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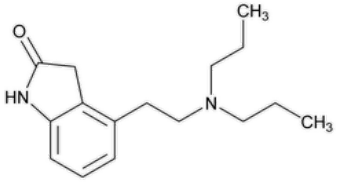
Ropinirole Hydrochloride



• HCl

$C_{16}H_{24}N_2O \cdot HCl$ 296.84

2*H*-Indol-2-one, 4-[2-(dipropylamino)ethyl]-1,3-dihydro-, monohydrochloride;

4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride CAS RN®: 91374-20-8; UNII: D7ZD41RZI9.

DEFINITION

Ropinirole Hydrochloride contains NLT 98.0% and NMT 102.0% of ropinirole hydrochloride ($C_{16}H_{24}N_2O \cdot HCl$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

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

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

Change to read:

• **C.** **Identification Tests—General ⟨191⟩, *Chemical Identification Tests, Chloride***

Sample: 20 mg/mL ▲of Ropinirole Hydrochloride in water▲ (USP 1-May-2021)

Acceptance criteria: Meets the requirements ▲▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

Buffer: 1.88 g of sodium 1-hexanesulfonate and 1 g of phosphoric acid in 1 L of water. Adjust with dilute triethylamine solution (1:10) to a pH of 6.5.

Diluent: Acetonitrile and water (20:80)

Mobile phase: Acetonitrile and *Buffer* (20:80)

Standard solution: 0.1 mg/mL of USP Ropinirole Hydrochloride RS in *Diluent*. Sonication may be used to aid dissolution.

Sample solution: 0.1 mg/mL of Ropinirole Hydrochloride in *Diluent*. Sonication may be used to aid dissolution.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 30°

Flow rate: 1.0 mL/min

Injection volume: 10 µL

Run time: ▲NLT▲ (USP 1-May-2021) 2.5 times the retention time of ropinirole

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.6

Relative standard deviation: ▲NMT 1.0%▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ropinirole hydrochloride ($C_{16}H_{24}N_2O \cdot HCl$) in the portion of Ropinirole Hydrochloride 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 the *Standard solution* (mg/mL)

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

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Change to read:

• **Limit of Palladium**

[Note—Perform this test if Palladium is a known inorganic impurity.]

Solution A: Dissolve 2.4 g of sodium hydroxide in 20 mL of water, and dilute with ▲glycerin▲ (USP 1-May-2021) to 100 mL.

Solution B: 40 mg/mL of thioacetamide in water. [Note—The solution may be filtered if necessary.]

Buffer: Carefully add 27 mL of hydrochloric acid to 25 g of ammonium acetate, and dilute with water to 100 mL.

Palladium standard solution: 10 ppm of Palladium from commercially available ICP grade 1000 ppm Palladium stock solution

Standard solution: Pipet 1.0 mL of *Palladium standard solution* into a platinum crucible, and gently evaporate to dryness. Moisten the residue with 0.5 mL of sulfuric acid, and heat over a Bunsen burner until fumes are no longer emitted. Place the crucible in a muffle furnace at 700°, and heat for 5 additional min. Cool, add 5 mL of hydrochloric acid to the residue, and evaporate to dryness. Add 1 mL of ▲2 N hydrochloric acid TS▲ (USP 1-May-2021) and, if necessary, dissolve the residue with gentle heating. When cool, transfer the contents to a 50-mL beaker. Wash the crucible twice with 1-mL aliquots of water, and add the washings to the beaker. Pass the solution through a membrane filter of 2-µm pore size into a centrifuge tube.

Sample solution: Transfer 1 g of Ropinirole Hydrochloride to a platinum crucible, and heat over a Bunsen burner until the material is completely carbonized. Moisten the contents with 0.5 mL of sulfuric acid, and heat over a Bunsen burner until fumes are no longer emitted. Place the crucible in a muffle furnace at 700°, and heat until all the organic material has been destroyed. When cool, add 5 mL of hydrochloric acid to the residue, and evaporate to dryness. Add 1 mL of ▲2 N hydrochloric acid TS▲ (USP 1-May-2021) and, if necessary, dissolve the residue with gentle heating. When cool, transfer the contents to a 50-mL beaker. Wash the crucible twice with 1-mL aliquots of water, and add the washings to the beaker. Pass the solution through a membrane filter of 2-µm pore size into a centrifuge tube.

Analysis

▲**Samples:** *Standard solution* and *Sample solution*▲ (USP 1-May-2021)

To the filtered *Standard solution* and *Sample solution* add 1 mL of *Solution A*, 0.2 mL of *Solution B*, and 2 mL of *Buffer*. Cap the centrifuge tubes securely, and incubate at 37° for 2 h. Pass the *Sample solution* and *Standard solution* through a membrane filter of 2-µm pore size, wash the membrane with 2-mL aliquots of water, and allow the membrane to dry.

Acceptance criteria: The intensity of the spot due to the sample is not more intense than the spot due to the standard (10 ppm).

• **Organic Impurities, Procedure 1**

If methylene ropinirole and propylidene ropinirole are known process impurities, *Organic Impurities, Procedure 2* is recommended. If ropinirole indole derivative and ropinirole oxime are known process impurities, *Organic Impurities, Procedure 3* is recommended.

Buffer and **Diluent:** Prepare as directed in the *Assay*.

Solution A: Acetonitrile and *Buffer* (15:85)

Solution B: Acetonitrile and water (60:40)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
30	60	40
50	60	40
55	100	0
65	100	0

System suitability solution: 1 mg/mL of USP Ropinirole Hydrochloride RS and 1.5 µg/mL of USP Ropinirole Related Compound B RS in *Diluent*

Sample solution: 1 mg/mL of Ropinirole Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *System suitability solution*

Suitability requirements

Resolution: NLT 1.5 between ropinirole and ropinirole related compound B

Tailing factor: NMT 2.0 for the ropinirole peak

Relative standard deviation: NMT 2.0% for the ropinirole peak

Analysis

Sample: *Sample solution*

Calculate the percentage of any individual impurity in the portion of Ropinirole Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times (1/F) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

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

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

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Open ring nitro derivative[a]	0.39	0.72	0.15
Monopropyl ropinirole[b]	0.58	1.1	0.15
N-Hydroxyropinirole[c]	0.84	0.65	0.15

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ropinirole related compound B	0.97	0.66	0.15
Ropinirole	1.0	—	—
Any individual unknown impurity	—	1.0	0.10
Total impurities[d]	—	—	1.0

[a] 2-{2-[2-(Dipropylamino)ethyl]-6-nitrophenyl}acetic acid.

[b] 4-[2-(Propylamino)ethyl]indolin-2-one.

[c] 4-[2-(Dipropylamino)ethyl]-1-hydroxyindolin-2-one.

[d] Includes impurities greater than or equal to 0.05%.

- **Organic Impurities, Procedure 2**

Solution A: 3.85 g/L of ammonium acetate. Adjust with phosphoric acid to a pH of 2.5.

Solution B: Acetonitrile and methanol (70:30)

Diluent: *Solution A* and *Solution B* (84:16)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	84	16
16	84	16
36	20	80
37	84	16
51	84	16

System suitability solution: 0.05 mg/mL each of USP Ropinirole Hydrochloride RS, USP Ropinirole Related Compound A RS, and USP Ropinirole Related Compound B RS in *Diluent*

Standard solution: 3 µg/mL of USP Ropinirole Related Compound B RS in *Diluent*

Sample solution: 1 mg/mL of Ropinirole Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

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

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 2.0 between ropinirole related compound A and ropinirole related compound B; NLT 3.0 between ropinirole related compound B and ropinirole, *System suitability solution*

Tailing factor: NMT 1.5 for ropinirole, *System suitability solution*

Relative standard deviation: NMT 5.0% for the ropinirole related compound B peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ropinirole related compound B in the portion of Ropinirole Hydrochloride taken:

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

r_U = peak response of ropinirole related compound B from the *Sample solution*

r_S = peak response of USP Ropinirole Related Compound B RS from the *Standard solution*

C_S = concentration of USP Ropinirole Related Compound B RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of any other individual impurity in the portion of Ropinirole Hydrochloride taken:

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

r_U = peak response of each individual impurity from the *Sample solution*

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

Acceptance criteria: See *Table 4*.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Monopropyl ropinirole[a]	0.37	0.2
Ropinirole related compound A[b]	0.70	—
Ropinirole related compound B	0.85	0.3
Ropinirole	1.0	—
Methylene ropinirole[c]	1.39	0.2
Ropinirole isohexyl analog[d]	1.64	0.3
Propylidene ropinirole[e]	1.70	0.2
Any individual unspecified impurity	—	0.10
Total impurities	—	1.0

[a] 4-[2-(Propylamino)ethyl]indolin-2-one.

[b] Only used for system suitability and peak identification. This impurity is not to be reported and not to be included in total impurities.

[c] 4-[2-(Dipropylamino)ethyl]-3-methyleneindolin-2-one.

[d] 4-[2-(2-Methylpentylamino)ethyl]indolin-2-one.

[e] (*Z*)-4-[2-(Dipropylamino)ethyl]-3-propylideneindolin-2-one.

Change to read:

• **Organic Impurities, Procedure 3**

Solution A: Dissolve 3.95 g of ammonium bicarbonate in 990 mL of water. Add 4 mL of 25% ammonia, and dilute with water to 1000 mL. The pH is 9.2–9.3.

Solution B: Acetonitrile

Diluent: Acetonitrile and water (32:68)

Mobile phase: See *Table 5*.

Table 5

Time (min)	Solution A (%)	Solution B (%)
0	68	32
12	68	32
28	20	80
34	20	80
34.1	68	32
40	68	32

System suitability solution: 1 mg/mL of USP Ropinirole Hydrochloride RS and 0.01 mg/mL of USP Ropinirole Related Compound B RS in *Diluent*

Standard solution: 1.2 µg/mL of USP Ropinirole Hydrochloride RS in *Diluent*

Sample solution: 1.2 mg/mL of Ropinirole Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 220 nm

Column: 3.9-mm × 15-cm; 5-µm packing L1

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between ropinirole and ropinirole related compound B, *System suitability solution*

Tailing factor: 0.8–1.5 for ropinirole, *Standard solution*

Relative standard deviation: NMT 5.0% for ropinirole, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Ropinirole Hydrochloride taken:

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

r_U = peak response ▲of each individual impurity▲ (USP 1-May-2021) from the *Sample solution*

r_S = peak response ▲of ropinirole▲ (USP 1-May-2021) from the *Standard solution*

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

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

F = relative response factor (see *Table 6*)

Acceptance criteria: See *Table 6*.

Table 6

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Ropinirole oxime[a]	0.69	1.0	0.15
Ropinirole	1.0	—	—
Ropinirole related compound B	1.2	1.0	0.15
Ropinirole indole derivative[b]	2.0	4.0	0.10
Any individual unspecified impurity	—	—	0.10
Total impurities	—	—	0.50

[a] 4-[2-(Dipropylamino)ethyl]-3-(hydroxyimino)indolin-2-one.

[b] *N*,*N*-Dipropyl-*N*-(2-indol-4-ylethyl)amine.

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I*, *Method Ic*:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store at room temperature.

• **Labeling:** The label states with which *Organic Impurities* procedure the article complies if *Organic Impurities, Procedure 1* is not used.

• **USP Reference Standards ⟨11⟩**

USP Ropinirole Hydrochloride RS

USP Ropinirole Related Compound A RS

4-(2-Hydroxyethyl)indolin-2-one.

$C_{10}H_{11}NO_2$ 177.20

USP Ropinirole Related Compound B RS

4-[2-(Dipropylamino)ethyl]indoline-2,3-dione hydrochloride.

$C_{16}H_{22}N_2O_2 \cdot HCl$ 310.82

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

Topic/Question	Contact	Expert Committee
ROPINIROLE HYDROCHLORIDE	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

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