_1(V_d/V_i)
\]

\[
m_3 = M_3 + M_2(V_d/V_2) + M_1(V_d/V_i)
\]

\[
m_4 = M_4 + M_3(V_d/V_3) + M_2(V_d/V_2) + M_1(V_d/V_i)
\]

Calculate the percentage of the labeled amount of estradiol released at each sampling time:

\[
\text{Result} = \frac{(m_4/L) \times 100}{100}
\]

\[M_1 = \text{amount of estradiol released into the Medium at a given sampling time (mg)}
\]

\[r_0 = \text{peak response from the Sample solution}\]

\[r_S = \text{peak response from the Standard solution}\]

\[C_1 = \text{concentration of the Standard solution (mg/mL)}\]

\[V_i = \text{corrected volume of the Medium at a given sampling time (mL)}\]

\[m_1 = \text{total amounts of estradiol released from the patch at given sampling times (mg)}\]

\[m_2 = \text{amounts of estradiol released into the Medium at given sampling times (mg)}\]

\[V_d = \text{volume of the aliquot taken from the dissolution vessel at each sampling time (mL)}\]

\[V_i = \text{volumes of Medium at given sampling times (mL)}\]

\[V_a = \text{Transdermal System label claim (mg)}\]

Tolerances: *See Table 2.· (RB 1-Feb-2017)

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15%–40%</td>
</tr>
<tr>
<td>4</td>
<td>45%–70%</td>
</tr>
<tr>
<td>8</td>
<td>70%–90%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

*The percentages of the labeled amount of estradiol (C18H24O2) released at the times specified conform to Drug Release (724), Acceptance Table 1.· (RB 1-Feb-2017)

Test 3: If the product complies with this test, the labeling indicates that it meets USP Drug Release Test 3.
Medium: 1% (w/v) polysorbate 40 in water; 900 mL
Apparatus 5: 50 rpm
Times: 4, 8, and 24 h
Standard stock solution: Known concentration (mg/mL) of USP Estradiol RS in methanol
**Official February 1, 2017**

- **Estradiol**

  **Revision Bulletin**

  **Tolerances:**

  - **Analysis:** Calculate the cumulative release rate as a percentage of the labeled amount of estradiol:

  \[
  \text{Result} = \left( \frac{[900(A - b)](1000 \times m \times L)}{100} \right) \times 100
  \]

  - **A** = peak area of estradiol in the Sample solution at each time interval
  - **b** = y-intercept of the calibration curve
  - **m** = slope of the calibration curve
  - **L** = Transdermal System label claim (mg)

  **Tolerances:** The percentages of the labeled amount of estradiol (C\textsubscript{18}H\textsubscript{24}O\textsubscript{2}) released at the times specified conform to Table 3, Table 4, and Table 5.

  **Table 3**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
</tr>
</tbody>
</table>

  **L2 (12 units)**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 12)</th>
<th>Amount Dissolved (individual values)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
</tr>
</tbody>
</table>

  **L3 (24 units)**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 24)</th>
<th>Amount Dissolved (individual for 22 units of 24)</th>
<th>Amount Dissolved (individual for 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
<td>29%–82%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
<td>43%–109%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
<td>NLT 60%</td>
</tr>
</tbody>
</table>

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

  **Medium:** Water; 500 mL for 0.25 mg/day and 0.0375 mg/day dosage; 900 mL for 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day dosage

  **Apparatus 6:** 50 rpm. Use a stainless steel cylinder assembly. Adhere the Transdermal System to the cylinder assembly using a strip of suitable double-sided transfer tape.

  **Times:** 2, 6, and 12 h

  **Buffer solution:** 25 mM of monobasic sodium phosphate, adjusted with phosphoric acid to a pH of 3.0

  **Mobile phase:** Acetonitrile and Buffer solution (40:60)

  **Standard stock solution:** 0.2 mg/mL of USP Estradiol RS in methanol

  **Chromatographic system**

  - Mode: LC
  - Detector: UV 225 nm
  - Column: 4.6-mm × 15-cm, 5-µm packing L1 for 9-cm\textsuperscript{2} systems; 4.6-mm × 12.5-cm, 5-µm packing L1 for 18-, 27-, or 36-cm\textsuperscript{2} systems. In any case, a guard column containing packing L1 is used.
  - Flow rate: 0.5 mL/min
  - Injection size: 50 µL

  **System suitability**

  - **Mode:** Standard solution
  - **Relative standard deviation:** NMT 2.0%

  **Analysis:** Calculate the cumulative release rate as a percentage of the labeled amount of estradiol:

  \[
  \text{Result} = \left( \frac{[C_S]}{C_i} \right) \times \text{L}
  \]

  - **C\textsubscript{S}** = concentration of USP Estradiol RS in the Standard solution (mg/mL)
  - **C\textsubscript{i}** = concentration of estradiol (C\textsubscript{18}H\textsubscript{24}O\textsubscript{2}) in the sample withdrawn from the vessel at time point \(t\)

  **Note:** The percentages of the labeled amount of estradiol (C\textsubscript{18}H\textsubscript{24}O\textsubscript{2}) released at the times specified conform to Table 3, Table 4, and Table 5.

  **Table 5**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (average of 24)</th>
<th>Amount Dissolved (individual for 24)</th>
<th>Amount Dissolved (individual for 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>40%–71%</td>
<td>34%–77%</td>
<td>29%–82%</td>
</tr>
<tr>
<td>8</td>
<td>58%–94%</td>
<td>50%–102%</td>
<td>43%–109%</td>
</tr>
<tr>
<td>24</td>
<td>NLT 75%</td>
<td>NLT 68%</td>
<td>NLT 60%</td>
</tr>
</tbody>
</table>

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Table 6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (release rate, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>20–40</td>
</tr>
<tr>
<td>6</td>
<td>48–68</td>
</tr>
<tr>
<td>12</td>
<td>70–90</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of estradiol (C_{18}H_{24}O_{2}) released at the times specified conform to USP Estradiol RS (711), Acceptance Table 2. [RB 1-Feb-2017]

**Uniformity of Dosage Units (905):** The results from the Transdermal Systems used in the Assay meet the requirements.

**Additional Requirements**

**Packaging and Storage:** Preserve in hermetic, light-resistant, unit-dose pouches.

**Change to read:**

- **Labeling:** The label states the total amount of estradiol in the Transdermal System and the release rate, in mg/day, for the duration of 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.

  [RB 1-Feb-2017]

- **USP Reference Standards (11)**
  USP Estradiol RS