Prazosin Hydrochloride Capsules

Type of Posting          Revision Bulletin
Posting Date            8-May-2023
Official Date           9-May-2023
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 Prazosin Hydrochloride Capsules monograph. The purpose of this revision is to add Dissolution Test 3 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution test(s). Existing references to reagents also have been updated for consistency with the reagent entry names.

- Dissolution Test 3 was validated using the Zorbax SIL brand of column with L3 packing. The typical retention time for prazosin is about 7 min.

The Prazosin Hydrochloride Capsules Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang, Senior Scientist II, (301-692-3623 or yanyin.yang@usp.org).
Prazosin Hydrochloride Capsules

DEFINITION
Prazosin Hydrochloride Capsules contain an amount of prazosin hydrochloride \((\text{C}_{19}\text{H}_{21}\text{N}_{5}\text{O}_{4} \cdot \text{HCl})\) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of prazosin \((\text{C}_{19}\text{H}_{21}\text{N}_{5}\text{O}_{4})\).

[CAUTION—Care should be taken to prevent inhaling particles of prazosin hydrochloride and to prevent it contacting any part of the body.]

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.** The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

- **Procedure**

  **Mobile phase:** Methanol, glacial acetic acid, and water (70:1:30). Add 0.2 mL of diethylamine to 1 L of Mobile phase, such that the retention time of prazosin is 6–10 min.

  **Solution A:** To 300 mL of water add 0.85 mL of hydrochloric acid in a 1000-mL volumetric flask. Dilute with methanol to volume, and mix. Transfer 300 mL of this solution to a 500-mL volumetric flask, and dilute with methanol to volume.

  **Standard stock solution:** 0.2 mg/mL of USP Prazosin Hydrochloride RS in Solution A

  **Standard solution:** 0.01 mg/mL of USP Prazosin Hydrochloride RS, prepared as follows. Transfer 5 mL of Standard stock solution to a 100-mL volumetric flask, add 45.0 mL of Solution A, dilute with methanol to volume, and mix.

  **Sample stock solution:** Nominally 0.02 mg/mL of prazosin in Solution A, prepared as follows. Transfer a portion of the contents of NLT 20 Capsules, equivalent to about 1 mg of prazosin, to a glass-stoppered flask containing 50.0 mL of Solution A, and shake by mechanical means for 30 min. Place the flask in an ultrasonic bath for 30 min, cool to room temperature, and pass the contents through a suitable filter of 5-µm or finer pore size.

  **Sample solution:** Nominally 0.01 mg/mL of prazosin prepared as follows. Transfer 25.0 mL of Sample stock solution to a 50-mL volumetric flask, and dilute with methanol to volume.

**Chromatographic system**

(See Chromatography (621), System Suitability.)

- **Mode:** LC
- **Detector:** UV 254 nm. For Identification B, use a diode array detector in the range of 200–400 nm.
- **Column:** 4.6-mm × 25-cm; 5-µm packing L3
- **Flow rate:** 0.6 mL/min
- **Injection volume:** 5 µL
- **Run time:** NLT 2 times the retention time of prazosin

**System suitability**
Sample: Standard solution

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) in the portion of Capsules taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{Mr_1}{Mr_2} \right) \times 100 \]

\( r_U \): peak response of prazosin from the Sample solution
\( r_S \): peak response of prazosin from the Standard solution
\( C_S \): concentration of USP Prazosin Hydrochloride RS in the Standard solution (mg/mL)
\( C_U \): nominal concentration of prazosin in the Sample solution (mg/mL)
\( Mr_1 \): molecular weight of prazosin, 383.41
\( Mr_2 \): molecular weight of prazosin hydrochloride, 419.87

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• Dissolution (711)

Test 1

Medium: 0.1 N hydrochloric acid containing 3% sodium dodecyl sulfate (RB 9-May-2023); 900 mL

Apparatus 1: 100 rpm

Time: 60 min

Standard solution: Known concentration of USP Prazosin Hydrochloride RS in Medium

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

Analysis

Samples: Standard solution and Sample solution

Determine the percentage of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) dissolved, using the procedure in the Assay.

Tolerances: NLT 75% (Q) of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) is dissolved.

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

Medium: Prepare as directed in Test 1.

Apparatus 1: 10-mesh basket; 100 rpm

Time: 30 min

Buffer: 3.4 g/L of sodium dihydrogen phosphate. Adjust with 10% sodium hydroxide solution to a pH of 7.5.

Mobile phase: Methanol and Buffer (50:50)

Standard stock solution: 120 μg/mL of USP Prazosin Hydrochloride RS, prepared as follows. In a suitable volumetric flask, dissolve a suitable amount of USP Prazosin Hydrochloride RS in 20% of the total volume of methanol. Dilute with Medium to volume.

Standard solution: (L/900) mg/mL of USP Prazosin Hydrochloride RS in Medium, where L is the label claim in mg/Capsule, from Standard stock solution
**Sample solution:** Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size.

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

- **Mode:** LC
- **Detector:** UV 254 nm
- **Column:** 4.6-mm × 10-cm; 5-µm packing L1
- **Column temperature:** 40°
- **Flow rate:** 1 mL/min
- **Injection volume:** 60 µL
- **Run time:** NLT 2 times the retention time of prazosin

**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 percentage of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{L} \right) \times V \times \left( \frac{M_{r_1}}{M_{r_2}} \right) \times 100
\]

- \( r_U \) = peak response of prazosin from the Sample solution
- \( r_S \) = peak response of prazosin from the Standard solution
- \( C_S \) = concentration of USP Prazosin Hydrochloride RS in the Standard solution (mg/mL)
- \( L \) = label claim (mg/Capsule)
- \( V \) = volume of the Medium, 900 mL
- \( M_{r_1} \) = molecular weight of prazosin, 383.41
- \( M_{r_2} \) = molecular weight of prazosin hydrochloride, 419.87

**Tolerances:** NLT 80% (Q) of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) is dissolved.

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

- **Medium:** pH 6.8 phosphate buffer containing 3% sodium dodecyl sulfate (Dissolve 6.9 g of sodium phosphate monobasic in 1000 mL of water. Adjust with 2 N sodium hydroxide to a pH of 6.8. Add 30 g of sodium dodecyl sulfate to 1000 mL of the resulted solution.); 900 mL, deaerated
- **Apparatus 2:** 100 rpm
- **Time:** 20 min

**Mobile phase:** Methanol, water, glacial acetic acid, and diethylamine (670: 330: 10: 0.2)

**Standard stock solution A:** 0.3 mg/mL of USP Prazosin Hydrochloride RS in methanol. Sonicate to dissolve if necessary.

**Standard stock solution B:** 0.024 mg/mL of USP Prazosin Hydrochloride RS from Standard stock solution A in Medium

**Standard solution:** \((L/900)\) mg/mL of prazosin from USP Prazosin Hydrochloride RS from Standard stock solution B in Medium, where \( L \) is the label claim in mg/Capsule
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size, discarding the first 3 mL of the filtrate.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 254 nm
Column: 4.6-mm × 25-cm; 5-μm packing L3
Flow rate: 0.8 mL/min
Injection volume: 50 μL
Run time: NLT 1.3 times the retention time of prazosin

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 prazosin (C₁₉H₂₁N₅O₄) dissolved:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times C_S \times V \times \left( \frac{M_{r1}}{M_{r2}} \right) \times \left( \frac{1}{L} \right) \times 100
\]

\( r_U \) = peak response of prazosin from the Sample solution
\( r_S \) = peak response of prazosin from the Standard solution
\( C_S \) = concentration of USP Prazosin Hydrochloride RS in the Standard solution (mg/mL)
\( V \) = volume of the Medium, 900 mL
\( M_{r1} \) = molecular weight of prazosin, 383.41
\( M_{r2} \) = molecular weight of prazosin hydrochloride, 419.87
\( L \) = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of prazosin (C₁₉H₂₁N₅O₄) is dissolved.▲(RB 9-May-
2023)

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

IMPURITIES

- Organic Impurities
  Solution A: 1.93 g of ammonium acetate in 1000 mL of water. Adjust the solution with glacial acetic acid to a pH of 5.0.
  Solution B: Acetonitrile and methanol (75:25)
  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>85</td>
<td>15</td>
</tr>
</tbody>
</table>
Diluent: Solution A and Solution B (85:15)

Standard stock solution: 0.5 mg/mL of USP Prazosin Hydrochloride RS in Diluent

Standard solution: 0.5 µg/mL of USP Prazosin Hydrochloride RS from Standard stock solution in Diluent

Sensitivity solution: 0.05 µg/mL of USP Prazosin Hydrochloride RS from Standard solution in Diluent

System suitability stock solution: 0.025 mg/mL each of USP Prazosin Related Compound D RS, USP Terazosin Related Compound A RS, and USP Terazosin Related Compound C RS, prepared as follows.
  Transfer 12.5 mg of each corresponding Reference Standard to a 500-mL volumetric flask. Add 75 mL of Solution B and sonicate. Dilute with Solution A to volume.

System suitability solution: 0.1 mg/mL of USP Prazosin Hydrochloride RS from Standard stock solution in Diluent, and 0.001 mg/mL each of USP Prazosin Related Compound D RS, USP Terazosin Related Compound A RS, and USP Terazosin Related Compound C RS in Diluent from System suitability stock solution

Sample solution: Nominally 0.1 mg/mL of prazosin hydrochloride in Diluent, prepared as follows.
  Transfer a suitable portion of the contents from NLT 20 Capsules to a suitable volumetric flask that doubles the volume of Diluent used, add an appropriate amount of Diluent, and mix. Centrifuge a portion of the solution. Use the supernatant. [Caution—Do not dilute to volume.]

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Column temperature: 35°

Flow rate: 0.7 mL/min

Injection volume: 15 µL

System suitability

Samples: Standard solution, Sensitivity solution, and System suitability solution

Suitability requirements

Resolution: NLT 3.0 between prazosin and terazosin related compound C, System suitability solution

Tailing factor: NMT 3.0 for terazosin related compound A, System suitability solution

Relative standard deviation: NMT 5.0%, Standard solution

Signal-to-noise ratio: NLT 10, Sensitivity solution
Analysis

**Samples: Standard solution and Sample solution**

Calculate the percentage of prazosin related compound D, terazosin related compound A, or any unspecified degradation product in the portion of Capsules taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{1}{F} \right) \times 100
\]

- \(r_U\) = peak response of each corresponding degradation product from the Sample solution
- \(r_S\) = peak response of prazosin from the Standard solution
- \(C_S\) = concentration of USP Prazosin Hydrochloride RS in the Standard solution (µg/mL)
- \(C_U\) = nominal concentration of prazosin hydrochloride in the Sample solution (µg/mL)
- \(F\) = relative response factor (see Table 2)

**Acceptance criteria:** See Table 2.

**Table 2**

<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>Prazosin related compound D</td>
<td>0.13</td>
<td>0.53</td>
<td>0.2</td>
</tr>
<tr>
<td>Terazosin related compound A</td>
<td>0.21</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Prazosin</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Terazosin related compound C*</td>
<td>1.1</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* For resolution measurement only. Not included in the total degradation products.

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in well-closed, light-resistant containers. Store at controlled room temperature.
- **Labeling:** When more than one test for Dissolution is given, the labeling states the Dissolution test used only if Test 1 is not used.

**USP Reference Standards (11)**

- USP Prazosin Hydrochloride RS
- USP Prazosin Related Compound D RS
- Furan-2-yl(piperazin-1-yl)methanone.
  \[C_9H_{12}N_2O_2\] 180.21
- USP Terazosin Related Compound A RS
- 6,7-Dimethoxy-2-(piperazin-1-yl)quinazolin-4-amine dihydrochloride.
  \[C_{14}H_{19}N_5O_2 \cdot 2\text{HCl}\] 362.26
USP Terazosin Related Compound C RS

2,2’-(Piperazine-1,4-diyl)bis(6,7-dimethoxyquinazolin-4-amine) dihydrochloride.

C$_{24}$H$_{28}$N$_8$O$_4$·2HCl  565.46