Status: Currently Official on 13-Feb-2025
Official Date: Official as of 01-May-2017
Document Type: USP Monographs
DocId: GUID-30C4B537-E2F1-457D-8C6C-EA85A6AADDC0_2_en-US
DOI: https://doi.org/10.31003/USPNF_M743_02_01
DOI Ref: qz6sh

Alprazolam Extended-Release Tablets

DEFINITION

Alprazolam Extended-Release Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$).

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: Acetonitrile, water, and phosphoric acid (350:650:1)

Standard solution: 0.05 mg/mL of USP Alprazolam RS in methanol

Sample solution: Nominally 0.05 mg/mL of alprazolam prepared as follows. Transfer an appropriate number of Tablets to a suitable volumetric flask. Sonicate in 80% of the flask volume of methanol for 15 min, and shake mechanically for 30 min. Dilute with methanol to final volume, filter a portion of the solution, and discard the first 3 mL of filtrate.

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 × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Column efficiency: NLT 3000 theoretical plates

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) 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 Alprazolam RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **Dissolution ⟨711⟩**

Test 1

Medium: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL

Apparatus 1: 100 rpm

Times: 1, 4, 8, and 12 h

Mobile phase: Acetonitrile, tetrahydrofuran, and *Medium* (7:1:12)

Standard stock solution: 0.5 mg/mL of USP Alprazolam RS in acetonitrile

Standard solution: (*L*/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, 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 × 10-cm; 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Column efficiency: NLT 3000 theoretical plates

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) 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 Alprazolam RS in the *Standard solution* (mg/mL)

L = label claim (mg/Tablet)

V = volume of *Medium*, 500 mL

Tolerances: See *Table 1*.

Table 1

Time (h)	Amount Dissolved		
	0.5-mg Tablet (%)	2-mg Tablet (%)	3-mg Tablet (%)
1	NMT 25	NMT 20	NMT 20
4	40–60	30–55	30–55
8	70–90	65–90	65–90
12	NLT 85	NLT 85	NLT 85

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released 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: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL

Apparatus 1: 100 rpm

Times: 1, 4, 8, and 16 h

Mobile phase: Acetonitrile, tetrahydrofuran, and *Medium* (35:5:60)

Standard stock solution: 0.05 mg/mL of USP Alprazolam RS in methanol

Standard solution: (*L*/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, 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; 5-µm packing L7

Flow rate: 1.3 mL/min

Injection volume: 80 µL

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 concentration (C_i) of alprazolam ($C_{17}H_{13}ClN_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of alprazolam from the *Sample solution* at each time point

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

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

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point (*i*):

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

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

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

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of alprazolam in the *Sample solution* at the specified time point (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 2*.

Table 2

Time Point (*i*)	Time (h)	Amount Dissolved			
		0.5-mg Tablet (%)	1-mg Tablet (%)	2-mg Tablet (%)	3-mg Tablet (%)
1	1	NMT 25	NMT 25	NMT 20	NMT 20
2	4	45–60	40–55	30–50	25–45
3	8	70–90	65–85	55–75	50–70
4	16	NLT 85	NLT 85	NLT 85	NLT 80

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released 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: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0 ± 0.1); 500 mL, deaerated

Apparatus 1: 100 rpm

Times: 1, 4, and 8 h for Tablets labeled to contain 0.5 mg or 1 mg; 1, 4, 8, and 16 h for Tablets labeled to contain 2 mg or 3 mg

Mobile phase: Acetonitrile and *Medium* (40:60)

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

Standard solution: (L/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 10-cm; 3-µm or 5-µm packing L7

Flow rate: 1 mL/min

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the concentration (C_i) of alprazolam ($C_{17}H_{13}ClN_4$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of alprazolam from the *Sample solution* at each time point

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

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

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point (i):

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

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

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

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of alprazolam in the *Sample solution* at the specified time point (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 3*.

Table 3

Time Point (i)	Time (h)	Amount Dissolved			
		0.5-mg Tablet (%)	1-mg Tablet (%)	2-mg Tablet (%)	3-mg Tablet (%)
1	1	15–35	10–30	10–30	5–25
2	4	50–75	45–65	30–55	25–50
3	8	NLT 75	NLT 70	60–80	50–75
4	16	—	—	NLT 85	NLT 80

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released 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: pH 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or potassium hydroxide to a pH of 6.0); 500 mL

Apparatus 1 (20-mesh basket): 100 rpm

Times: 1, 4, 8, and 16 h

Mobile phase: Acetonitrile and *Medium* (32:68)

Standard stock solution: 0.4 mg/mL of USP Alprazolam RS in methanol

Standard solution: (*L*/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, where *L* is the label claim in mg/Tablet. Pass through a suitable filter of 0.45-µm pore size, and use the filtrate.

Sample solution: At the end of specified time intervals, withdraw a known volume (V_S) of the solution from the dissolution vessel, and replace an equal volume of fresh *Medium* into the dissolution vessel. Pass the withdrawn sample through a suitable filter of 0.45-µm pore size, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

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

Flow rate: 1.5 mL/min

Injection volume: 100 µL

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 concentration (C_i) of alprazolam ($C_{17}H_{13}ClN_4$) in the sample withdrawn from the vessel at each time point (*i*):

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

r_U = peak response of alprazolam from the *Sample solution* at each time point

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

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

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point (*i*):

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

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

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

$$\text{Result}_4 = \{[C_4 \times V] + [(C_3 + C_2 + C_1) \times V_S]\} \times (1/L) \times 100$$

C_i = concentration of alprazolam in the *Sample solution* at the specified time point (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 and replaced with *Medium* (mL)

Tolerances: See *Table 4*.

Table 4

Time Point (*i*)	Time (h)	Amount Dissolved			
		0.5-mg Tablet (%)	1-mg Tablet (%)	2-mg Tablet (%)	3-mg Tablet (%)
1	1	NMT 40	NMT 35	NMT 35	NMT 35
2	4	50–75	45–65	35–55	30–55
3	8	NLT 75	70–90	55–75	50–70
4	16	NLT 85	NLT 85	NLT 85	NLT 75

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released 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 6.0 phosphate buffer (8.0 g/L of monobasic potassium phosphate and 2.0 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 6.0); 500 mL

Apparatus 1: 100 rpm

Times: 1, 4, 8, and 16 h

Mobile phase: Acetonitrile, water, and phosphoric acid (350:650:1)

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

Standard solution: (L/500) mg/mL of USP Alprazolam RS in *Medium* from the *Standard stock solution*, 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, and use the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 50 µL

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 concentration (C_i) of alprazolam ($C_{17}H_{13}ClN_4$) in the sample withdrawn from the vessel at each time point (i):

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

r_U = peak response of alprazolam from the *Sample solution* at each time point

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

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

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved at each time point (i):

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

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

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

$$\text{Result}_4 = (\{C_4 \times [V - (3 \times V_S)]\} + [(C_3 + C_2 + C_1) \times V_S]) \times (1/L) \times 100$$

C_i = concentration of alprazolam in the *Sample solution* at the specified time point (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 5*.

Table 5

Time Point (i)	Time (h)	Amount Dissolved (%)
1	1	NMT 25
2	4	40–65
3	8	65–95

Time Point (*i*)	Time (h)	Amount Dissolved (%)
4	16	NLT 85

The percentages of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) released at the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.

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

IMPURITIES

• **Organic Impurities**

Buffer: 5.4 g/L of monobasic potassium phosphate (KH_2PO_4) in water. Adjust with phosphoric acid to a pH of 3.4.

Solution A: Acetonitrile, methanol, and *Buffer* (27:10:63)

Solution B: Acetonitrile, methanol, and *Buffer* (7:3:10)

Mobile phase: See *Table 6*.

Table 6

Time (min)	Solution A (%)	Solution B (%)
0	95	5
22	95	5
25	15	85
60	15	85
60.1	95	5
70	95	5

System suitability solution: 1 µg/mL each of USP Chlordiazepoxide Related Compound A RS, USP Alprazolam Related Compound A RS, and USP Nordazepam RS; and 0.4 µg/mL of USP Alprazolam RS in methanol

Standard solution: 0.4 µg/mL of USP Alprazolam RS in methanol

Sample solution: From NLT 20 Tablets ground to a fine powder, transfer an amount of powder to a suitable flask to obtain a nominal concentration of 0.2 mg/mL of alprazolam in methanol. [Note—Sonicate for 15 min to dissolve the contents.] Filter a portion, and discard the first 1 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[Note—The relative retention times are listed in *Table 7*.]

Suitability requirements

Resolution: NLT 1.5 between nordazepam and alprazolam; NLT 1.5 between chlordiazepoxide related compound A and alprazolam related compound A, *System suitability solution*

Tailing factor: NMT 2.0 for the alprazolam peak, *System suitability solution*

Relative standard deviation: NMT 5%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity 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 the impurity from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

F = relative response factor (see *Table 7*)

Acceptance criteria: See *Table 7*.

Table 7

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Chlordiazepoxide related compound A[a]	0.36	1.0	0.2
Alprazolam related compound A	0.45	0.7	0.5
Nordazepam[a,b]	0.8	1.0	0.2
Alprazolam	1.0	—	—
2-Amino-5-chloro-benzophenone	1.8	0.9	0.5
Amino-derivative[c]	2.2	1.2	0.5
Any other individual degradation product	—	1.0	0.2
Total impurities	—	—	2.0

[a] If possible from the manufacturing process.

[b] 7-Chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

[c] 7-Chloro-1-methyl-5-phenyl[1,2,4]triazolo[4,3-*a*]quinolin-4-amine.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers, and store at room temperature.
- **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP Reference Standards** ⟨11⟩

USP Alprazolam RS

USP Alprazolam Related Compound A RS

2-(2-Acetylhydrazino)-7-chloro-5-phenyl-3*H*-1,4-benzodiazepine.

$C_{17}H_{15}ClN_4O$ 326.78

USP Chlordiazepoxide Related Compound A RS

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide.

$C_{15}H_{11}ClN_2O_2$ 286.71

USP Nordazepam RS

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

Topic/Question	Contact	Expert Committee
ALPRAZOLAM EXTENDED-RELEASE TABLETS	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 41(4)

Current DocID: GUID-30C4B537-E2F1-457D-8C6C-EA85A6AADDC0_2_en-US

Previous DocID: GUID-30C4B537-E2F1-457D-8C6C-EA85A6AADDC0_1_en-US
DOI: https://doi.org/10.31003/USPNF_M743_02_01
DOI ref: qz6sh