Diltiazem Hydrochloride Extended-Release Capsules

Type of Posting: Notice of Intent to Revise
Posting Date: 31–Jul–2020
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Diltiazem Hydrochloride Extended-Release Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 22.

- The analytical procedure in Dissolution Test 22 was validated using an X-Bridge C18 brand of L1 column. The typical retention time for diltiazem is about 3 min.

The revision also necessitates a change in the table numbering in the test for Organic Impurities.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.1

Should you have any questions, please contact Tsion Bililign, Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-816-8286 or tb@usp.org).

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1 This text is not the official version of a USP–NF monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the USP–NF for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product’s final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the Pharmacopeial Forum must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the USP–NF.
Diltiazem Hydrochloride Extended-Release Capsules

**DEFINITION**
Diltiazem Hydrochloride Extended-Release Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl).

**IDENTIFICATION**
- **A.** The UV-Vis spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **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**
  - **Solution A:** 0.79 g/L of ammonium bicarbonate in water. Adjust with diluted ammonia solution or acetic acid to a pH of 8.0.
  - **Solution B:** Acetonitrile
  - **Mobile phase:** See *Table 1*.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>2.0</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>5.0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>13.0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>16.0</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>20.0</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>20.1</td>
<td>95</td>
<td>5</td>
</tr>
<tr>
<td>25.0</td>
<td>95</td>
<td>5</td>
</tr>
</tbody>
</table>

**Diluent:** Acetonitrile and water (40:60)

**Standard solution:** 0.05 mg/mL of USP Diltiazem Hydrochloride RS in Diluent

**Sample stock solution:** Nominally 0.5 mg/mL of diltiazem hydrochloride from the Capsules in Diluent prepared as follows. Transfer a portion of finely powdered contents of NLT 20 Capsules to a suitable volumetric flask. Add Diluent equivalent to 80% of the flask volume, mechanically shake for 30 min, and sonicate for 60 min. Dilute with the Diluent to volume. Centrifuge and use the supernatant.

**Sample solution:** Nominally 0.05 mg/mL of diltiazem hydrochloride prepared in Diluent from Sample stock solution

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

**Mode:** LC
**Detector:** UV 240 nm. For Identification A, use a diode array detector in the range of 190–400 nm.
**Column:** 2.1-mm × 15-cm; 1.7-µm packing

**Flow rate:** 0.3 mL/min

**Injection volume:** 2.0 µL

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

- **Tailing factor:** NMT 2.0
- **Relative standard deviation:** NMT 1.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \( r_U \) = peak response of diltiazem from the *Sample solution*
- \( r_S \) = peak response of diltiazem from the *Standard solution*
- \( C_S \) = concentration of *USP Diltiazem Hydrochloride RS* in the *Standard solution* (mg/mL)
- \( C_U \) = nominal concentration of diltiazem hydrochloride in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

For products labeled for dosing every 12 h

**Test 1:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 1*.

- **Medium:** Water; 900 mL
- **Apparatus 2:** 100 rpm
- **Times:** 3, 9, and 12 h
- **Detector:** UV 237 nm

**Standard solution:** *USP Diltiazem Hydrochloride RS* in *Medium*

**Sample solution:** Sample per *Dissolution (711)*. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

**Tolerances:** See *Table 2*.

**Table 2**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>10–25</td>
</tr>
<tr>
<td>9</td>
<td>45–85</td>
</tr>
<tr>
<td>12</td>
<td>NLT 70</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to *Dissolution (711)*, *Acceptance Table 2*.

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

- **Medium:** Water; 900 mL
**Apparatus 2:** 100 rpm  
**Times:** 4, 8, 12, and 24 h  
**Detector:** UV 237 nm  
**Standard solution:** USP Diltiazem Hydrochloride RS in Medium  
**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.  
**Tolerances:** See Table 3.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>10–25</td>
</tr>
<tr>
<td>8</td>
<td>35–60</td>
</tr>
<tr>
<td>12</td>
<td>55–80</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 5:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.

**Medium:** 0.05 M phosphate buffer, pH 7.2; 900 mL  
**Apparatus 2:** 50 rpm  
**Times:** 1, 3, and 8 h  
**Detector:** UV 237 nm  
**Standard solution:** USP Diltiazem Hydrochloride RS in Medium  
**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.  
**Tolerances:** See Table 4.

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 15</td>
</tr>
<tr>
<td>3</td>
<td>45–70</td>
</tr>
<tr>
<td>8</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 10:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 10.

**Buffer:** Dissolve 7.1 g of anhydrous dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5.

**Medium:** Buffer; 900 mL  
**Apparatus 1:** 100 rpm  
**Times:** 1, 6, 9, and 24 h  
**Detector:** UV 237 nm
Standard solution: USP Diltiazem Hydrochloride RS in Medium

Sample solution: Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.

Tolerances: See Table 5.

### Table 5

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 10</td>
</tr>
<tr>
<td>6</td>
<td>10–30</td>
</tr>
<tr>
<td>9</td>
<td>34–60</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

For products labeled for dosing every 24 h

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

**Medium:** Water; 900 mL

**Apparatus 2:** 100 rpm

**Times:** 1, 4, 10, and 15 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.

Tolerances: See Table 6.

### Table 6

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5–20</td>
</tr>
<tr>
<td>4</td>
<td>30–50</td>
</tr>
<tr>
<td>10</td>
<td>70–90</td>
</tr>
<tr>
<td>15</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

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

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 100 rpm

**Times:** 6, 12, 18, 24, and 30 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.
Tolerances: See Table 7.

Table 7

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>20–45</td>
</tr>
<tr>
<td>12</td>
<td>25–50</td>
</tr>
<tr>
<td>18</td>
<td>35–70</td>
</tr>
<tr>
<td>24</td>
<td>NLT 70</td>
</tr>
<tr>
<td>30</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 6: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 6.

Medium: Water; 900 mL
Apparatus 1: 100 rpm
Times: 2, 4, 8, 12, and 16 h
Detector: UV 237 nm

Standard solution: USP Diltiazem Hydrochloride RS in Medium
Sample solution: Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.

Tolerances: See Table 8.

Table 8

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 25</td>
</tr>
<tr>
<td>4</td>
<td>25–50</td>
</tr>
<tr>
<td>8</td>
<td>60–85</td>
</tr>
<tr>
<td>12</td>
<td>NLT 70</td>
</tr>
<tr>
<td>16</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

Test 7: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 7.

Buffer: Transfer 115 mL of acetic acid to a 10-L volumetric flask, dilute with water to volume, and mix (Solution A). Transfer 165.4 g of anhydrous sodium acetate to a 10-L volumetric flask, dilute with water to volume, and mix (Solution B). Mix 4410 mL of Solution A with 1590 mL of Solution B. Adjust, if necessary, with the addition of Solution A or Solution B to a pH of 4.2 ± 0.05.

Medium: Buffer; 900 mL
Apparatus 2: 100 rpm
Times: 1, 4, 10, and 15 h
Detector: UV 237 nm
**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See Table 9.

### Table 9

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 10</td>
</tr>
<tr>
<td>4</td>
<td>15–35</td>
</tr>
<tr>
<td>10</td>
<td>65–85</td>
</tr>
<tr>
<td>15</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S · HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 8:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 8.

- **Medium:** Water; 900 mL
- **Apparatus 2:** 100 rpm
- **Times:** 1, 4, 10, and 15 h
- **Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per Dissolution (711). Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See Table 10.

### Table 10

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5–20</td>
</tr>
<tr>
<td>4</td>
<td>30–50</td>
</tr>
<tr>
<td>10</td>
<td>60–90</td>
</tr>
<tr>
<td>15</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S · HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 9:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 9.

[Note—Perform the test separately in each of the two media.]

- **Medium 1:** 0.1 N hydrochloric acid; 900 mL
- **Medium 2:** Simulated intestinal fluid TS, prepared without enzyme and adjusted to a pH of 7.5 ± 0.1; 900 mL
- **Apparatus 2:** 75 rpm
- **Time for Medium 1:** 2 h
- **Times for Medium 2:** 2, 12, 18, and 24 h
- **Detector:** UV 237 nm
**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per *Dissolution (711).* Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See Table 11.

---

**Table 11**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved, Medium 1 (%)</th>
<th>Amount Dissolved, Medium 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0–5</td>
<td>20–45</td>
</tr>
<tr>
<td>12</td>
<td>—</td>
<td>35–55</td>
</tr>
<tr>
<td>18</td>
<td>—</td>
<td>NLT 60</td>
</tr>
<tr>
<td>24</td>
<td>—</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S · HCl) dissolved at the times specified conform to *Dissolution (711)*, *Acceptance Table 2*.

**Test 11:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 11.*

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 100 rpm

**Times:** 1, 6, 12, and 18 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per *Dissolution (711).* Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See Table 12.

---

**Table 12**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMT 10</td>
</tr>
<tr>
<td>6</td>
<td>30–40</td>
</tr>
<tr>
<td>12</td>
<td>36–58</td>
</tr>
<tr>
<td>18</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S · HCl) dissolved at the times specified conform to *Dissolution (711)*, *Acceptance Table 2*.

**Test 12:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 12.* Proceed as directed in *Dissolution (711), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms.*

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 2, 8, 14, and 24 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium
Sample solution: Sample per *Dissolution (711)*. Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See *Table 13.*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 20</td>
</tr>
<tr>
<td>8</td>
<td>30–55</td>
</tr>
<tr>
<td>14</td>
<td>NLT 65</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride \((C_{22}H_{26}N_2O_4S \cdot HCl)\) dissolved at the times specified conform to *Dissolution (711)*, Acceptance Table 2.

**Test 13:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 13. Proceed as directed in *Dissolution (711), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms.*

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 2, 8, 14, and 24 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Sample per *Dissolution (711)*. Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Tolerances:** See *Table 14.*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 20</td>
</tr>
<tr>
<td>8</td>
<td>30–55</td>
</tr>
<tr>
<td>14</td>
<td>60–80</td>
</tr>
<tr>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride \((C_{22}H_{26}N_2O_4S \cdot HCl)\) dissolved at the times specified conform to *Dissolution (711)*, Acceptance Table 2.

**Test 14:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 14. Proceed as directed in *Dissolution (711), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms.*

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 100 rpm

**Times:** 6, 12, 18, 24, and 30 h

**Detector:** UV 237 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium
**Sample solution:** Sample per *Dissolution (711)*. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

**Tolerances:** See *Table 15*.

### Table 15

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>20–45</td>
</tr>
<tr>
<td>12</td>
<td>25–50</td>
</tr>
<tr>
<td>18</td>
<td>35–70</td>
</tr>
<tr>
<td>24</td>
<td>NLT 70</td>
</tr>
<tr>
<td>30</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S·HCl) dissolved at the times specified conform to *Dissolution (711), Acceptance Table 2*.

**Test 15:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 15*. Proceed as directed in *Dissolution (711), Procedure, Apparatus 1 and Apparatus 2, Extended-Release Dosage Forms*.

- **Medium:** 0.05 M phosphate buffer, pH 7.5; 900 mL
- **Apparatus 2:** 75 rpm
- **Times:** 2, 4, 8, 12, and 16 h
- **Detector:** UV 237 nm
- **Standard solution:** USP Diltiazem Hydrochloride RS in *Medium*
- **Sample solution:** Sample per *Dissolution (711)*. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

**Tolerances:** See *Table 16*.

### Table 16

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>NMT 25</td>
</tr>
<tr>
<td>4</td>
<td>20–40</td>
</tr>
<tr>
<td>8</td>
<td>60–85</td>
</tr>
<tr>
<td>12</td>
<td>NLT 70</td>
</tr>
<tr>
<td>16</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C$_{22}$H$_{26}$N$_2$O$_4$S·HCl) dissolved at the times specified conform to *Dissolution (711), Acceptance Table 2*.

**Test 16:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 16*. Proceed as directed for *Test 3*.

- **Detector:** UV 238 nm
- **Tolerances:** See *Table 17*.
The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to \textit{Dissolution (711), Acceptance Table 2}.

**Test 17:** If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 17}.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Apparatus 2:** 100 rpm, with wire helix sinkers

**Times:** 6, 12, and 30 h

**Detector:** UV 238 nm

**Standard solution:** USP Diltiazem Hydrochloride RS in Medium

**Sample solution:** Dilute with Medium, if necessary, to a concentration that is similar to that of the Standard solution.

**Blank:** Medium

**Tolerances:** See \textit{Table 18}.

### Table 17

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>20–45</td>
</tr>
<tr>
<td>12</td>
<td>30–55</td>
</tr>
<tr>
<td>18</td>
<td>40–75</td>
</tr>
<tr>
<td>24</td>
<td>NLT 70</td>
</tr>
<tr>
<td>30</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

Test 18: If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 18}.

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Times:** 2, 4, 8, and 12 h

**Detector:** UV 237 nm

**Standard stock solution:** 0.28 mg/mL of USP Diltiazem Hydrochloride RS in Medium prepared as follows. To a suitable amount of USP Diltiazem Hydrochloride RS in a suitable volumetric flask, add Medium to 50% of the volume of the flask and sonicate for 5 min to dissolve. Dilute with Medium to volume.

**Standard solution:** 0.014 mg/mL of USP Diltiazem Hydrochloride RS in Medium from the Standard stock solution

**Sample solution:** At the times specified, withdraw 10 mL of the solution under test. Replace the aliquots withdrawn for analysis with equal volumes of fresh portions of Medium maintained at 37°. Pass the
solution through a PVDF filter of 0.45-µm pore size. Discard the first 2 mL of filtrate. Dilute with Medium to a concentration that is similar to that of the Standard solution.

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the concentration of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) in the sample withdrawn from the vessel at each time point \( i \):

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times C_S \times D
\]

- \( A_U \) = absorbance of diltiazem from the Sample solution at each time point
- \( A_S \) = absorbance of diltiazem from the Standard solution
- \( C_S \) = concentration of USP Diltiazem Hydrochloride RS in the Standard solution (mg/mL)
- \( D \) = dilution factor for the Sample solution

Calculate the percentage of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at each time point \( i \):

\[
\text{Result}_1 = C_i \times V \times (1/L) \times 100
\]

\[
\text{Result}_2 = \left[ (C_2 \times V) + (C_1 \times V_S) \right] \times (1/L) \times 100
\]

\[
\text{Result}_3 = \left[ (C_3 \times V) + [ (C_2 + C_1) \times V_S] \right] \times (1/L) \times 100
\]

\[
\text{Result}_4 = \left[ (C_4 \times V) + [ (C_3 + C_2 + C_1) \times V_S] \right] \times (1/L) \times 100
\]

- \( C_i \) = concentration of diltiazem hydrochloride in the Sample solution withdrawn at the specified time point (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Capsule)
- \( V_S \) = volume of the Sample withdrawn at each time point (mL)

**Tolerances:** See Table 19.

<table>
<thead>
<tr>
<th>Time Point (( i ))</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>33–58</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>68–88</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C_{22}H_{26}N_{2}O_{4}S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 19:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 19.

**Medium:** 0.1 N hydrochloric acid; 900 mL

**Temperature:** 37.0°–37.5°
**Apparatus 2**: 100 rpm, with a suitable sinker

**Times**: 1, 4, 12, 18, and 24 h

**Detector**: UV 238 nm

**Cell**: 0.5 mm

**Standard solution**: 0.4 mg/mL of USP Diltiazem Hydrochloride RS in Medium

**Sample solution**: A portion of the solution under test at the time points specified

**Analysis**

**Samples**: Standard solution and Sample solution

Use an automatic dissolution system with an appropriate dissolution software.

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at each time point $i$:

$$\text{Result} = \left(\frac{A_U}{A_S}\right) \times \left(\frac{C_S}{L}\right) \times V \times 100$$

$A_U$ = absorbance of diltiazem from the Sample solution at each time point

$A_S$ = absorbance of diltiazem from the Standard solution

$C_S$ = concentration of USP Diltiazem Hydrochloride RS in the Standard solution (mg/mL)

$L$ = label claim (mg/Capsule)

$V$ = volume of Medium, 900 mL

**Tolerances**: See Table 20.

<table>
<thead>
<tr>
<th>Time Point ($i$)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>NMT 10</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>15–35</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>30–50</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>50–70</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride ($C_{22}H_{26}N_2O_4S \cdot HCl$) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

**Test 20**: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 20. Dissolution Test 20 is suitable for products labeled to contain 360 mg of diltiazem hydrochloride.

**Medium**: 0.1 N hydrochloric acid; 900 mL

**Apparatus 2**: 100 rpm

**Times**: 6, 12, 18, and 24 h

**Detector**: UV 237 nm

**Cell**: 0.05 cm

**Standard solution**: 0.4 mg/mL of USP Diltiazem Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Diltiazem Hydrochloride RS into a suitable volumetric flask, and add methanol to 5% of the total volume of the flask to dissolve. Dilute with Medium to volume.

**Sample solution**: Pass a portion of the solution under test through a suitable filter at the time points specified.
**Blank:** Medium  
**Analysis**  
**Samples:** *Standard solution* and *Sample solution*

Calculate the concentration of diltiazem hydrochloride \( (C_{22}H_{26}N_2O_4S \cdot HCl) \) in the sample withdrawn from the vessel at each time point \((i)\):

\[
\text{Result} = \left( \frac{A_i}{A_S} \right) \times C_S
\]

\(A_i\) = absorbance of diltiazem from the *Sample solution* at each time point  
\(A_S\) = absorbance of diltiazem from the *Standard solution*  
\(C_S\) = concentration of *USP Diltiazem Hydrochloride RS* in the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of diltiazem hydrochloride \( (C_{22}H_{26}N_2O_4S \cdot HCl) \) dissolved at each time point \((i)\):

\[
\text{Result}_1 = C_i \times V \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_2 = \left\{ \left( C_2 \times (V - V_S) \right) + \left( C_1 \times V_S \right) \right\} \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_3 = \left\{ \left( C_3 \times \left( V - (2 \times V_S) \right) \right) + \left( C_2 + C_1 \times V_S \right) \right\} \times \left( \frac{1}{L} \right) \times 100
\]

\[
\text{Result}_4 = \left\{ \left( C_4 \times \left( V - (3 \times V_S) \right) \right) + \left( (C_3 + C_2 + C_1) \times V_S \right) \right\} \times \left( \frac{1}{L} \right) \times 100
\]

\(C_i\) = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)  
\(V\) = volume of *Medium*, 900 mL  
\(L\) = label claim (mg/Capsule)  
\(V_S\) = volume of the *Sample* withdrawn at each time point (mL)

**Tolerances:** See *Table 21.*

### Table 21

<table>
<thead>
<tr>
<th>Time Point ((i))</th>
<th>Time ((h))</th>
<th>Amount Dissolved ((%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>30–50</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>35–55</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td>50–70</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride \( (C_{22}H_{26}N_2O_4S \cdot HCl) \) dissolved at the times specified conform to *Dissolution (711)*, *Acceptance Table 2.*

**Test 21:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 21.*

**Medium:** 0.1 N hydrochloric acid; 900 mL, deaerated  
**Apparatus 2:** 100 rpm  
**Times:** 2, 4, 14, 18, and 24 h  
**Standard stock solution:** 1.33 mg/mL of *USP Diltiazem Hydrochloride RS* in Medium  
**Standard solution:** \((L/900)\) mg/mL of *USP Diltiazem Hydrochloride RS* from the *Standard stock solution* in *Medium*, where \(L\) is the label claim in mg/Capsule
Sample solution: Pass a portion of the solution under test at the time points specified through a suitable filter.

Instrumental conditions
(See Ultraviolet-Visible Spectroscopy (857).)

Mode: UV

Analytical wavelength: 237 nm for 120 mg, 180 mg, and 240 mg strength Capsules.
260 nm for 300 mg and 360 mg strength Capsules.

Cell: 1 mm for 120 mg, 180 mg, and 240 mg strength Capsules.
2 mm for 300 mg and 360 mg strength Capsules.

Blank: Medium

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of diltiazem hydrochloride (C₂₂H₂₆N₂O₄S·HCl) dissolved at each time point (i):

\[
\text{Result} = \left( \frac{A_U}{A_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times 100
\]

\(A_U\) = absorbance of diltiazem from the Sample solution at each time point

\(A_S\) = absorbance of diltiazem from the Standard solution

\(C_S\) = concentration of USP Diltiazem Hydrochloride RS in the Standard solution (mg/mL)

\(L\) = label claim (mg/Capsule)

\(V\) = volume of Medium, 900 mL

Tolerances: See Table 22.

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 20</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>35–55</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>70–90</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (C₂₂H₂₆N₂O₄S·HCl) dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.

^Test 22: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 22.

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 100 rpm

Times: 1, 6, 12, and 24 h

Mobile phase: Acetonitrile and water (35:65). Add 0.5 mL of trifluoroacetic acid for every liter of the solution.

Standard stock solution: 1.7 mg/mL of USP Diltiazem Hydrochloride RS in Medium prepared as follows.

Weigh and transfer a portion of USP Diltiazem Hydrochloride RS to an appropriate volumetric flask, add Medium to 30% of the volume and sonicate to dissolve. Dilute with Medium to volume.
**Standard solution:** \((L/900)\) mg/mL of **USP Diltiazem Hydrochloride RS** from the **Standard stock solution** in Medium, where \(L\) is the label claim in mg/Capsule.

**Sample solution:** At the specified **Times**, withdraw 10 mL of the solution under test, pass through a suitable filter of 0.45-\(\mu\)m pore size, and collect the filtrate by discarding the first few milliliters. Replace with 10 mL of Medium.

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

**Mode:** LC

**Detector:** UV 238 nm

**Column:** 4.6-mm \(\times\) 15-cm; 5-\(\mu\)m packing L1

**Column temperature:** 40°

**Flow rate:** 1.5 mL/min

**Injection volume:** 5 \(\mu\)L

**Run time:** NLT 1.7 times the retention time of diltiazem

**System suitability**

**Sample:** **Standard solution**

[Note—The relative retention times of desacetyl diltiazem and diltiazem are 0.67 and 1.00, respectively.]

**Suitability requirements**

- **Tailing factor:** NMT 2.0 for diltiazem
- **Relative standard deviation:** NMT 2.0% for the sum of the peak areas of desacetyl diltiazem and diltiazem

**Analysis**

**Samples:** **Standard solution** and **Sample solution**

Calculate the concentration \((C_i)\) of diltiazem hydrochloride \((C_{22}H_{26}N_2O_4S\cdot HCl)\) in the sample withdrawn from the vessel at each time point \((i)\):

\[
Result_i = \left(\frac{r_T}{r_S}\right) \times C_S
\]

- \(r_T\) = sum of the peak responses of desacetyl diltiazem and diltiazem from the **Sample solution**
- \(r_S\) = sum of the peak responses of desacetyl diltiazem and diltiazem from the **Standard solution**
- \(C_S\) = concentration of **USP Diltiazem Hydrochloride RS** in the **Standard solution** (mg/mL)

Calculate the percentage of the labeled amount of diltiazem hydrochloride \((C_{22}H_{26}N_2O_4S\cdot HCl)\) dissolved at each time point \((i)\):

\[
Result_1 = C_1 \times V \times \frac{1}{L} \times 100
\]

\[
Result_2 = \left[\left(C_2 \times V\right) + \left(C_1 \times V_S\right)\right] \times \frac{1}{L} \times 100
\]

\[
Result_3 = \left\{\left(C_3 \times V\right) + \left[C_1 + C_2\right] \times V_S\right\} \times \frac{1}{L} \times 100
\]

\[
Result_4 = \left\{\left(C_4 \times V\right) + \left[C_1 + C_2 + C_3\right] \times V_S\right\} \times \frac{1}{L} \times 100
\]

- \(C_i\) = concentration of diltiazem hydrochloride in the portion of sample withdrawn at each time point \((i)\) (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Capsule)
- \(V_S\) = volume of the **Sample solution** withdrawn at each time point (10 mL)

**Tolerances:** See **Table 22**.
**Table 23**

<table>
<thead>
<tr>
<th>Time Point (i)</th>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0–10</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>NMT 55</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>50–95</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of diltiazem hydrochloride (\(C_{22}H_{26}N_2O_4S \cdot HCl\)) dissolved at the times specified conform to *Dissolution (711)*, *Acceptance Table 2*.▲ (TBD)

**Uniformity of Dosage Units (905):** Meet the requirements

**Impurities**

*Change to read:*

**Organic Impurities**

**Solution A, Solution B, Mobile phase, Diluent, and Chromatographic system:** Proceed as directed in the Assay.

**Standard solution:** 2.5 µg/mL each of USP Desacetyl Diltiazem Hydrochloride RS and USP Diltiazem Hydrochloride RS in Diluent

**Sample solution:** Nominally 0.5 mg/mL of diltiazem hydrochloride from the Capsules in Diluent prepared as follows. Transfer a portion of the finely powdered contents of NLT 20 Capsules to a suitable volumetric flask. Add Diluent equivalent to 80% of the flask volume, mechanically shake for 30 min, and sonicate for 60 min. Dilute with Diluent to volume. Centrifuge and use the supernatant.

**System suitability**

**Sample:** Standard solution

[NOTE—For relative retention times see ▲ Table 24.▲ (TBD)]

**Suitability requirements**

- **Resolution:** NLT 2.0 between desacetyl diltiazem and diltiazem
- **Relative standard deviation:** NMT 3.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of desacetyl diltiazem hydrochloride in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \(r_U\) = peak response of desacetyl diltiazem from the Sample solution
- \(r_S\) = peak response of desacetyl diltiazem from the Standard solution
- \(C_S\) = concentration of USP Desacetyl Diltiazem Hydrochloride RS in the Standard solution (µg/mL)
- \(C_U\) = nominal concentration of diltiazem hydrochloride in the Sample solution (µg/mL)

Calculate the percentage of any individual unspecified impurity in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100
\]

- \(r_U\) = peak response of each unspecified impurity from the Sample solution
- \(r_S\) = peak response of diltiazem from the Standard solution
\[ C_S = \text{concentration of USP Diltiazem Hydrochloride RS in the Standard solution (µg/mL)} \]
\[ C_U = \text{nominal concentration of diltiazem hydrochloride in the Sample solution (µg/mL)} \]

**Acceptance criteria:** See \[ \text{Table 24, (TBD)} \] Disregard limit: 0.05%.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem related compound H(^{b,b})</td>
<td>0.44</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem related compound G(^{b,c})</td>
<td>0.52</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem related compound C(^{b,d})</td>
<td>0.58</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem related compound D(^{b,e})</td>
<td>0.61</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem related compound E(^{b,f})</td>
<td>0.66</td>
<td>—</td>
</tr>
<tr>
<td>Desacetyl diltiazem(^{g})</td>
<td>0.75</td>
<td>1.5</td>
</tr>
<tr>
<td>Diltiazem related compound A(^{b,h})</td>
<td>0.83</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem related compound B(^{b,i})</td>
<td>0.89</td>
<td>—</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified impurity</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

\(^a\) (2S,3S)-5-(2-Aminoethyl)-3-hydroxy-2-(4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one.
\(^b\) These are impurities related to the drug substance. They are not to be reported for the drug product and should not be included in the total impurities.
\(^c\) (2S,3S)-3-Hydroxy-2-(3-methoxyphenyl)-5-(2-(methylamino)ethyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4(5H)-one.
\(^d\) (2S,3S)-5-[2-(Dimethylamino)ethyl]-2-(4-hydroxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.
\(^e\) (2S,3S)-2-(4-Methoxyphenyl)-5-[2-(methylamino)ethyl]-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl acetate.
\(^f\) (2S,3S)-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine-4(5H)-one.
\(^g\) \(d\)-cis-3-Hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one. The acceptance criteria for this impurity is based on the hydrochloride form.
\(^h\) (2R,3S)-5-[2-(Dimethylamino)ethyl]-2-(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.
\(^i\) (2S,3S)-2-(4-Methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-3-yl acetate.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING and STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **LABELING:** The labeling indicates the Dissolution test with which the product complies.
- **USP Reference Standards (11)**
  - USP Desacetyl Diltiazem Hydrochloride RS
  - \(d\)-cis-3-Hydroxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(p-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride.
  \[ \text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_5\text{S} \cdot \text{HCl} = 408.95 \]
  - USP Diltiazem Hydrochloride RS