Status: Currently Official on 17-Feb-2025
Official Date: Official as of 01-May-2020
Document Type: USP Monographs
DocId: GUID-9957CE88-D2A3-4EEB-97B1-BF397BF344DF_3_en-US
DOI: https://doi.org/10.31003/USPNF_M2061_03_01
DOI Ref: uf7kc

Zolpidem Tartrate Extended-Release Tablets

DEFINITION

Zolpidem Tartrate Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: **197U**▲ (CN 1-May-2020)

Sample: 25 µg/mL of zolpidem tartrate in 0.01 M hydrochloric acid from a suitable quantity of powder obtained by grinding 1 Tablet

Acceptance criteria: Meet the requirements

• **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: 3.3 mL of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 5.5.

Mobile phase: Acetonitrile, methanol, and *Buffer* (4:5:11)

Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in a mixture of alcohol and 0.01 M hydrochloric acid (4:1)

Standard solution: 0.1 mg/mL of USP Zolpidem Tartrate RS from the *Standard stock solution* in *Mobile phase*

Sample stock solution: Finely powder NLT 8 Tablets. Transfer the powder quantitatively to a suitable volumetric flask to obtain nominally 0.5 mg/mL of zolpidem tartrate. Add 70% of the flask volume of a mixture of alcohol and 0.01 M hydrochloric acid (5:2), and stir on a magnetic stirrer for 1 h. Dilute with alcohol to volume. Allow solid particles to settle, and pass the supernatant through a suitable filter (Whatman 40 or equivalent).

Alternatively, the *Sample stock solution* can be prepared as follows. Transfer NLT 20 Tablets to a suitable volumetric flask to obtain a nominal concentration of 0.5 mg/mL of zolpidem tartrate. Add 10% of the flask volume of alcohol and stir for 30 min or until the Tablets have completely disintegrated. Add another 10% of the flask volume of alcohol and stir for another 90 min. Add 10% of the flask volume of 0.01 M hydrochloric acid followed by 40% of the flask volume of a mixture of alcohol and 0.01 M hydrochloric acid (5:2). Continue to stir for another 30 min. Remove the stirrer bar and rinse with alcohol. Dilute with alcohol to volume.

Sample solution: Nominally 0.1 mg/mL of zolpidem tartrate from filtered *Sample stock solution* in *Mobile phase*. If the *Sample stock solution* is prepared using the alternative procedure, dilute the required volume of the *Sample stock solution* with *Mobile phase* and centrifuge instead of filtering before use.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 15 µL

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 ($C_{42}H_{48}N_6O_8$) 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 the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Test 1

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Times: 30, 90, and 240 min

Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (*L*/500) mg/mL, where *L* is the label claim in mg/Tablet

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

Detector: UV 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) 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 the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: See *Table 1*.

Table 1

Time (min)	Amount Dissolved
30	50%–70%
90	70%–85%
240	NLT 90%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

Medium, Apparatus, and **Times:** Proceed as directed in *Test 1*.

Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (*L*/500) mg/mL, 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 ($C_{42}H_{48}N_6O_8$) 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 the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: See *Table 2*.

Table 2

Time (min)	Amount Dissolved
30	55%–75%
90	70%–90%
240	NLT 85%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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; 500 mL

Apparatus 1: 100 rpm

Times: 30, 90, and 120 min

Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (L/500) mg/mL, 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: 237 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) 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 the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: See *Table 3*.

Table 3

Time (min)	Amount Dissolved
30	25%–45%
90	65%–85%
120	NLT 80%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Times: 30, 60, and 120 min

Standard solution: Solution of USP Zolpidem Tartrate RS in *Medium* containing (L/500) mg/mL, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter. Replace the volume withdrawn with an equal volume of *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 294 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at each time point (Q_i):

$$Q_{30} = (A_U/A_S) \times C_S \times V \times (1/L) \times 100$$

$$Q_{60} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [Q_{30} \times (V_S/V)]$$

$$Q_{120} = [(A_U/A_S) \times C_S \times V \times (1/L) \times 100] + [(Q_{30} + Q_{60}) \times (V_S/V)]$$

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)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the sample withdrawn (mL)

Tolerances: See *Table 4*.

Table 4

Time (min)	Amount Dissolved
30	30%–55%
60	55%–80%
120	NLT 85%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 5: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 5*.

Medium: pH 6.8 phosphate buffer (Dissolve 6.8 g of monobasic potassium phosphate and 0.8 g of sodium hydroxide in 1 L of water. Adjust with phosphoric acid or 1 N sodium hydroxide to a pH of 6.8.); 900 mL

Apparatus 1: 50 rpm

Times: 60, 180, and 360 min

Buffer: Dissolve 5.6 g of phosphoric acid in 1 L of water. Adjust with triethylamine to a pH of 5.5.

Mobile phase: Methanol, acetonitrile, and *Buffer* (28:22:50)

Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in methanol

Standard solution: (*L*/900) mg/mL of USP Zolpidem Tartrate RS from *Standard stock solution* 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.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 7.5-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 25 µL

Run time: NLT 2.5 times the retention time of zolpidem

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 ($C_{42}H_{48}N_6O_8$) dissolved:

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

r_U = peak response of the *Sample solution*

r_S = peak response of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

Tolerances: See *Table 5*.

Table 5

Time (min)	Amount Dissolved
60	55%–75%
180	NLT 75%
360	NLT 85%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution ⟨711⟩, Acceptance Table 2*.

Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Times: 15, 60, and 120 min

Diluent: Methanol and water (50:50)

Standard stock solution: 0.25 mg/mL of USP Zolpidem Tartrate RS in *Diluent*. Sonication may be used to aid complete dissolution.

Standard solution: (*L*/500) mg/mL of USP Zolpidem Tartrate RS from *Standard stock solution* 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. Replace the volume withdrawn with an equal volume of *Medium*.

Instrumental conditions

Mode: UV

Analytical wavelength: 295 nm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) in the sample withdrawn at each time point (*i*):

$$C_i = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount (Q_i) of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at each time point (*i*):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = [(C_2 \times V) + (C_1 \times V_S)] \times (1/L) \times 100$$

$$\text{Result}_3 = \{(C_3 \times V) + [(C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of zolpidem tartrate in the portion of sample withdrawn at time point *i* (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn from the *Medium* (mL)

Tolerances: See *Table 6*.

Table 6

Time Point (*i*)	Time (min)	Amount Dissolved
1	15	45%–65%
2	60	63%–83%
3	120	NLT 80%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

Test 7: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Times: 30, 90, and 240 min

Standard stock solution: 0.5 mg/mL of USP Zolpidem Tartrate RS in methanol. Sonication may be used to aid complete dissolution.

Standard solution: 0.0125 mg/mL of USP Zolpidem Tartrate RS from *Standard stock solution* in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discarding the first 2 mL of filtrate.

Instrumental conditions

Mode: UV

Analytical wavelength: 237 nm

Cell: 5.0 mm

Blank: *Medium*

Analysis

Samples: *Standard solution*, *Sample solution*, and *Blank*

Correct the instrument by using the *Blank*.

Calculate the concentration (C_i) of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at each time point (i):

$$C_i = (A_U/A_S) \times C_S$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

Calculate the percentage of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at each time point (i):

$$\text{Result}_1 = C_1 \times V \times (1/L) \times 100$$

$$\text{Result}_2 = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

$$\text{Result}_3 = (\{C_3 \times [V - (2 \times V_S)]\} + [(C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of zolpidem tartrate in the portion of sample withdrawn at the specified time point i (mg/mL)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

V_S = volume of the *Sample solution* withdrawn at each time point (mL)

Tolerances: See *Table 7*.

Table 7

Time Point (*i*)	Time (min)	Amount Dissolved
1	30	70%–90%
2	90	NLT 75%
3	240	NLT 80%

The percentages of the labeled amount of zolpidem tartrate ($C_{42}H_{48}N_6O_8$) dissolved at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, Standard stock solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

System suitability solution: Dissolve a suitable amount of USP Zolpidem Related Compound A RS in the *Standard stock solution* to obtain a solution containing 1 µg/mL of zolpidem related compound A. Dilute 1 mL of the resulting solution with *Mobile phase* to 5 mL.

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between zolpidem related compound A and zolpidem

Tailing factor: NMT 3.0 for the zolpidem peak

Relative standard deviation: NMT 2.0% for the zolpidem peak

Analysis

Sample: *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response for each impurity from the *Sample solution*

r_T = sum of all the peak responses from the *Sample solution*

F = relative response factor of the corresponding impurity (see *Table 8*)

Acceptance criteria: See *Table 8*.

Table 8

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Zolpidem acid[a]	0.3	1.2	0.20
Zolpidem related compound A[b]	0.9	1.0	0.20
Zolpidem	1.0	—	—
Any unspecified degradation product	—	1.0	0.20
Total impurities	—	—	0.5

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

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

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 Related Compound A RS

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

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

USP Zolpidem Tartrate RS

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

Topic/Question	Contact	Expert Committee
ZOLPIDEM TARTRATE EXTENDED-RELEASE TABLETS	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 35(3)
Current DocID: GUID-9957CE88-D2A3-4EEB-97B1-BF397BF344DF_3_en-US
DOI: https://doi.org/10.31003/USPNF_M2061_03_01
DOI ref: uf7kc