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Olanzapine Tablets

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DEFINITION
Olanzapine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$).

IDENTIFICATION

• **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K

Standard: Dissolve 10 mg of USP Olanzapine RS in 10 mL of chloroform. Evaporate to dryness on a water bath maintained at 55°. Use about 2 mg of the residue to prepare a potassium bromide pellet.

Sample: Crush NLT 5 Tablets, and transfer the powder equivalent to 30 mg of olanzapine to a suitable container. Add 30 mL of chloroform, and sonicate for 15 min to dissolve. Pass through a suitable filter, and evaporate the filtrate to dryness on a water bath maintained at 55°. Use about 2 mg of the residue to prepare a potassium bromide pellet.

Acceptance criteria: Meet the requirements

ASSAY

• **Procedure**

[Note—A few drops of acetonitrile, not to exceed 5% of the final volume, may be added to the *Standard solution* and *Sample solution* before final dilution to reduce foaming.]

Buffer 1: 6.9 g/L of monobasic sodium phosphate. Adjust with phosphoric acid to a pH of 2.5.

Buffer 2: 12 g/L of sodium dodecyl sulfate in *Buffer 1*

Mobile phase: Acetonitrile and *Buffer 2* (1:1)

System suitability solution: 0.1 mg/mL of USP Olanzapine RS and 0.01 mg/mL of USP Olanzapine Related Compound A RS in *Mobile phase*

Standard solution: 0.1 mg/mL of USP Olanzapine RS in *Mobile phase*

Sample solution: Transfer a known quantity of Tablets (NLT 5), equivalent to NLT 25 mg of olanzapine, to a suitable volumetric flask. Dilute with *Mobile phase* to volume, mix, and sonicate for 10 min. Centrifuge a portion of this solution, and dilute the clear supernatant with *Mobile phase* to obtain a solution containing about 0.1 mg/mL of olanzapine. [Note—Agitation of the flask may be necessary before sonication to prevent Tablets from adhering to the flask, making disintegration and dissolution difficult.]

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

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

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for olanzapine related compound A and olanzapine are 0.89 and 1.0, respectively.]

Suitability requirements

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

Tailing factor: NMT 1.8, *Standard solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Test 1

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Mobile phase: 10 g/L of ammonium acetate in a mixture of methanol and water (2:3). Adjust with hydrochloric acid to a pH of 4.0.

Standard solution: (*L*/1000) mg/mL of USP Olanzapine RS in *Medium*, where *L* is the label claim in mg/Tablet. Transfer 5.0 mL of this solution to a tube, and add 2.0 mL of *Mobile phase*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a tube, and add 2.0 mL of *Mobile phase*.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-µm packing L10

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Olanzapine 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 olanzapine ($C_{17}H_{20}N_4S$) 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; 900 mL

Apparatus 2: 50 rpm

Time: 20 min

Mobile phase: 10 g/L of ammonium acetate in a mixture of methanol and water (2:3). Adjust with hydrochloric acid to a pH of 4.0. Pass through a suitable filter of 0.45-µm pore size.

Standard stock solution: 0.28 mg/mL of USP Olanzapine RS prepared as follows. Transfer a suitable amount of USP Olanzapine RS to a suitable volumetric flask. Add about 8% of the final flask volume of acetonitrile. Sonicate to dissolve the Reference Standard. Dilute with *Medium* to volume.

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Standard solution: (*L*/900) mg/mL of USP Olanzapine RS in *Medium* from *Standard stock solution*, where *L* is the label claim in mg/Tablet. Transfer 5.0 mL of this solution to a tube, and add 2.0 mL of *Mobile phase*.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate to a tube, and add 2.0 mL of *Mobile phase*.

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

Column: 4.6-mm × 15-cm; 5-µm packing L11

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of olanzapine ($C_{17}H_{20}N_4S$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of USP Olanzapine 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 olanzapine ($C_{17}H_{20}N_4S$) is dissolved.

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

IMPURITIES

Change to read:

• **Organic Impurities**

[Note—A few drops of acetonitrile, not to exceed 5% of the final volume, may be added to the *Standard solution* and *Sample solution* before final dilution to reduce foaming.]

Buffer 1: 3.3 mL/L of phosphoric acid. Adjust with 50% sodium hydroxide to a pH of 2.5.

Buffer 2: 8.7 g/L of sodium dodecyl sulfate in *Buffer 1*

Buffer 3: 18.6 mg/L of edetate disodium (EDTA) in *Buffer 2*

Solution A: Acetonitrile and *Buffer 2* (12:13)

Solution B: Acetonitrile and *Buffer 2* (7:3)

Diluent: Acetonitrile and *Buffer 3* (2:3)

System suitability solution: 20 µg/mL of USP Olanzapine RS and 2 µg/mL each of USP Olanzapine Related Compound B RS and USP Olanzapine Related Compound C RS in *Diluent*

Standard solution: 0.002 mg/mL of USP Olanzapine RS in *Diluent*

Sensitivity solution: 0.4 µg/mL of USP Olanzapine RS in *Diluent* from the *Standard solution*

Sample solution: Nominally 0.375–0.500 mg/mL of olanzapine from a suitable number of Tablets prepared as follows. Transfer a known quantity of Tablets to a suitable volumetric flask, and dilute with *Diluent* to volume. Centrifuge a portion of this solution, and use the supernatant. [Note—Immediate agitation of the flask may be necessary to prevent Tablets from adhering to the flask, making dissolution and disintegration difficult. [**Caution—**Do not sonicate.] The *Sample solution* is stable for 12 h at room temperature and 48 h if refrigerated.]

Mobile phase: See *Table 1*.

Table 1

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Time (min)	Solution A (%)	Solution B (%)
0	100	0
10	100	0
20	0	100
25	0	100
27	100	0
35	100	0

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

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

Column temperature: 35°

Flow rate: 1.5 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between olanzapine and olanzapine related compound C, *System suitability solution*

Tailing factor: NMT 1.5 for the olanzapine peak, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity 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 each impurity from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

F = relative response factor for each impurity listed in *Table 2*

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Olanzapine open ring analog [a] (if present)	0.18	1.0	▲0.5▲ (RB 1-Jul-2023)
Olanzapine lactam[b]	0.26	1.0	0.50

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Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Olanzapine related compound B	0.30	2.3	0.50
Olanzapine thiolactam[c]	0.34	1.0	0.50
Olanzapine acetyl open ring analog[d] (if present)	0.37	1.0	▲0.5▲ (RB 1-Jul-2023)
Olanzapine related compound C	0.83	0.76	0.50
Olanzapine	1.0	—	—
Any individual unspecified degradation product	—	1.0	0.20
Total impurities	—	—	1.5

[a] (*Z*)-3-(Hydroxymethylene)-4-(4-methylpiperazin-1-yl)-1,3-dihydro-2*H*-benzo[*b*][1,4]diazepine-2-thione.

[b] (*Z*)-4-(4-Methylpiperazin-1-yl)-3-(2-oxopropylidene)-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-one.

[c] (*Z*)-1-{4-(4-Methylpiperazin-1-yl)-2-thioxo-1*H*-benzo[*b*][1,4]diazepin-3(2*H*)-ylidene}propan-2-one.

[d] (*Z*)-(4-(4-Methylpiperazin-1-yl)-2-thioxo-1,2-dihydro-3*H*-benzo[*b*][1,4]diazepin-3-ylidene)methyl acetate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant 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 Olanzapine RS

USP Olanzapine Related Compound A RS

5-Methyl-2-((2-nitrophenyl)amino)-3-thiophenecarbonitrile.

$C_{12}H_9N_3O_2S$ 259.28

USP Olanzapine Related Compound B RS

2-Methyl-10*H*-thieno-[2,3-*b*][1,5]benzodiazepin-4[5*H*]-one.

$C_{12}H_{10}N_2OS$ 230.29

USP Olanzapine Related Compound C RS

2-Methyl-4-(4-methylpiperazin-1-yl)-10*H*-benzo[*b*]thieno[2,3-*e*][1,4]diazepine 4'-*N*-oxide.

$C_{17}H_{20}N_4OS$ 328.43

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

Topic/Question	Contact	Expert Committee
OLANZAPINE 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

https://trungtamthuoc.com/
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