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Aripiprazole Tablets

DEFINITION
Aripiprazole Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$).

IDENTIFICATION

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

Standard: Add 30 mL of ethyl acetate to 30 mg of USP Aripiprazole RS. Shake for 10 min, centrifuge for NLT 5 min, and pass the supernatant through a suitable membrane filter. To the filtrate add 15 mL of water, shake for 5 min, and centrifuge for NLT 10 min. Transfer 20 mL of the upper layer to a container and add anhydrous magnesium sulfate, as needed. Shake well, pass through a suitable membrane filter, and evaporate the ethyl acetate on a water bath under reduced pressure. Use the residue. [Note—A centrifuge speed of 2000 rpm may be suitable.]

Sample: Grind a suitable number of Tablets and transfer a suitable portion of the ground Tablets, equivalent to 30 mg of aripiprazole, to an appropriate container. Add 30 mL of ethyl acetate, shake for 10 min, centrifuge for NLT 5 min, and pass the supernatant through a suitable membrane filter. To the filtrate add 15 mL of water, shake for 5 min, and centrifuge for NLT 10 min. Transfer 20 mL of the upper layer to a container and add a suitable amount of anhydrous magnesium sulfate. Shake well, pass through a suitable membrane filter, and evaporate the ethyl acetate on a water bath under reduced pressure. Use the residue. [Note—A centrifuge speed of 2000 rpm may be suitable.]

Analysis

Samples: *Standard* and *Sample*

Acceptance criteria: Meet the requirements

• **B.** The retention time of the aripiprazole peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **Procedure**

Solution A: 2.8 g/L of anhydrous sodium sulfate in water

Mobile phase: Acetonitrile, methanol, *Solution A*, and glacial acetic acid (33:11:56:1)

Internal standard solution: 0.33 mg/mL of USP Propylparaben RS in *Mobile phase*

Standard stock solution: 1 mg/mL of USP Aripiprazole RS in *Mobile phase*

Standard solution: 0.2 mg/mL of USP Aripiprazole RS prepared as follows. Transfer 10.0 mL of *Standard stock solution* and 10.0 mL of *Internal standard solution* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume.

Sample solution: Nominally 0.2 mg/mL of aripiprazole from Tablets prepared as follows. Powder NLT 20 Tablets and transfer a suitable portion of the powder to an appropriate volumetric flask. Add 40% of the final flask volume of *Mobile phase* and 20% of the final flask volume of *Internal standard solution*. Shake for 10 min, and dilute with *Mobile phase* to volume. Centrifuge, if necessary, and pass the supernatant through a suitable filter of NMT 0.5-µm pore size, discard the first 1 mL of filtrate, and use the subsequent filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: NLT 2 times the retention time of aripiprazole

System suitability

Sample: *Standard solution*

[Note—The relative retention times for aripiprazole and propylparaben are about 1.0 and 1.5, respectively.]

Suitability requirements

Resolution: NLT 8 between aripiprazole and propylparaben

Tailing factor: NMT 1.7 for aripiprazole and for propylparaben

Relative standard deviation: NMT 2.0% for the peak response ratio of aripiprazole to propylparaben

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) in the portion of Tablets taken:

$$\text{Result} = (R_U / R_S) \times (C_S / C_U) \times 100$$

R_U = peak response ratio of aripiprazole to propylparaben from the *Sample solution*

R_S = peak response ratio of aripiprazole to propylparaben from the *Standard solution*

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

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Test 1

Medium: pH 1.2 hydrochloric acid buffer (Transfer 250 mL of 14.9 g/L of potassium chloride in water to a 1-L volumetric flask, add 425 mL of 0.2 N hydrochloric acid, and dilute with water to volume. Degas the resulting solution or pass the resulting solution through a filter under vacuum.), degassed; 900 mL

Apparatus 2: 60 rpm

Time: 30 min

Procedure: Determine the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved by using either the *Spectrometric procedure* or the *Chromatographic procedure* described below.

Spectrometric procedure

Standard stock solution: 1 mg/mL of USP Aripiprazole RS in alcohol

Standard solution: (L/900) mg/mL of USP Aripiprazole 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, discarding the first 5 mL of filtrate.

Instrumental conditions

Mode: UV

Analytical wavelengths: 249 and 325 nm

Cell length: 1 cm

Blank: *Medium*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

$$\text{Result} = (A_U / A_S) \times C \times V \times (1/L) \times 100$$

A_U = absorbance at 249 nm minus the absorbance at 325 nm of the *Sample solution*

A_S = absorbance at 249 nm minus the absorbance at 325 nm of the *Standard solution*

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Chromatographic procedure

Solution A: 2.8 g/L of anhydrous sodium sulfate

Solution B: 13.9 g/L of glacial acetic acid and 23.9 g/L of sodium acetate in water

Mobile phase: Acetonitrile, methanol, *Solution A*, and glacial acetic acid (40:10:50:1)

Diluent: *Solution B* and methanol (50:50)

Internal standard solution: 0.67 µg/mL of USP Propylparaben RS in *Diluent*

Standard stock solution A: 1 mg/mL of USP Aripiprazole RS in *Mobile phase*

Standard stock solution B: 0.002 mg/mL of USP Aripiprazole RS from *Standard stock solution A* in *Medium* passed through a suitable filter of NMT 0.5-µm pore size, discarding the first 6 mL of filtrate

Standard solution: 0.001 mg/mL of USP Aripiprazole RS from *Standard stock solution B* prepared by combining 5 mL of *Standard stock solution B* and 5 mL of *Internal standard solution*

Sample stock solution: Pass a portion of the solution under test through a suitable filter of NMT 0.5-µm pore size, discarding NLT the first 6 mL of filtrate.

Sample solution: Combine 2 mL of *Sample stock solution* with 2 mL of *Internal standard solution*.

Chromatographic system: Proceed as directed in the *Assay* except as follows.

Injection volume: 100 µL

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for aripiprazole and propylparaben are about 1.0 and 1.8, respectively.]

Suitability requirements

Resolution: NLT 10 between aripiprazole and propylparaben

Relative standard deviation: NMT 1.5% for the peak response ratio of aripiprazole to propylparaben

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

$$\text{Result} = (R_U / R_S) \times C_S \times V \times {}^{\blacktriangle}D \times {}_{\blacktriangle\ \text{(ERR 1-Sep-2023)}} (1/L) \times 100$$

R_U = peak response ratio of aripiprazole to propylparaben from the *Sample solution*

R_S = peak response ratio of aripiprazole to propylparaben from the *Standard solution*

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

V = volume of *Medium*, 900 mL

${}^{\blacktriangle}D$ = dilution factor of the *Sample solution*, $2_{\blacktriangle\ \text{(ERR 1-Sep-2023)}}$

L = label claim (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) 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: 60 rpm

Time: 15 min

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Adjust with 1 N phosphoric acid TS to a pH of 3.0.

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

Standard stock solution: 0.11 mg/mL of USP Aripiprazole RS in solution prepared as follows. Transfer a suitable amount of USP Aripiprazole RS to an appropriate volumetric flask. Add 2% of the flask volume of acetonitrile and 70% of the flask volume of *Medium*. Sonication may be used to promote dissolution. Dilute with *Medium* to volume.

Standard solution: (L/900) mg/mL of USP Aripiprazole 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, discarding NLT the first 5 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 5 µL

Run time: NLT 1.6 times the retention time of aripiprazole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

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

r_U = peak response of aripiprazole from the *Sample solution*

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

C = concentration of USP Aripiprazole 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 aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) is dissolved.

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

Medium: 5.82 g/L of dibasic sodium phosphate and 16.7 g/L of citric acid monohydrate in water

For Tablets labeled to contain 2 and 5 mg: 500 mL

For Tablets labeled to contain 10, 15, 20, and 30 mg: 900 mL

Apparatus 1

For Tablets labeled to contain 2 and 5 mg: 50 rpm

For Tablets labeled to contain 10, 15, 20, and 30 mg: 100 rpm

Times

For Tablets labeled to contain 2 and 5 mg: 15 min

For Tablets labeled to contain 10, 15, 20, and 30 mg: 30 min

Mobile phase: Acetonitrile and water (40:60). Add 2 mL of triethylamine to each liter of the mixture. Adjust with phosporic acid to a pH of 3.0.

Diluent: Acetonitrile and water (40:60). Add 2 mL of triethylamine to each liter of the mixture. Adjust with phosphoric acid to a pH of 2.5.

Standard stock solution A: 0.4 mg/mL of USP Aripiprazole RS in *Diluent*. Sonicate to dissolve, if necessary.

Standard stock solution B: 0.28 mg/mL of USP Aripiprazole RS in *Diluent*. Sonicate to dissolve, if necessary.

Standard solution A (for Tablets labeled to contain 2 and 5 mg)**:** (*L*/500) mg/mL of USP Aripiprazole RS from *Standard stock solution A* in *Medium*, where *L* is the label claim in mg/Tablet

Standard solution B (for Tablets labeled to contain 10, 15, 20, and 30 mg)**:** (*L*/900) mg/mL of USP Aripiprazole RS from *Standard stock solution B* 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, discarding the first 5 mL of the filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 217 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of aripiprazole

System suitability

Sample: *Standard solution A* or *B*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution A* or *B* and *Sample solution*

Calculate the percentage of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) dissolved:

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

r_U = peak response of aripiprazole from the *Sample solution*

r_S = peak response of aripiprazole from *Standard solution A* or *Standard solution B*

C_S = concentration of USP Aripiprazole RS in *Standard solution A* or *Standard solution B* (mg/mL)

V = volume of corresponding *Medium*, 500 or 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of aripiprazole ($C_{23}H_{27}Cl_2N_3O_2$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Protect solutions from light.

Buffer: 9.6 g/L of dibasic ammonium citrate, 1.6 g/L of citric acid, and 2.9 g/L of sodium dodecyl sulfate in water. Adjust with 11 g/L of dibasic ammonium citrate in water or 9.6 g/L of anhydrous citric acid in water to a pH of 4.7, if needed.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Diluent: Acetonitrile, water, and glacial acetic acid (40:60:1)

System suitability solution: 0.5 mg/mL of USP Aripiprazole RS, and 0.0005 mg/mL each of USP Aripiprazole Related Compound F RS and USP Aripiprazole Related Compound G RS in *Diluent*

Sample solution: Nominally 0.5 mg/mL of aripiprazole from Tablets prepared as follows. Powder NLT 20 Tablets, transfer a suitable portion of the powder equivalent to NLT 4 mg of aripiprazole to an appropriate container, and add a suitable volume of *Diluent*. Shake for 10 min and centrifuge, if necessary. Pass the supernatant through a suitable filter of NMT 0.5-µm pore size, discard the first 1 mL of filtrate, and use the subsequent 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 mL/min

Injection volume: 20 µL

Run time: NLT 2 times the retention time of aripiprazole

System suitability

Sample: *System suitability solution*

[NOTE—See *Table 1* for the relative retention times.]

Suitability requirements

Resolution: NLT 3 between aripiprazole related compound G and aripiprazole

Signal-to-noise ratio: NLT 10 for aripiprazole related compound F and aripiprazole related compound G

Analysis

Sample: *Sample solution*

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

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

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

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

Acceptance criteria: See *Table 1*. Disregard peaks that are less than 0.1% of the aripiprazole peak.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Aripiprazole related compound F	0.54	0.3
Aripiprazole related compound G	0.81	0.3
Aripiprazole	1.0	—
Any individual unspecified degradation product	—	0.2
Total degradation products	—	1.0

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.
- **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Aripiprazole RS

USP Aripiprazole Related Compound F RS

4-(2,3-Dichlorophenyl)-1-[4-(2-oxo-1,2,3,4-tetrahydroquinolin-7-yloxy)butyl]piperazine 1-oxide.

$C_{23}H_{27}Cl_2N_3O_3$ 464.38

USP Aripiprazole Related Compound G RS

7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}quinolin-2(1*H*)-one.

$C_{23}H_{25}Cl_2N_3O_2$ 446.37

USP Propylparaben RS

Topic/Question	Contact	Expert Committee
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