

BRIEFING

Risperidone Orally Disintegrating Tablets. A new USP Pending Monograph is proposed for this dosage form. The proposed methods for the *Assay* and the test for *Dissolution* are based on analyses performed with the Kromasil-C18 brand of 5- μ m L1 column, in which the typical retention time for risperidone is about 5.4 min. The proposed method for the *Organic Impurities* test is based on analyses performed with the Prodigy ODS(2) brand of 5- μ m L1 column, manufactured by Phenomenex, in which the typical retention time for risperidone is about 38 min.

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Add the following:

Risperidone Orally Disintegrating Tablets

Draft 1

DEFINITION

Risperidone Orally Disintegrating Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of Risperidone ($C_{23}H_{27}FN_4O_2$).

IDENTIFICATION

- The retention time of the major peak from the *Sample solution* corresponds to that from the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Diluent A: Methanol, 0.1 N hydrochloric acid (1:1)

Diluent B: Methanol, 0.1 N hydrochloric acid, and buffer (1:2:2)

0.1 N hydrochloric acid: 8.5 mL/L of hydrochloric acid

Buffer: 5 g/L of ammonium acetate, the pH adjusted to 6.5 with glacial acetic acid or ammonia solution

Mobile phase: Methanol and buffer (11:9)

Standard solution: 0.2 mg/mL of USP Risperidone RS in *Diluent B*. [NOTE—The solution is stable for 24 h at 5°.]

Sample solution: Transfer a number of Tablets to a volumetric flask to obtain a solution having a nominal concentration of 0.2 mg/mL of risperidone. Sonicate for 10 min in 20% of the flask volume of 0.1 N hydrochloric acid. Add an additional 40% of the flask volume of *Diluent A*, and sonicate for 20 min. Dilute with *Buffer* to volume. Pass a portion of this solution through a suitable 0.45- μ m porosity membrane filter. [NOTE—The solution is stable for 24 h at 5°.]

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC
Detector: UV 260 nm
Column: 4.6-mm \times 15-cm; 5- μ m packing L1
Temperature: 35°
Flow rate: 1.5 mL/min
Injection size: 10 μ L
Run time: Two times the retention time of risperidone

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 $C_{23}H_{27}FN_4O_2$ 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 Risperidone 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

- **DISINTEGRATION** <701>: NMT 30 s

- **DISSOLUTION** <711>

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 10 min

Diluent: Methanol and water (1:1)

Buffer and Mobile phase: Prepare as directed in the *Assay*.

Standard stock solution: 0.05 mg/mL of USP Risperidone RS in *Diluent*

Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain a final concentration of L/500 mg/mL, where L is the Tablet label claim, in mg.

Sample solution: Pass a portion of the solution under test through a suitable 0.45- μ m filter.

Chromatographic system: Prepare as directed in the *Assay*. [NOTE—Use an injection size of 100 μ L.]

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 risperidone dissolved:

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

r_U = peak response for risperidone in the *Sample solution*

r_S = peak response for risperidone in the *Standard solution*

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

L = tablet label claim (mg)

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V = volume of *Medium* (mL)

Tolerances: NLT 80% (Q) of the labeled amount of risperidone is dissolved.

- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

IMPURITIES

Organic Impurities

• **PROCEDURE**

Buffer: 5 g/L of ammonium acetate and 1 g/L of tetrabutylammonium hydrogen sulfate in water

Solution A: 3 g/L of ammonium acetate

Solution B: Methanol

Diluent: Methanol, *Buffer* (1:1)

Standard solution: 2 µg/mL of USP Risperidone RS in *Diluent*. [NOTE—Sonication may be used to aid in dissolution. The solution is stable for 24 h at 5°.]

Sample solution: Transfer a number of Tablets to a volumetric flask to obtain a solution having a nominal concentration of 0.2 mg/mL of risperidone. Sonicate for 30 min in 60% of the flask volume of *Diluent* with intermittent shaking. Dilute with *Diluent* to volume. Pass a portion of this solution through a suitable membrane filter having a 0.45-µm porosity. [NOTE—The solution is stable for 24 h.]

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	70	30
10	58	42
30	54	46
50	39	61
60	30	70
62	70	30
75	70	30

Chromatographic system

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

Mode: LC

Detector: UV 275 nm

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

Temperature: 45°

Flow rate: 1.0 mL/min

Injection size: 100 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 5.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Identify the peaks using the relative retention times given in *Impurity Table 1*. Calculate the percentage of each impurity in the portion of Tablets taken:

$$\text{Result} = (r_u/r_s) \times (C_s/C_u) \times 100$$

r_u = peak response for any impurity from the *Sample solution*

r_s = peak response for risperidone from the *Standard solution*

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

C_u = nominal concentration of risperidone in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: See *Impurity Table 1*.

Total impurities: NMT 1.5%. [NOTE—Disregard any peak that is less than 0.05% for calculating total impurities.]

Impurity Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT %
E-Oxime* ¹	0.55	—
Z-Oxime* ²	0.60	—
9-Hydroxy risperidone* ³	0.73	—
Risperidone	1.0	—
6-Methylrisperidone* ⁴	1.2	—
Any individual unspecified degradation product	—	0.20

*This is a process impurity for peak identification only.

¹[3-[2-[4-[(E)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one].

²[3-[2-[4-[(Z)-(2,4-Difluorophenyl)(hydroxyimino)methyl]piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one].

³(9R)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-9-hydroxy-2-methyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one.

⁴(6R)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2,6-dimethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed, light-resistant containers, and store at controlled room temperature.

- **USP REFERENCE STANDARDS (11)**

USP Risperidone RS₁ (1-Nov-2009)