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Alprazolam Orally Disintegrating Tablets

DEFINITION

Alprazolam Orally Disintegrating 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**

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.5.

Diluent: Acetonitrile and water (60:40)

Mobile phase: Acetonitrile, methanol, and *Buffer* (35:10:55)

Standard solution: 10 µg/mL of USP Alprazolam RS in *Diluent*

Sample solution: Nominally 10 µg/mL of alprazolam from Tablets prepared as follows. Transfer 10 Tablets to a suitable volumetric flask. Add *Diluent* to volume and pass through a suitable filter. [Note—Sonicate with intermittent shaking to help dissolve, if necessary.]

Chromatographic system

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

Mode: LC

Detector: UV 221 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: 1.5 mL/min

Injection volume: 30 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 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* (µg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

- **Disintegration ⟨701⟩**

Test 1

Time: NMT 60 s

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

Time: NMT 30 s

- **Dissolution ⟨711⟩**

Test 1

Medium: pH 6.0 phosphate buffer (8 g/L of monobasic potassium phosphate and 2 g/L of dibasic potassium phosphate in water. Adjust with phosphoric acid or diluted potassium hydroxide to a pH of 6.0 ± 0.1); 900 mL

Apparatus 2: 50 rpm

Time: 10 min

Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*, except use an *Injection volume* of 100 µL.

Standard stock solution: 0.05 mg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]

Standard solution: (*L*/1000) mg/mL of USP Alprazolam RS from the *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 nylon membrane filter of 0.45-µm pore size, discarding the first few mL.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) dissolved:

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

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)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) is dissolved.

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 g/L of monobasic potassium phosphate and 2 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 2: 50 rpm

Time: 10 min

Buffer: 1.36 g/L of monobasic potassium phosphate. Adjust with dilute sodium hydroxide to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (35:65)

Standard stock solution: 0.05 mg/mL of USP Alprazolam RS in methanol. [NOTE—Sonicate to help dissolve, if necessary.]

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

Sample solution: Pass a 5-mL aliquot of the solution under test through a suitable filter of 0.45-µm pore size, discarding the first 3 mL.

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 7.5-cm; 5-µm packing L7

Flow rate: 1.5 mL/min

Injection volume: 40 µL

Run time: 3 times the retention time of alprazolam

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 alprazolam ($C_{17}H_{13}ClN_4$) dissolved:

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

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)

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 70% (Q) of the labeled amount of alprazolam ($C_{17}H_{13}ClN_4$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Diluent: Prepare as directed in the *Assay*.

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Solution A: Acetonitrile, methanol, and *Buffer* (25:20:55)

Solution B: Acetonitrile, methanol, and *Buffer* (40:5:55)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
12	100	0
15	0	100
60	0	100
65	100	0
70	100	0

Standard solution: 0.6 µg/mL of USP Alprazolam RS in *Diluent*

Sample solution: Nominally 200 µg/mL of alprazolam in *Diluent*. Prepare using 10 Tablets, and pass through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

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

Column temperature: 30°

Flow rate: 1.2 mL/min

Injection volume: 25 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Theoretical plates: NLT 2000

Tailing factor: NMT 1.5

Relative standard deviation: NMT 6.0%

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 each impurity from the *Sample solution*

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

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

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

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peaks less than 0.05%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Alprazolam related compound A[a,b]	0.8	—	—
Alprazolam	1.0	—	—
2-Amino-5-chlorobenzophenone	2.9	1.9	0.5
Any other unknown impurity	—	1.0	0.5
Total impurities	—	—	2.0

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

[b] Disregard the peak due to alprazolam related compound A, because it is a process impurity in alprazolam.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

• **Labeling:** When more than one *Disintegration* test is given, the labeling states the *Disintegration* test used only if *Test 1* is not used. 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 Alprazolam RS

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

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

Chromatographic Database Information: Chromatographic Database

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