In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Tramadol Hydrochloride Extended-Release Tablets monograph. The purpose for the revision is to add **Dissolution Test 4** for drug products approved by the FDA.

The liquid chromatographic procedure in **Dissolution Test 4** was validated using a Luna C18 (2) brand of L1 column. The typical retention time for tramadol is about 1.4 minutes.

The Tramadol Hydrochloride Extended-Release Tablets Revision Bulletin supersedes the currently official Tramadol Hydrochloride Extended-Release Tablets monograph. The Revision Bulletin will be incorporated in the **USP 40–NF 35**.

Should you have any questions, please contact Hillary Cai (301–230-3379 or hzc@usp.org).
Tramadol Hydrochloride Extended-Release Tablets

**DEFINITION**
Tramadol Hydrochloride Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of tramadol hydrochloride (C_{16}H_{25}NO_2 · HCl).

**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.
- **B. ULTRAVIOLET ABSORPTION (1976)**
  
  **Sample solution:** Use the Sample solution from the Assay.
  
  **Analysis:** Using separate 1-cm cells, record the UV spectrum of the Sample solution and Standard solution.
  
  **Acceptance criteria:** The UV absorption spectrum of the Sample solution exhibits maxima and minima at the same wavelength as that of a similar solution of the Standard solution.

**ASSAY**

- **PROCEDURE**
  
  **Mobile phase:** Tetrahydrofuran, trifluoroacetic acid, triethylamine, and water (10: 0.1: 0.1: 90). [NOTE—Maintain at a pH range of 2.2–2.4.]

  **Standard stock solution:** 1 mg/mL of USP Tramadol Hydrochloride RS prepared by dissolving in 50% of the flask volume of methanol. Sonicate if necessary, and dilute with water to volume.

  **Standard solution:** 0.13 mg/mL of USP Tramadol Hydrochloride RS in Mobile phase, from the Standard stock solution.

  **Sample solution:** Nominally 0.13 mg/mL of tramadol hydrochloride in Mobile phase. Prepare by dissolving 10 Tablets in 20% of the flask volume of methanol, in a water bath for 60 min, at about 60° with intermittent shaking. Sonicate for 10 min. Add 40% of the flask volume of water, and sonicate for 30 min. If all Tablets are not fully disintegrated, then continue to sonicate until disintegration is completed. Shake the flask vigorously for 10 min using a mechanical shaker, and dilute with water to volume. Centrifuge a portion of the solution, pass through a suitable nylon filter, and collect the filtrate after discarding the first 2 mL. Pipet 5.0 mL of the filtrate into a 200-mL volumetric flask, and dilute with Mobile phase to volume.

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

  **Mode:** LC

  **Detector:** UV 216 nm

  **Column:** 4.6-mm × 15-cm; 5-µm packing L11

  **Column temperature:** 40°

  **Flow rate:** 1 mL/min

  **Injection volume:** 10 µL

  **System suitability**

  **Sample:** Standard solution

  **Suitability requirements**

  **Column efficiency:** NLT 2000 theoretical plates

  **Tailing factor:** NMT 2.0

  **Relative standard deviation:** NMT 2.0%

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of tramadol hydrochloride (C_{16}H_{25}NO_2 · HCl) in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{r_u}{r_i} \right) \times (C_S/C_u) \times 100
  \]

  \(r_u = \) peak response from the Sample solution

  \(r_i = \) peak response from the Standard solution

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

  \(C_u = \) nominal concentration of tramadol hydrochloride in the Sample solution (mg/mL)

  **Acceptance criteria:** 90.0%–110.0%

  **PERFORMANCE TESTS**

  **Change to read:**

  **Dissolution (711)**

  **Test 1**

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

  **Apparatus 1:** 75 rpm

  **Times:** 2, 4, 8, 10, and 16 h

  **Standard solution:** (L/900) mg/mL of USP Tramadol Hydrochloride RS in Medium, where L is the label claim in mg/Tablet.

  **Sample solution:** Withdraw 10 mL of the solution under test, and pass through a suitable filter of 0.45-µm pore size, discarding the first 4 mL of the filtrate. Replace the volume withdrawn with the same volume of Medium preheated at 37.0 ± 0.5°.

  **Instrumental conditions**

  **Mode:** UV

  **Analytical wavelength:** 271 nm

  **Cell:** 5 cm

  **Blank:** Medium

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the concentration (C_i), in mg/mL, of tramadol hydrochloride (C_{16}H_{25}NO_2 · 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 the Sample solution

  \(A_S = \) absorbance of the Standard solution

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

  Calculate the percentage of the labeled amount of tramadol hydrochloride (C_{16}H_{25}NO_2 · HCl) dissolved at each time point (i):

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

  \[
  \text{Result}_2 = \left( \frac{\left[ \left( C_i \times V \right) + \left( C_i \times V_3 \right) \right]}{\left[ \left( C_i \times V_2 \right) + \left( C_i \times V_3 \right) \right]} \right) \times (1/L) \times 100
  \]

  \[
  \text{Result}_3 = \left( \frac{\left[ \left( C_i \times V \right) + \left( C_i \times V_3 \right) \right]}{\left[ \left( C_i \times V_2 \right) + \left( C_i \times V_3 \right) \right]} \right) \times (1/L) \times 100
  \]

  \[
  \text{Result}_4 = \left( \frac{\left[ \left( C_i \times V \right) + \left( C_i \times V_3 \right) \right]}{\left[ \left( C_i \times V_2 \right) + \left( C_i \times V_3 \right) \right]} \right) \times (1/L) \times 100
  \]

  \[
  \text{Result}_5 = \left( \frac{\left[ \left( C_i \times V \right) + \left( C_i \times V_3 \right) \right]}{\left[ \left( C_i \times V_2 \right) + \left( C_i \times V_3 \right) \right]} \right) \times (1/L) \times 100
  \]

  \(C_i = \) concentration of tramadol hydrochloride in the portion of the sample withdrawn at the specified time point (mg/mL)

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

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

  \(V_i = \) volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)
Tolerances: See Table 1.

<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>4</td>
<td>10-40</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>50-80</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>65-95</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>NLT 80</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of tramadol hydrochloride (C₁₆H₂₅NO₂·HCl) released at the times specified conform to Dissolution (711), Acceptance Table 2.

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

- **Medium:** 0.1 N hydrochloric acid; 900 mL
- **Apparatus 1:** 75 rpm
- **Times:** 2, 4, 8, 10, and 16 h
- **Standard stock solution:** 5 mg/mL of USP Tramadol Hydrochloride RS in water
- **Standard solution:** Dilute the Standard stock solution with Medium to obtain a concentration of USP Tramadol Hydrochloride RS (see Table 2).

Table 2

<table>
<thead>
<tr>
<th>Label Claim (mg/Tablet)</th>
<th>Concentration of USP Tramadol Hydrochloride RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.075</td>
</tr>
<tr>
<td>200</td>
<td>0.100</td>
</tr>
<tr>
<td>300</td>
<td>0.200</td>
</tr>
</tbody>
</table>

Sample solution: Pass a portion of the solution under test through a suitable filter.

Instrumental conditions

- **Mode:** LC
- **Analytical wavelength:** 271 nm
- **Cell:**
  - For Tablets labeled to contain 100 mg: 1 cm
  - For Tablets labeled to contain 200 and 300 mg: 0.5 cm

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of tramadol hydrochloride (C₁₆H₂₅NO₂·HCl) dissolved at each time point (i):

Result\(_i\) = \((A_U/A_S) \times C_S \times V \times (1/L) \times 100\)

- \(A_U\) = absorbance of the Sample solution
- \(A_S\) = absorbance of the Standard solution
- \(C_S\) = concentration of USP Tramadol Hydrochloride RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim (mg/Tablet)

Tolerances: See Table 3.

<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>4</td>
<td>10-30</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of tramadol hydrochloride (C₁₆H₂₅NO₂·HCl) released at the times specified conform to Dissolution (711), Acceptance Table 2.

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

- **Medium:** 0.1 N hydrochloric acid; 900 mL
- **Apparatus 1:** 75 rpm
- **Times:** 2, 4, 8, and 16 h
- **Buffer:** Trifluoroacetic acid and water \(2:1000\)
- **Mobile phase:** Acetonitrile and Buffer \(30:70\)
- **Standard stock solution:** 0.53 mg/mL of USP Tramadol Hydrochloride RS in water
- **Standard solution:** \((L/900)\) mg/mL of USP Tramadol Hydrochloride RS in Medium from the Standard stock solution, where \(L\) is the label claim of tramadol hydrochloride, in mg/Tablet. Pass the solution through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of filtrate.
- **Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Replace the portion of solution withdrawn with an equal volume of Medium. Discard the first 3 mL of filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 270 nm
- **Column:** 4.6-mm \(\times\) 25-cm; 5-µm packing L1
- **Temperatures:**
  - **Autosampler:** 10°
  - **Column:** 25°
- **Flow rate:** 1.0 mL/min
- **Injection volume:** 20 µL

System suitability

Sample: Standard solution

Suitability requirements

- Column efficiency: NLT 2000 theoretical plates
- Tailing factor: NMT 2.0
- Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the concentration \((C_i)\), in mg/mL, of tramadol hydrochloride \((C₁₆H₂₅NO₂·HCl)\) in the sample withdrawn from the vessel at each time point \((i)\):

Result\(_i\) = \((r_U/r_S) \times C_S\)

- \(r_U\) = peak response of tramadol from the Sample solution
- \(r_S\) = peak response of tramadol from the Standard solution
- \(C_S\) = concentration of USP Tramadol Hydrochloride RS in the Standard solution (mg/mL)
Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point ($i$):

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

\[ \text{Result}_2 = \left( [C_i \times V] + [C_i \times 2] \right) \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left( [C_i \times V] + [C_i \times 2 + C_i \times 3] \right) \times (1/L) \times 100 \]

\[ \text{Result}_4 = \left( [C_i \times V] + [C_i \times 2 + C_i \times 3 + C_i \times 4] \right) \times (1/L) \times 100 \]

$C_i$ = concentration of tramadol hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

$V$ = volume of medium, 900 mL

$L_i$ = label claim (mg/Tablet)

$V_S$ = volume of the Sample solution withdrawn at each time point and replaced with Medium (mL)

**Tolerances:** See Table 4.

### Table 4

<table>
<thead>
<tr>
<th>Time Point ($i$)</th>
<th>Time ($h$)</th>
<th>100 mg/Tablet and 300 mg/Tablet</th>
<th>200 mg/Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>NMT 40</td>
<td>NMT 35</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>45–75</td>
<td>32–62</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>NLT 70</td>
<td>NLT 70</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>NLT 85</td>
<td>NLT 85</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to Dissolution (711), Acceptance Table 2.

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

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

**Apparatus 1:** 75 rpm  

**Times:** 2, 4, 8, 10, and 16 h  

**Buffer:** Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water and adjust with phosphoric acid to a pH of 3.0.  

**Mobile phase:** Acetonitrile and Buffer (20:80)  

**Standard solution:** 0.22 mg/mL of USP Tramadol Hydrochloride RS in Medium. Sonication may be necessary for complete dissolution.  

**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.  

**Chromatographic system**  

(See Chromatography (621), System Suitability.)  

**Mode:** LC  

**Detector:** UV 270 nm  

**Column:** 4.6-mm x 5-cm; 3-µm packing L1  

**Flow rate:** 1.5 mL/min  

**Injection volume:** 10 µL  

**Run time:** NLT 6 times the retention time of tramadol.

System suitability  

**Sample:** Standard solution  

**Suitability requirements**  

Column efficiency: NLT 1000 theoretical plates  

Relative standard deviation: NMT 2%

**Analysis**  

**Samples:** Standard solution and Sample solution  

Calculate the concentration ($C_i$) in mg/mL, of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) in the sample withdrawn from the vessel at each time point ($i$):

\[ \text{Result}_1 = \left( \frac{n_i}{n_S} \right) \times C_i \]

$n_i$ = peak response of tramadol from the Sample solution

$n_S$ = peak response of tramadol from the Standard solution

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

Calculate the percentage of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) dissolved at each time point ($i$):

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

\[ \text{Result}_2 = \left( [C_i \times V] + [C_i \times 2] \right) \times (1/L) \times 100 \]

\[ \text{Result}_3 = \left( [C_i \times V] + [C_i \times 2 + C_i \times 3] \right) \times (1/L) \times 100 \]

\[ \text{Result}_4 = \left( [C_i \times V] + [C_i \times 2 + C_i \times 3 + C_i \times 4] \right) \times (1/L) \times 100 \]

$C_i$ = concentration of tramadol hydrochloride in the portion of sample withdrawn at the specified time point (mg/mL)

$V$ = volume of Medium, 900 mL

$L_i$ = label claim (mg/Tablet)

$V_S$ = volume of the Sample solution withdrawn at each time point (mL)

**Tolerances:** See Table 5.

### Table 5

<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 35</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>35–60</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>60–85</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>NLT 65</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>NLT 75</td>
</tr>
</tbody>
</table>

The percentages of the labeled amount of tramadol hydrochloride ($C_{16}H_{25}NO_2 \cdot HCl$) released at the times specified conform to Dissolution (711), Acceptance Table 2.

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

Change to read:

- ORGANIC IMPURITIES
  Mobile phase: Acetonitrile, trifluoroacetic acid, and water (20:0.1:80)
  Diluent: Methanol and water (1:4)
  System suitability stock solution: 0.05 mg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in Diluent prepared by dissolving in 20% of the flask volume of methanol. Sonicate if necessary, and dilute with water to volume.
  System suitability solution: 2.5 µg/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS in Diluent, from the System suitability stock solution
  Standard stock solution: 0.05 mg/mL of USP (impurity D)
  Diluent prepared by dissolving in 20% of the flask volume of methanol.

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

Mode: LC
Detector: UV 216 nm
Column: 2.1-mm × 10-cm; 1.7-µm packing L1
Column temperature: 50°C
Flow rate: 0.6 mL/min
Injection volume: 3 µL
Run time: 6 min

System suitability
Samples: System suitability solution and Standard solution

Suitability requirements
Resolution: NLT 3.0 between tramadol related compound A and tramadol, System suitability solution
Column efficiency: NLT 5000 theoretical plates, Standard solution
Capacity factor, k': NLT 1.5, Standard solution
Tailing factor: NMT 2.0, Standard solution
Relative standard deviation: NMT 6.0%, Standard solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of each impurity in the portion of Tablets taken:
  \[ \text{Result} = (r_C/r_S) \times (C_G/C_S) \times (1/F) \times 100 \]
  \[ r_C = \text{peak response of each individual impurity from the Sample solution} \]
  \[ r_S = \text{peak response of tramadol from the Standard solution} \]
  \[ C_C = \text{concentration of USP Tramadol Hydrochloride RS in the Standard solution (mg/mL)} \]
  \[ C_G = \text{nominal concentration of tramadol hydrochloride in the Sample solution (mg/mL)} \]
  \[ F = \text{relative response factor (see Table 6)} \]

Acceptance criteria: See Table 6

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desmethyl tramadol</td>
<td>0.57</td>
<td>1.0</td>
<td>0.2 (01-Oct-2015)</td>
</tr>
<tr>
<td>Tramadol related compound A</td>
<td>0.84</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Tramadol hydrochloride</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1,6 Olefin</td>
<td>2.78</td>
<td>3.0</td>
<td>—</td>
</tr>
<tr>
<td>1,2 Olefin</td>
<td>3.28</td>
<td>2.2</td>
<td>—</td>
</tr>
<tr>
<td>Individual unspecified impurity</td>
<td>—</td>
<td>1.0</td>
<td>0.20 (01-Oct-2015)</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>—</td>
<td>0.60 (01-Oct-2015)</td>
</tr>
</tbody>
</table>

ADDITIONAL REQUIREMENTS

- PACKAGING AND STORAGE: Preserve in tight containers, and store at controlled room temperature.
- LABELING: When more than one test for Dissolution is given, the labeling states the test for Dissolution used only if Test 1 is not used.

Change to read:

- USP REFERENCE STANDARDS (11)
  USP Tramadol Hydrochloride RS
  RS, SR-1-(3-Methoxophenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.
  C_{16}H_{23}NO_{2}·HCl 299.84
  USP Tramadol Related Compound A RS
  C_{16}H_{23}NO_{2}·HCl 299.84