Acetaminophen and Tramadol Hydrochloride Tablets

DEFINITION
Acetaminophen and Tramadol Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of acetaminophen (C$_8$H$_9$NO$_2$) and tramadol hydrochloride (C$_{16}$H$_{25}$NO$_2$·HCl).

IDENTIFICATION
• The retention times of the major peaks in the Tramadol sample solution and the Acetaminophen sample solution correspond to those of the Standard solution, as obtained in the Assay.

ASSAY
• PROCEDURE
  Mobile phase: Tetrahydrofuran, triethylamine, water, and trifluoroacetic acid (8:0.1:92:0.1). [Note—The apparent pH of the final solvent mixture should be between 2.2 and 2.4.]
  Diluent: Methanol and water (1:9)
  Standard solution: 0.065 mg/mL of USP Acetaminophen RS and 0.075 mg/mL of USP Tramadol Hydrochloride RS in Diluent. [Note—Sonication may be used to aid dissolution.]
  Sample stock solution: Weigh NLT 20 Tablets, and determine the average Tablet weight. Grind the Tablets into a fine powder, and transfer an amount equivalent to one Tablet to a 50-mL volumetric flask. Add 30 mL of Diluent with continuous shaking to disperse the powder. Sonicate for 15 min with intermittent shaking, and shake the flask on a mechanical shaker for 30 min. Dilute with Diluent to volume, and mix well. Centrifuge the suspension, and use the supernatant for subsequent dilutions.

  Tramadol sample solution: 75 µg/mL of tramadol hydrochloride in Diluent from the Sample stock solution
  Acetaminophen sample solution: 65 µg/mL of acetaminophen in Diluent from the Sample stock solution

  Chromatographic system
  (See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: 216 nm for tramadol hydrochloride and 249 nm for acetaminophen
  Column: 4.6-mm × 15-cm; 5-µm packing L11
  Column temperature: 50°C
  Flow rate: 1.0 mL/min
  Injection size: 20 µL
  Run time: Four times the retention time of acetaminophen

  System suitability
  Sample: Standard solution
  Suitability requirements
  Resolution: NLT 10.0 between acetaminophen and tramadol hydrochloride
  Column efficiency: NLT 2000 theoretical plates for each analyte
  Tailing factor: NMT 2.0 for each analyte
  Relative standard deviation: NMT 2.0% for each analyte

  Analysis
  Samples: Standard solution, Tramadol sample solution, and Acetaminophen 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:

  Result = ($r_U/r_S$) × (C$_S$/C$_U$) × 100

  $r_U$ = peak response from the Tramadol sample solution
  $r_S$ = peak response from the Standard solution

  Acceptance criteria:
  NLT 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)

  Test 1 (88 1-Oct 2010)
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 2: 50 rpm
  Time: 30 min
  Standard solution: 0.36 mg/mL of USP Acetaminophen RS and 0.04 mg/mL of USP Tramadol Hydrochloride RS in Medium
  Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.
  Buffer solution: 6.8 mg/mL of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.50.

  Mobile phase: Acetonitrile and Buffer solution (1:4)

  Chromatographic system
  (See Chromatography (621), System suitability.)
  Mode: LC
  Detector: UV 272 nm
  Column: 4.6 mm × 15 cm; 5-µm packing L7
  Column temperature: 25°C
  Flow rate: 1.0 mL/min
  Injection size: 25 µL

  System suitability
  Sample: Standard solution
  [Note—The relative retention times for acetaminophen and tramadol hydrochloride are about 0.5 and 1.0, respectively.]
  Suitability requirements
  Resolution: NLT 5.0 between the peaks for acetaminophen and tramadol hydrochloride
  Relative standard deviation: NMT 2.0% for both the acetaminophen and tramadol hydrochloride peaks

  Analysis
  Samples: Standard solution and Sample solution
  Record the chromatograms for two times the retention time of tramadol hydrochloride. Calculate the percentage of the labeled amount of acetaminophen (C$_8$H$_9$NO$_2$) and tramadol hydrochloride (C$_{16}$H$_{25}$NO$_2$·HCl) dissolved:

  Result = ($r_U/C_S$ × V × 100)/(r$_S$ × L)

  $r_U$ = peak response of acetaminophen or tramadol hydrochloride from the Sample solution
  C$_S$ = concentration of USP Acetaminophen RS or USP Tramadol Hydrochloride RS in the Standard solution (mg/mL)
  V = volume of Medium, 900 mL

  $r_S$ = peak response from the Standard solution

  Acceptance criteria:
  NLT 90.0%–110.0%
Acetaminophen

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of \( p \)-aminophenol in the portion of Tablets taken:

\[
Result = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_s}{C_d} \right) \times 100
\]

\( r_d \) = absorbance from the Sample solution
\( r_s \) = absorbance from the Standard solution
\( C_s \) = concentration of USP \( p \)-Aminophenol RS in the Standard solution (mg/mL)
\( C_d \) = nominal concentration of acetaminophen in the Sample solution (mg/mL)

Acceptance criteria: NMT 0.01%  

IMPURITIES

Organic Impurities

Procedure

Mobile phase, Diluent, and Sample stock solution: Proceed as directed in the Assay.

Standard solution: 0.75 \( \mu \)g/mL each of USP Tramadol Hydrochloride RS and USP Tramadol Related Compound A RS

Sample solution: Pass a suitable volume of the Sample stock solution through a nylon membrane filter of 0.45-\( \mu \)m pore size. Use the filtrate after discarding the first 4 mL of filtrate.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC
Detector: 216 nm
Column: 4.6-mm \times 15-cm; 5-\( \mu \)m packing L11
Column temperature: 50\( ^\circ \)
Flow rate: 1.0 mL/min
Injection size: 30 \( \mu \)L

System suitability

Sample: Standard solution

Suitability requirements

Resolution: NLT 2.0 between tramadol related compound A and tramadol hydrochloride
Column efficiency: NLT 2000 theoretical plates for tramadol hydrochloride
Relative standard deviation: NMT 6.0% for tramadol hydrochloride

Analysis

Samples: Diluent, Standard solution, and Sample solution

[NOTE—Disregard the peaks due to the Diluent.]

Calculate the percentage of each known and unknown impurity in the portion of Tablets taken:

\[
Result = \left( \frac{r_d}{r_s} \right) \times \left( \frac{C_s}{C_d} \right) \times 100
\]

\( r_d \) = peak response of each individual impurity from the Sample solution
\( r_s \) = peak response of tramadol hydrochloride from the Standard solution
\( C_s \) = concentration of USP Tramadol Hydrochloride RS in the Standard solution (\( \mu \)g/mL)
\( C_d \) = nominal concentration of tramadol hydrochloride in the Sample solution (\( \mu \)g/mL)

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Acceptance criteria: See Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O-Desmethyl-tramadol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.60</td>
<td>0.2</td>
</tr>
<tr>
<td>Tramadol related compound A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.80</td>
<td>0.2</td>
</tr>
<tr>
<td>Tramadol hydrochloride</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>0.38</td>
<td>—</td>
</tr>
<tr>
<td>Any other individual, unspecified degradation product</td>
<td>—</td>
<td>0.2</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.8</td>
</tr>
</tbody>
</table>

<sup>a</sup> 3-{(1RS,2RS)-2-[(Dimethylamino)methyl]-1-hydroxycyclohexyl}phenol.

<sup>b</sup> (RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.

### ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

### Add the following:

- **LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.

- **USP Reference Standards (11)**
  - USP Acetaminophen RS
  - 4'-Hydroxyacetanilide.
  - \( \text{C}_{6}\text{H}_{7}\text{NO} \) \( 151.16 \)
  - USP \( p \)-Aminophenol RS
  - 4-Amino-1-hydroxybenzene.
  - \( \text{C}_{6}\text{H}_{5}\text{NO} \) \( 109.13 \)
  - USP Tramadol Hydrochloride RS
  - (S)-\( \text{C}_{16}\text{H}_{25}\text{NO}_{2} \cdot \text{HCl} \) \( 299.84 \)
  - USP Tramadol Related Compound A RS
  - RS,SR-1-(3-Methoxyphenyl)-2-(dimethylaminomethyl)cyclohexanol hydrochloride.