Diltiazem Hydrochloride Extended-Release Capsules

Type of Posting    Revision Bulletin
Posting Date       26-Feb-2021
Official Date      1-Mar-2021
Expert Committee   Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts, the Small Molecules 2 Expert Committee has revised the Diltiazem Hydrochloride Extended-Release Capsules monograph. The purpose for the revision is to add **Dissolution Test 24** to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). The revision also necessitates a change in the table numbering in the test for **Organic Impurities**.

- **Dissolution Test 24** was validated using a Waters Symmetry C18 brand of L1 column. The typical retention time for diltiazem is about 2 min.

The Diltiazem Hydrochloride Extended-Release Capsules Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Behnaz Almasi, Scientific Liaison (301-692-3412 or ba@usp.org).
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 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 L1

**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 \((\text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl})\) 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>
<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 \((\text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl})\) 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 \( \text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl} \) 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 \( \text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl} \) 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 \((C_{22}H_{26}N_2O_4S\cdot HCl)\) 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 \((C_{22}H_{26}N_2O_4S\cdot HCl)\) 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>
<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>
<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>
<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>
<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 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$_2$O$_4$S·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 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 \((\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl})\) dissolved at the times specified conform to \textit{Dissolution (711), Acceptance Table 2}.

**Test 14:** If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 14}. Proceed as directed in \textit{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 \textit{Medium}

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

  **Tolerances:** See \textit{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 \((\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl})\) dissolved at the times specified conform to \textit{Dissolution (711), Acceptance Table 2}.

**Test 15:** If the product complies with this test, the labeling indicates that it meets USP \textit{Dissolution Test 15}. Proceed as directed in \textit{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 \textit{Medium}

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

  **Tolerances:** See \textit{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>Time (h)</td>
<td>Amount Dissolved (%)</td>
</tr>
<tr>
<td>---------</td>
<td>---------------------</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 ($\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_4\text{S} \cdot \text{HCl}$) 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*.

**Medium, Apparatus 2, Times, Standard solution, and Sample solution:** Proceed as directed for Test 3.

**Detector:** UV 238 nm

**Tolerances:** See *Table 17*.

*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>

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

**Test 17:** If the product complies with this test, the labeling indicates that it meets USP *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 *Table 18*.

*Table 18*

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Dissolved (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>20–40</td>
</tr>
<tr>
<td>12</td>
<td>35–55</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 18:** If the product complies with this test, the labeling indicates that it meets USP *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*:

\[
\text{Result} = (A_U / A_S) \times C_S \times D
\]

- \(A_U\) = 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*:

\[
\text{Result}_1 = C_1 \times V \times (1/L) \times 100
\]

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

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

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

\(C_i\) = concentration of diltiazem hydrochloride in the *Sample solution* withdrawn at the specified time point (mg/mL)
\[ V = \text{volume of Medium, 900 mL} \]

\[ L = \text{label claim (mg/Capsule)} \]

\[ V_S = \text{volume of the Sample withdrawn at each time point (mL)} \]

**Tolerances:** See *Table 19.*

**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 \((C_{22}H_{26}N_2O_4S\cdot HCl)\) 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 \(i\):

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

\[ A_U = \text{absorbance of diltiazem from the Sample solution at each time point} \]

\[ A_S = \text{absorbance of diltiazem from the Standard solution} \]

\[ C_S = \text{concentration of USP Diltiazem Hydrochloride RS in the Standard solution (mg/mL)} \]

\[ L = \text{label claim (mg/Capsule)} \]

\[ V = \text{volume of Medium, 900 mL} \]

**Tolerances:** See *Table 20.*

**Table 20**

\[ S_{22} \cdot S_{26} \cdot S_{2} \cdot S_{4} \cdot S_{2} \cdot S_{1} \]
The percentages of the labeled amount of diltiazem hydrochloride ($\text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl}$) 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 ($\text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl}$) in the sample withdrawn from the vessel at each time point ($i$):

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

$A_U$ = 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)

Calculate the percentage of the labeled amount of diltiazem hydrochloride ($\text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl}$) dissolved at each time point ($i$):

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

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

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

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

$C_i$ = 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 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>

Table 21

The percentages of the labeled amount of diltiazem hydrochloride (\( \text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl} \)) 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 (\( \text{C}_{22}\text{H}_{26}\text{N}_{2}\text{O}_{4}\text{S} \cdot \text{HCl} \)) 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)
\[ V = \text{volume of Medium}, \text{ 900 mL} \]

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

### 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 \((C_{22}H_{26}N_{2}O_{4}S \cdot HCl)\) dissolved at the times specified conform to *Dissolution (711), Acceptance Table 2.*

**Test 24:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 24.*

**Medium:** *Water,* 900 mL, degassed

**Apparatus 1:** 100 rpm

**Times:** 2, 6, 16, and 24 h

**Mobile phase:** *Methanol* and *water* (53:47). Add 1 mL of *trifluoroacetic acid* to each liter of the mixture.

**Standard solution:** 0.3 mg/mL of USP *Diltiazem Hydrochloride RS* in Medium

**Sample solution:** At the specified times, withdraw 10 mL of the solution under test and pass through a suitable filter of 0.45-µm pore size, discarding the first 3 mL of filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 270 nm

**Column:** 4.6-mm × 7.5-cm; 3.5-µm packing \(L_1\)

**Column temperature:** 40°

**Flow rate:** 1.1 mL/min

**Injection volume:** 10 µL

**Run time:** NLT 3 times the retention time of diltiazem

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

- **Tailing factor:** NMT 2.0
- **Relative standard deviation:** NMT 3.0%

**Analysis**

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

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

\[
C_i = \left(\frac{r_i}{r_S}\right) \times C_S
\]

- \(r_U\): 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)

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

\[
\text{Result}_1 = C_1 \times V \times (1/L) \times 100
\]
\[
\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)] \times (1/L) \times 100
\]
\[
\text{Result}_3 = \{[C_3 \times (V - (2 \times V_S))] + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100
\]
\[
\text{Result}_4 = \{[C_4 \times (V - (3 \times V_S))] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100
\]

$C_i$ = concentration of diltiazem hydrochloride in the portion of sample 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 solution withdrawn at each time point (mL)

**Tolerances:** See 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>2</td>
<td>NMT 15</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>25–45</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>55–75</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 dissolved at the times specified conform to Dissolution (711), Acceptance Table 2.▲ (RB 1-Mar-2021)

**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.▲ (RB 1-Mar-2021)]

**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*
- \( C_S \) = concentration of USP Diltiazem Hydrochloride RS in the *Standard solution* (µg/mL)
- \( C_U \) = nominal concentration of diltiazem hydrochloride in the *Sample solution* (µg/mL)

**Acceptance criteria**: See Table ▲24.▲ (RB 1-Mar-2021) Disregard limit: 0.05%.

**Table ▲24▲ (RB 1-Mar-2021)**

<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-Aminomethyl)-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-benzothiazepine-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.
    \[C_{20}H_{24}N_2O_5S \cdot HCl\] 408.95
    - USP Diltiazem Hydrochloride RS

**Page Information:**

Not Applicable

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