

Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-Sep-2023
Document Type: USP Monographs
DocId: GUID-FE838E7C-0F59-472A-A202-F31123B3E867_10_en-US
DOI: https://doi.org/10.31003/USPNF_M89918_10_01
DOI Ref: p29ou

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Ziprasidone Capsules

DEFINITION

Ziprasidone Capsules contain an amount of ziprasidone hydrochloride equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$).

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

Change to read:

PROCEDURE

Buffer: 0.3% (v/v) of [triethylamine](#) in [water](#)

Mobile phase: [Acetonitrile](#) and *Buffer* (35:65). Adjust with [glacial acetic acid](#) to a pH of 6.0.

Diluent: [Acetonitrile](#), [water](#), and [glacial acetic acid](#) (70:30:5)

Standard stock solution: 1.0 mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Diluent*

Standard solution: 0.2 mg/mL of [USP Ziprasidone Hydrochloride RS](#) from the *Standard stock solution* in *Mobile phase*

Sample stock solution: Nominally 1 mg/mL of ziprasidone prepared as follows. Empty the contents of NLT 20 Capsules into a container.

Blend the contents. Transfer an amount of the contents, equivalent to NLT 50 mg of ziprasidone, to a suitable volumetric flask. Dissolve the contents in 60% of the flask volume of *Diluent*. Sonicate for NLT 5 min. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45- μ m pore size and use the filtrate to prepare the *Sample solution*.

Sample solution: Nominally 0.2 mg/mL of ziprasidone prepared from the filtered *Sample stock solution* and *Mobile phase*

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 254 nm. For *Identification B*, a diode array detector may be used in the wavelength range of 200–300 nm.

Column: 4.6-mm \times 15-cm; 5- μ m packing [L1](#)

Flow rate: 2.0 mL/min

Injection volume: 20 μ L

Run time: 1.5 times the retention time of ziprasidone

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 ziprasidone ($C_{21}H_{21}ClN_4OS$) 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 ziprasidone from the *Sample solution*

r_S = peak response of ziprasidone from the *Standard solution*

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of ziprasidone free base, 412.94

M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, \blacktriangle 449.39 \blacktriangle (ERR 1-Sep-2023) for the anhydrous form

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- [DISSOLUTION \(711\)](#)

Test 1

Tier 1

Phosphate buffer, pH 7.5: Dissolve 7.8 g of [monobasic sodium phosphate dihydrate](#) and 20 g of [sodium dodecyl sulfate](#) in 1 L [water](#).

Sonicate to dissolve and adjust with [phosphoric acid](#) or \blacktriangle [sodium hydroxide solution](#) \blacktriangle (ERR 1-Sep-2023) to a pH of 7.5.

Medium: *Phosphate buffer, pH 7.5*; 900 mL

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 45 min

Buffer: 0.3% (v/v) of [triethylamine](#) in [water](#). Adjust with [glacial acetic acid](#) to a pH of 6.0.

Mobile phase: [Acetonitrile](#) and *Buffer* (45:55)

Diluent: [Acetonitrile](#), [water](#), and [glacial acetic acid](#) (70:30:5)

Standard stock solution: 0.24 mg/mL of [USP Ziprasidone Hydrochloride RS](#) prepared as follows. Dissolve a suitable amount of [USP Ziprasidone Hydrochloride RS](#) in a suitable volumetric flask first in 60% of the flask volume of *Diluent*, and then dilute with *Diluent* to volume.

Standard solution: 0.024 mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Medium* from the *Standard stock solution*

Sample solution: Pass a portion of the solution through a suitable filter of 0.45- μ m pore size. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing [L1](#)

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

Run time: 1.5 times the retention time of ziprasidone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) 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 ziprasidone from the *Sample solution*

r_S = peak response of ziprasidone from the *Standard solution*

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

M_r = molecular weight of ziprasidone free base, 412.94

M_r = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, \blacktriangle 449.39 \blacktriangle (ERR 1-Sep-2023) for the anhydrous form

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.

If the above tolerance cannot be met, proceed to *Tier 2*.

Tier 2

Solution A: Dissolve 7.8 g of [monobasic sodium phosphate dihydrate](#) in 1 L of [water](#). Sonicate to dissolve and adjust with [phosphoric acid](#) or \blacktriangle [sodium hydroxide solution](#) \blacktriangle (ERR 1-Sep-2023) to a pH of 7.5. Dissolve 10 g of [pancreatin](#) in the resulting solution.

Solution B: Dissolve 7.8 g of [monobasic sodium phosphate dihydrate](#) in 1 L of [water](#). Adjust with [phosphoric acid](#) or \blacktriangle [sodium hydroxide solution](#) \blacktriangle (ERR 1-Sep-2023) to a pH of 7.5. Dissolve 90 g of [sodium dodecyl sulfate](#) in the resulting solution. Sonicate to dissolve.

Medium: Transfer 700 mL of *Solution A* to the dissolution vessel and equilibrate at 37° for 15 min. Add 200 mL of *Solution B*; 900 mL.

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 45 min

Analyze the *Sample solution* using the liquid chromatographic procedure described in *Tier 1*.

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.

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

Tier 1

Medium: 2% [sodium lauryl sulfate](#) in pH 7.5 phosphate buffer (dissolve 6.9 g of [monobasic sodium phosphate monohydrate](#) and 1.6 g of [sodium hydroxide](#) in 900 mL of [water](#), adjust with [1 N sodium hydroxide](#) to a pH of 7.5 and dilute with [water](#) to 1000 mL); 900 mL

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 60 min

Tier 2

Medium A: pH 7.5 phosphate buffer (dissolve 6.9 g of [monobasic sodium phosphate monohydrate](#) and 1.6 g of [sodium hydroxide](#) in 900 mL of [water](#), adjust with [1 N sodium hydroxide](#) to a pH of 7.5 and dilute with [water](#) to 1000 mL) with 1% pancreatin; 700 mL

Medium B: pH 7.5 phosphate buffer with 9% of [sodium lauryl sulfate](#); 200 mL

Apparatus 2: 75 rpm. Use a suitable sinker, if necessary.

Time: 15 min for *Medium A*; 45 min for *Medium A* with the addition of *Medium B*

Solution A: Dissolve 2.7 g of [monobasic sodium phosphate monohydrate](#) in 1 L of [water](#). Adjust with [1 N sodium hydroxide](#) to a pH of 6.0.

Mobile phase: [Acetonitrile](#) and *Solution A* (50:50)

Diluent: [Acetonitrile](#) and [water](#) (50:50)

Standard stock solution: 0.48 mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Diluent*

Standard solution: ($L/900$) mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Medium* from *Standard stock solution*, where L is the label claim of ziprasidone in mg/Capsules

Sample solution: Pass a portion of the solution through a suitable filter of 0.45- μ m pore size.

Procedure: Perform the test using the conditions in *Tier 1*. In the presence of cross-linking repeat the test with new Capsules using the conditions in *Tier 2* as follows. After 15 min with 700 mL of *Medium A*, stop the dissolution bath and timer and add 200 mL of *Medium B* pre-equilibrated at $37 \pm 0.5^\circ$. Restart the bath and timer, and continue the dissolution for an additional 45 min.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm \times 15-cm; 5- μ m packing [L1](#)

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 20 μ L

Run time: 1.8 times the retention time of ziprasidone

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 ziprasidone ($C_{21}H_{21}ClN_4OS$) 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 ziprasidone from the *Sample solution*

r_S = peak response of ziprasidone from the *Standard solution*

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

L = label claim (mg/Capsule)

V = volume of *Medium*, 900 mL

M_{r1} = molecular weight of ziprasidone, 412.94

1

M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate form, ▲449.39▲ (ERR 1-Sep-2023) for the anhydrous form

Tolerances: NLT 75% (Q) of the labeled amount of ziprasidone (C₂₁H₂₁ClN₄OS) is dissolved.

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

Tier 1

Medium: 2% [sodium lauryl sulfate](#) in pH 7.5 phosphate buffer (6.9 g/L of [monobasic sodium phosphate](#) pH adjusted with 5 N sodium hydroxide); 900 mL

Apparatus 2: 75 rpm. Use a suitable sinker.

Time: 60 min

Tier 2

Medium A: pH 7.5 phosphate buffer (6.9 g/L of [monobasic sodium phosphate](#) pH adjusted with 5 N sodium hydroxide) with 1% pancreatin; 700 mL

Medium B: pH 7.5 phosphate buffer (6.9 g/L of [monobasic sodium phosphate](#) pH adjusted with 5 N sodium hydroxide) with 9% [sodium lauryl sulfate](#); 200 mL

Apparatus 2: 75 rpm. Use a suitable sinker.

Time: 15 min for *Medium A*; 45 min for *Medium A* with the addition of *Medium B*

Buffer: 6.8 g/L of [monobasic potassium phosphate](#). To each liter of this solution, add 1 mL of [triethylamine](#) and adjust with [phosphoric acid](#) to a pH of 3.0.

Mobile phase: [Acetonitrile](#) and *Buffer* (30:70)

Diluent

Diluent 1: [Acetonitrile](#) and [methanol](#) (35:65)

Diluent 2

Tier 1: *Medium*

Tier 2: *Medium A* and *Medium B* (70:20)

Standard stock solution 1: 0.5 mg/mL of [USP Ziprasidone Hydrochloride RS](#) in *Diluent 1*

Standard stock solution 2: Prepare solutions of [USP Ziprasidone Hydrochloride RS](#) in *Diluent 2* at concentrations given in [Table 1](#) as follows. Transfer a suitable volume of *Standard stock solution 1* into a suitable volumetric flask and dilute with *Diluent 2* to volume.

Table 1

Strength of Ziprasidone Capsules (mg)	Concentration of Ziprasidone (mg/mL)
20	0.025
40	0.050
60	0.080
80	0.100

Standard solution: Transfer 5 mL of *Standard stock solution 2* to a 25-mL volumetric flask and dilute with *Mobile phase* to volume.

Sample solution: Centrifuge a portion of the solution under test. Dilute the supernatant with *Mobile phase* to volume to obtain nominal concentration of ziprasidone similar to that of the *Standard solution*. Pass through a suitable filter of 0.45-µm pore size. [NOTE—A

centrifuge speed of 4000 rpm for 10 min may be suitable.]

Procedure: Perform the test using the conditions in *Tier 1*. In the presence of cross-linking repeat the test with new Capsules using the conditions in *Tier 2* as follows. After 15 min with 700 mL of *Medium A*, stop the dissolution bath and timer and add 200 mL of *Medium B* pre-equilibrated at $37 \pm 0.5^\circ$. Restart the bath and timer, and continue the dissolution for an additional 45 min.

Chromatographic system

(See [Chromatography \(621\)](#), [System Suitability](#).)

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing [L1](#)

Flow rate: 1.3 mL/min

Injection volume: 10 μ L

Run time: 1.3 times the retention time of ziprasidone

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) dissolved:

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

r_U = peak response of ziprasidone from the *Sample solution*

r_S = peak response of ziprasidone from the *Standard solution*

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

V = volume of *Medium (Tier 1 or Tier 2)*, 900 mL

D = dilution factor for the *Sample solution*, 5

L = label claim (mg/Capsule)

M_{r1} = molecular weight of ziprasidone, 412.94

1

M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate form, \blacktriangle 449.39 \blacktriangle (ERR 1-Sep-2023) for the anhydrous form

2

Tolerances: NLT 70% (Q) of the labeled amount of ziprasidone ($C_{21}H_{21}ClN_4OS$) is dissolved.

- [UNIFORMITY OF DOSAGE UNITS \(905\)](#): Meet the requirements

IMPURITIES

Change to read:

- ORGANIC IMPURITIES

Buffer: 0.05 M [monobasic potassium phosphate](#)

Solution A: [Methanol](#) and *Buffer* (33:67). Adjust with [phosphoric acid](#) to a pH of 3.0.

Solution B: [Acetonitrile](#), [methanol](#), and *Buffer* (55:5:40). Adjust with \blacktriangle [potassium hydroxide solution](#) \blacktriangle (ERR 1-Sep-2023) to a pH of 6.0.

Mobile phase: See [Table 2](#).

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0

Time (min)	Solution A (%)	Solution B (%)
15	100	0
20	85	15
30	85	15
40	55	45
55	40	60
65	25	75
70	20	80
71	100	0
75	100	0

Diluent: [Acetonitrile](#), [methanol](#), and [water](#) (40:10:50). Adjust with [phosphoric acid](#) to a pH of 2.5.

System suitability solution: 0.5 mg/mL of [USP Ziprasidone Hydrochloride RS](#) and 0.05 mg/mL each of [USP Ziprasidone Related Compound B RS](#) and [USP Ziprasidone Related Compound F RS](#) in *Diluent*

Standard solution: 0.002 mg/mL each of [USP Ziprasidone Hydrochloride RS](#) and [USP Ziprasidone Related Compound B RS](#) in *Diluent*.
Sonication may be used to aid in dissolution.

Sample solution: Nominally 1.0 mg/mL of ziprasidone in *Diluent* from a portion of contents of Capsules (NLT 20) prepared as follows.

Transfer a suitable amount of Capsule contents to a suitable volumetric flask. Add 60% of the flask volume of *Diluent*. Sonicate for 10 min. Dilute with *Diluent* to volume. Pass through a suitable filter of 0.45- μ m pore size.

Chromatographic system

(See [Chromatography \(621\), System Suitability](#).)

Mode: LC

Detector: UV 229 nm

Column: 4.6-mm \times 15-cm; 5- μ m packing [L7](#)

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

System suitability

Samples: *System suitability solution* and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between ziprasidone related compound B and related compound F; NLT 2.0 between ziprasidone related compound F and ziprasidone, *System suitability solution*

Tailing factor: NMT 1.5 for ziprasidone, *Standard solution*

Relative standard deviation: NMT 5.0% for both ziprasidone and ziprasidone related compound B, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ziprasidone related compound B in the portion of Capsules taken:

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

r_U = peak response of ziprasidone related compound B from the *Sample solution*

r_S = peak response of ziprasidone related compound B from the *Standard solution*

C_S = concentration of [USP Ziprasidone Related Compound B RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)

Calculate the percentage of ziprasidone sulfoxide analog or any individual unspecified degradation product in the portion of Capsules taken:

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

r_U = peak response of ziprasidone sulfoxide analog or each unspecified degradation product from the *Sample solution*

r_S = peak response of ziprasidone from the *Standard solution*

C_S = concentration of [USP Ziprasidone Hydrochloride RS](#) in the *Standard solution* (mg/mL)

C_U = nominal concentration of ziprasidone in the *Sample solution* (mg/mL)

F = relative response factor

M_{r1} = molecular weight of ziprasidone free base, 412.94

M_{r2} = molecular weight of ziprasidone hydrochloride; 467.41 for the monohydrate, ▲449.39▲ (ERR 1-Sep-2023) for the anhydrous form

Acceptance criteria: See [Table 3](#). Disregard any peak with an area below 0.05% in the *Sample solution*.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ziprasidone sulfoxide analog (if present) ^a	0.11	0.49	0.5
Ziprasidone related compound A ^{b,c}	0.22	—	—
Chloroindolinone ^{b,d}	0.59	—	—
Ziprasidone related compound B	0.70	—	0.20
Ziprasidone related compound F ^b	0.84	—	—
Ziprasidone	1.0	—	—
Ziprasidone related compound C ^{b,e}	1.84	—	—
Ziprasidone related compound D ^{b,f}	2.18	—	—
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	0.8

^a 6-Chloro-5-(2-[4-(1-oxidobenzisothiazol-3-yl)piperazin-1-yl]ethyl)indolin-2-one.

^b Process impurity included in the table for identification only; controlled in the drug substance. Process impurities are controlled in the drug substance and are not to be reported or included in the total impurities for the drug product.

- c 3-(Piperazin-1-yl)benzo[d]isothiazole; also known as 3-(Piperazin-1-yl)benzisothiazole monohydrochloride.
- d 6-Chloroindolin-2-one.
- e 5,5'-Bis{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-6,6'-dichloro-3-hydroxy-3,3'-biindoline-2,2'-dione; also known as 5,5'-Bis{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6,6'-dichloro-3-hydroxy-3,3'-biindoline-2,2'-dione.
- f 3-(Benzo[d]isothiazol-3-yl)-5-{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindolin-2-one; also known as 3-(Benzisothiazol-3-yl)-5-{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindolin-2-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **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 Ziprasidone Hydrochloride RS](#)

[USP Ziprasidone Related Compound B RS](#)

5-{2-[4-(Benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindoline-2,3-dione; also known as 5-{2-[4-(Benzisothiazol-3-yl)piperazin-1-yl]ethyl}-6-chloroindoline-2,3-dione.

$C_{21}H_{19}ClN_4O_2S$ 426.92

[USP Ziprasidone Related Compound F RS](#)

Sodium 2-(2-amino-5-{2-[4-(benzo[d]isothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate; also known as Sodium 2-(2-amino-5-{2-[4-(benzisothiazol-3-yl)piperazin-1-yl]ethyl}-4-chlorophenyl)acetate monohydrate

$C_{21}H_{22}ClN_4NaO_2S \cdot H_2O$ 470.95

Auxiliary Information - Please [check for your question in the FAQs](#) before contacting USP.

Topic/Question	Contact	Expert Committee
ZIPRASIDONE CAPSULES	Documentary Standards Support	SM42020 Small Molecules 4
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM42020 Small Molecules 4

Chromatographic Database Information: [Chromatographic Database](#)

Most Recently Appeared In:

Pharmacopeial Forum: Volume No. PF 41(5)

Current DocID: [GUID-FE838E7C-0F59-472A-A202-F31123B3E867_10_en-US](#)

DOI: https://doi.org/10.31003/USPNF_M89918_10_01

DOI ref: [p29ou](#)