Trazodone Hydrochloride Tablets

Type of Posting  Revision Bulletin
Posting Date  30–Mar–2018
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Expert Committee  Chemical Medicines Monographs 4
Reason for Revision  Compliance

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 4 Expert Committee has revised the Trazodone Hydrochloride Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate drug products that were approved with different dissolution conditions. A Labeling section also has been added.

- Dissolution Test 2 was validated using the Inertsil ODS-3V brand of L1 column. The typical retention time for trazodone is about 3.8 min.

The Trazodone Hydrochloride Tablets Revision Bulletin supersedes the currently official monograph. The Revision Bulletin will be incorporated in the USP 42–NF 37.

Should you have any questions, please contact Sridevi Ramachandran, Ph.D., Associate Scientific Liaison (sdr@usp.org).
Trazodone Hydrochloride Tablets

**DEFINITION**

Trazodone Hydrochloride Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of trazodone hydrochloride (C_{19}H_{22}ClN_{5}O·HCl).

**IDENTIFICATION**

Delete the following:

- **A. THIN-LAYER CHROMATOGRAPHIC IDENTIFICATION TEST** (201)
  - Standard solution: 20 mg/mL of USP Trazodone Hydrochloride RS in methanol
  - Sample solution: Nominally 20 mg/mL of trazodone hydrochloride in methanol from a suitable number of Tablets (equivalent to NLT 150 mg) prepared as follows. Place the Tablets in a tube. Add the required amount of methanol, and sonicate until the Tablets have disintegrated. Shake the tube, by hand, for a few seconds to mix, and then filter.
  - Application volume: 1 µL
  - Developing solvent system: Cyclohexane, alcohol, toluene, and diethylamine (80:30:20:20)
  - Analysis
    - Samples: Standard solution and Sample solution
    - Proceed as directed in the chapter, except locate the spots on the plate by examination under long-wavelength UV light.

Add the following:

- **A.** The UV 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**

**Change to read:**

- **PROCEDURE**
  - Buffer: 1.15 g/L of monobasic ammonium phosphate, adjusted with sodium hydroxide to a pH of 6.0
  - Mobile phase: Methanol and Buffer (75:25)
  - Standard solution: 0.1 mg/mL of USP Trazodone Hydrochloride RS in 0.01 N hydrochloric acid
  - Sample solution: Nominally 0.1 mg/mL of trazodone hydrochloride from NLT 20 finely powdered Tablets. Transfer a suitable quantity of the powder to a suitable volumetric flask. Dissolve in 0.01 N hydrochloric acid and dilute with 0.01 N hydrochloric acid to volume. Sonicate for about 30 min, and pass through a suitable filter of 0.45-µm pore size.

  **Chromatographic system**
  - (See Chromatography (621), System Suitability.)
  - Mode: LC
  - Detector: UV 246 nm.
  - For Identification A, use a diode array detector in the range of 200–400 nm.
  - Column: 5-mm x 10-cm; 4-µm packing L1
  - Flow rate: 1.5 mL/min
  - Injection volume: 20 µL
  - Run time: NLT 4.5 times the retention time of trazodone.

- **ASSAY**
  - **Change to read:**
  - **DISTRIBUTION** (711)
  - Test 1: A. (BB 3-Apr-2018)
    - Medium: 0.01 N hydrochloric acid TS_{1S (USP41)· HCl} 900 mL
    - Apparatus 2: 50 rpm
    - Time: 60 min
  - Buffer: Mobile phase, Standard solution, Chromatographic system, and System suitability: Proceed as directed in the Assay.
  - Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

  **Analysis**
  - Samples: Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of trazodone hydrochloride (C_{19}H_{22}ClN_{5}O·HCl) dissolved:

  \[
  \text{Result} = \left( \frac{r_s}{r_u} \right) \times \left( \frac{C_u}{C_s} \right) \times V \times \left( \frac{1}{L} \right) \times 100
  \]

  \( r_u \) = peak response of trazodone from the Sample solution
  
  \( r_s \) = peak response of trazodone from the Standard solution
  
  \( C_s \) = concentration of USP Trazodone Hydrochloride RS in the Standard solution (mg/mL)
  
  \( C_u \) = nominal concentration of trazodone hydrochloride in the Sample solution (mg/mL)

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

**PERFORMANCE TESTS**

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- Column efficiency: NLT 900 theoretical plates
- Relative standard deviation: NMT 2.0%

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of trazodone hydrochloride (C_{19}H_{22}ClN_{5}O·HCl) in the portion of Tablets taken:

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

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

\( r_s \) = peak response of trazodone from the Standard solution

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

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

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Sample solution: Pass the solution through a suitable filter of 0.45-µm pore size. Discard the first 5 mL of the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 246 nm
Column: 4.6-mm x 15-cm; 5-µm packing L1
Column temperature: 45°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 1.6 times the retention time of trazodone

System suitability
Sample: Standard solution
Suitability requirements
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 trazodone hydrochloride (C19H22ClN3O.HCl) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_x \times \frac{V}{L} \times \left( \frac{1}{1/L} \right) \times 100
\]

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

**Impurities**

**Organic impurities**
Solution A: 6.75 g/L of monobasic potassium phosphate. Add 1.0 mL of triethylamine for each liter of the solution, and mix.
Solution B: Acetonitrile
Mobile phase: See Table 1.

**Diluent**: Methanol, water, and hydrochloric acid (650:350:3)

**System suitability solution**: 0.7 µg/mL of USP Trazodone Hydrochloride RS and 1.5 µg/mL of USP Trazodone Related Compound C RS in Diluent

**Sample solution**: Nominally 500 µg/mL of trazodone from finely powdered Tablets (NLT 20) prepared as follows. Transfer a portion of powdered Tablets (NLT 50 mg) to a suitable volumetric flask. Add about 80% of the flask volume of Diluent, and sonicate for 10 min. Dilute with Diluent to volume. Pass a portion of the solution through a suitable membrane filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 254 nm
Column: 4.0-mm x 15-cm; 3-µm packing L1
Flow rate: 0.7 mL/min
Injection volume: 10 µL

System suitability
Samples: System suitability solution and Standard solution

**Acceptance criteria**: See Table 2.
<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
</tr>
<tr>
<td>Total ▲degradation products ▲15 (USP41)</td>
<td>—</td>
<td>2.0</td>
</tr>
</tbody>
</table>

▲ Process impurity included for identification only. ▲ Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product ▲15 (USP41) ▲11 (USP41)

1-{3-Chlorophenyl)piperazine.

3-[4-(3-Chlorophenyl)piperazin-1-yl]propan-1-ol.

1-[3-[4-(3-Chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyrimidin-1-ium-3-olate.

1,1-Bis{2-chloro-[4-(3-{1,2,4-triazolo[4,3-a]pyridin-3-(2H)-on-2-yl]propyl}piperazin-1-yl]phenyl}ethane trihydrochloride.

1-(3-Chlorophenyl)-4-(3-chloropropyl)piperazine.

1,3-Bis(3-chlorophenyl)piperazin-1-yl)propane.

### ADDITIONAL REQUIREMENTS

**PACKAGING AND STORAGE:** Preserve in tight, light-resistant 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. ▲ (RB 1-Apr-2018)

**USP REFERENCE STANDARDS (11)**

- USP Trazodone Hydrochloride RS
- USP Trazodone Related Compound C RS
- Z-[3-[4-(4-Chlorophenyl)piperazin-1-yl]propyl]-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one hydrochloride. C19H22ClN2O·HCl 408.32

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