Prazosin Hydrochloride Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	24-Feb-2023
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Prazosin Hydrochloride Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Prazosin Hydrochloride Capsules monograph to add *Dissolution Test 3*. Existing references to reagents also have been updated for consistency with the reagent entry names.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

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

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

Prazosin Hydrochloride Capsules

DEFINITION

Prazosin Hydrochloride Capsules contain an amount of prazosin hydrochloride ($C_{19}H_{21}N_5O_4 \cdot HCl$) equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of prazosin ($C_{19}H_{21}N_5O_4$).

[**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*, diluted 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 ($C_{19}H_{21}N_5O_4$) in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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* (μg/mL)

C_U = nominal concentration of prazosin in the *Sample solution* (μg/mL)

M_{r1} = molecular weight of prazosin, 383.41

M_{r2} = molecular weight of prazosin hydrochloride, 419.86

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▲ (TBD); 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 ($C_{19}H_{21}N_5O_4$) dissolved, using the procedure in the *Assay*.

Tolerances: NLT 75% (*Q*) of the labeled amount of prazosin ($C_{19}H_{21}N_5O_4$) 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* ⟨621⟩, *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 ($C_{19}H_{21}N_5O_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times (M_{r1}/M_{r2}) \times 100$$

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* (µg/mL)

L = label claim (mg/Capsule)

V = volume of the *Medium*, 900 mL

M_{r1} = molecular weight of prazosin, 383.41

M_{r2} = molecular weight of prazosin hydrochloride, 419.86

Tolerances: NLT 80% (Q) of the labeled amount of prazosin ($C_{19}H_{21}N_5O_4$) 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 ($C_{19}H_{21}N_5O_4$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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 ($C_{19}H_{21}N_5O_4$) is dissolved. ▲ (TBD)

- **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 1

Time (min)	Solution A (%)	Solution B (%)
0	85	15
15.0	85	15

Time (min)	Solution A (%)	Solution B (%)
66.0	45	55
75.0	45	55
76.0	85	15
85.0	85	15

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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

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

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Prazosin related compound D	0.13	0.53	0.2
Terazosin related compound A	0.21	1.0	0.2
Prazosin	1.0	—	—
Terazosin related compound C[a]	1.1	1.0	—
Any unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	1.0

[a] 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.

$C_{14}H_{19}N_5O_2 \cdot 2HCl$ 362.26

USP Terazosin Related Compound C RS

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

$C_{24}H_{28}N_8O_4 \cdot 2HCl$	565.46

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Not Applicable

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