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Zolpidem Tartrate Tablets

DEFINITION

Zolpidem Tartrate Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$.

IDENTIFICATION

- **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

- **Procedure**

Buffer: 3.4 g/L of monobasic potassium phosphate in water, adjusted with ammonium hydroxide to a pH of 5.5

Mobile phase: Acetonitrile, methanol, and *Buffer* (30:20:50)

Standard stock solution: 0.8 mg/mL of USP Zolpidem Tartrate RS in 0.01 N hydrochloric acid TS

Standard solution: 0.16 mg/mL of USP Zolpidem Tartrate RS in *Mobile phase*, from the *Standard stock solution*

Sample stock solution: Nominally 0.4 mg/mL of zolpidem tartrate from NLT 20 Tablets prepared as follows. Transfer the Tablets to a suitable volumetric flask and add 40% of the flask volume of 0.125 N hydrochloric acid TS. Mix well until the Tablets disintegrate, and add 50% of the flask volume of *Mobile phase*. Dilute with water to volume, and stir for 30 min using a magnetic stirrer. Allow solid particles to settle, and pass the supernatant through a suitable filter.[1]

Sample solution: Nominally 0.16 mg/mL of zolpidem tartrate in *Mobile phase*, from the *Sample stock solution*

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 1.2 mL/min

Injection volume: 10 µL

Run time: NLT 2.5 times the retention time of zolpidem tartrate

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 3.0 for zolpidem

Relative standard deviation: NMT 2.0% for zolpidem

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium: 0.01 N hydrochloric acid TS; 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 15 min

▲Perform the analysis by using either the *Spectrophotometric procedure* or the *Chromatographic procedure*.

Spectrophotometric procedure▲ (USP 1-Aug-2020)

Standard solution: (*L*/1000) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

▲**Chromatographic procedure**

Solution A: 5.6 g/L of phosphoric acid in water, adjusted with triethylamine to a pH of 5.5

Mobile phase: Acetonitrile, methanol, and *Solution A* (18:23:59)

Standard solution: (*L*/900) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where *L* is the label claim of zolpidem tartrate in mg/Tablet. Sonicate as needed.

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

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

Run time: NLT 1.5 times the retention time of zolpidem tartrate

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 zolpidem tartrate $[(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6]$ dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL▲ (USP 1-Aug-2020)

Tolerances: NLT 80% (*Q*) of the labeled amount of zolpidem tartrate [$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$] is dissolved.

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

Medium: 0.1 N hydrochloric acid VS; 900 mL

Apparatus 2: 50 rpm

Time: 20 min

Standard solution: (*L*/900) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where *L* is the label claim in mg/Tablet

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

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate [$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$] dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (*Q*) of the labeled amount of zolpidem tartrate [$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$] is dissolved.

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

Medium: 0.01 N hydrochloric acid TS; 900 mL

Apparatus 2: 50 rpm

Time: 15 min

Standard solution: (*L*/900) mg/mL of USP Zolpidem Tartrate RS in *Medium*, where *L* is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate [$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$] dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: NLT 85% (Q) of the labeled amount of zolpidem tartrate [$(C_{19}H_{21}N_3O)_2 \cdot C_4H_6O_6$] is dissolved.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

• **Organic Impurities**

Solution A: 3.3 mL/L of phosphoric acid in water, adjusted with triethylamine to a pH of 6.0

Solution B: Acetonitrile

Solution C: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)	Solution C (%)
0	76	14	10
35.0	48	16	36
36.5	48	16	36
37.5	76	14	10
42.0	76	14	10

Diluent: *Solution B*, *Solution C*, and *Solution A* (15:10:75)

System suitability solution: 0.5 mg/mL of USP Zolpidem Tartrate RS and 0.0008 mg/mL of USP Zolpidem Related Compound A RS in *Diluent*

Standard solution: 0.005 mg/mL of USP Zolpidem Tartrate RS in *Diluent*

Sample solution: Nominally equivalent to 0.5 mg/mL of zolpidem tartrate in *Diluent* from NLT 10 Tablets, prepared as follows. Transfer the Tablets to a suitable volumetric flask, add 70% of the flask volume of *Diluent*, and stir for 30 min. Dilute with *Diluent* to volume. Centrifuge a portion of the solution and use the clear supernatant.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 254 nm

Column: 3.9-mm × 15-cm; 4-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between zolpidem and zolpidem related compound A, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product from the *Sample solution*

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

C_S = concentration of USP Zolpidem Tartrate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of zolpidem tartrate in the *Sample solution* (mg/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 (%)
Tolyloyl propionic acid[a,b]	0.15	—	—
Zolpidem acid[c]	0.18	1.0	0.3
Tolyloyl propionamide[b,d]	0.54	—	—
Tolyloyl acrylamide[b,e]	0.65	—	—
Zolpidem related compound B[f]	0.83	1.1	0.3
Zolpidem related compound A	0.91	1.1	0.20
Zolpidem	1.0	—	—
Tolyloyl bromopropionamide[b,g]	1.14	—	—
Zolpidem related compound C[h]	1.20	1.1	0.3
Zolpidem 3-carbaldehyde[i]	1.65	1.4	0.3
Any individual unspecified degradation product	—	1.0	0.2
Total degradation products	—	—	0.5

[a] 4-Oxo-4-(*p*-tolyl)butanoic acid.

[b] Process impurities related to specific manufacturing process of the drug substance; included for peak identification purposes only and are not to be reported or included in the total degradation products.

[c] 2-(6-Methyl-2-*p*-tolylimidazo[1,2-α]pyridin-3-yl)acetic acid.

[d] *N,N*-Dimethyl-4-oxo-4-(*p*-tolyl)butanamide.

[e] *N,N*-Dimethyl-4-oxo-4-(*p*-tolyl)but-2-enamide.

[f] *N,N*-Dimethyl-2-(6-methyl-2-*p*-tolylimidazo[1,2-α]pyridin-3-yl)-2-oxoacetamide.

[g] 3-Bromo-*N,N*-dimethyl-4-oxo-4-(*p*-tolyl)butanamide.

[h] 4-Methyl-*N*-(5-methylpyridin-2-yl)benzamide.

[i] 6-Methyl-2-*p*-tolylimidazo[1,2-α]pyridine-3-carbaldehyde.

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 Zolpidem Tartrate RS

USP Zolpidem Related Compound A RS

N,N-Dimethyl-2-(7-methyl-2-*p*-tolylimidazo[1,2-α]pyridin-3-yl)acetamide.

$C_{19}H_{21}N_3O$ 307.39

[1] The Whatman #40 filter or equivalent may be suitable.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

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

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