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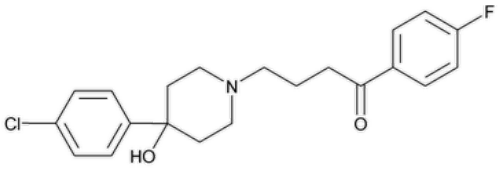
Haloperidol

Change to read:



$C_{21}H_{23}ClFNO_2$ ▲375.87▲ (USP 1-May-2021)

1-Butanone, 4-[4-(4-chlorophenyl)-4-hydroxy-1-piperidinyl]-1-(4-fluorophenyl)-;

4-[4-(*p*-Chlorophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone;

▲4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one.▲ (USP 1-May-2021) CAS RN®: 52-86-8; UNII: J6292F8L3D.

DEFINITION

Haloperidol contains NLT 98.0% and NMT 102.0% of haloperidol ($C_{21}H_{23}ClFNO_2$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-May-2021)

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

ASSAY

Change to read:

• **Procedure**

▲Protect solutions containing haloperidol from light.

Solution A: 6.8 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 4.0.

Solution B: Methanol

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	45	55
6	45	55
12	25	75
14	25	75
15	45	55
21	45	55

Diluent: Methanol

System suitability solution: 0.2 mg/mL of USP Haloperidol RS and 0.02 mg/mL of USP Haloperidol Related Compound B RS in *Diluent*

Standard solution: 0.2 mg/mL of USP Haloperidol RS in *Diluent*

Sample solution: 0.2 mg/mL of Haloperidol in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 247 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Flow rate: 0.8 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times for haloperidol related compound B and haloperidol are 0.85 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between the haloperidol related compound B and haloperidol peaks, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 0.73%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of haloperidol ($C_{21}H_{23}ClFNO_2$) in the portion of Haloperidol taken:

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

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

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

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

C_U = concentration of Haloperidol in the *Sample solution* (mg/mL)▲ (USP 1-May-2021)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

Change to read:

• **ORGANIC IMPURITIES**

Prepare the solutions immediately before use, and protect ▲solutions containing haloperidol▲ (USP 1-May-2021) from light.

Solution A: 17 g/L of tetrabutylammonium hydrogen sulfate▲in water▲ (USP 1-May-2021)

Solution B: Acetonitrile

Mobile phase: See ▲*Table 2*.

Table 2▲ (USP 1-May-2021)

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
17	50	50
22	50	50

System suitability solution: 10 mg/mL of USP Haloperidol RS and 20 µg/mL each of USP Haloperidol Related Compound A RS and USP Haloperidol Related Compound B RS in methanol. [NOTE—Haloperidol related compound A is used for identification purposes only.]

▲**Sensitivity solution:** 5 µg/mL of USP Haloperidol RS in methanol▲ (USP 1-May-2021)

Standard solution: ▲0.01 mg/mL▲ (USP 1-May-2021) of USP Haloperidol RS in methanol

Sample solution: 10 mg/mL of Haloperidol in methanol

Chromatographic system

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

Mode: LC

Detector: UV 230 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

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

[NOTE—The relative retention times for the peaks are given in *Table 3*.]▲ (USP 1-MAY-2021)

Suitability requirements

Resolution: NLT 3.0 between haloperidol related compound B and haloperidol, ▲*System suitability solution*

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

Signal-to-noise ratio: NLT 10, *Sensitivity solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any individual impurity in the portion of Haloperidol taken:

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

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

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

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

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

F = relative response factor (see ▲*Table 3*)▲ (USP 1-May-2021)

Acceptance criteria: See ▲*Table 3*. The reporting threshold is 0.05%.

Table 3▲ (USP 1-May-2021)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Haloperidol related compound B	0.9	1.4	0.3
Haloperidol	1.0	—	—
Haloperidol related compound A	1.6	1.0	0.2
Any ▲▲ (USP 1-May-2021) individual ▲unspecified▲ (USP 1-May-2021) impurity	—	1.0	0.10
Total impurities	—	—	0.5

SPECIFIC TESTS

• **Loss on Drying** ⟨731⟩

Analysis: Dry a sample under vacuum at 60° for 3 h.

Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Haloperidol RS

USP Haloperidol Related Compound A RS

▲4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-{4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]phenyl}butan-1-one; also known as▲ (USP 1-May-2021) 4,4'-Bis[4-*p*-chlorophenyl)-4-hydroxypiperidino]butyrophenone.

$C_{32}H_{36}Cl_2N_2O_3$ ▲567.55▲ (USP 1-May-2021)

USP Haloperidol Related Compound B RS

4-[4-(4-Chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(2-fluorophenyl)butan-1-one.

$C_{21}H_{23}ClFNO_2$ ▲375.87▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
HALOPERIDOL	Documentary Standards Support	SM42020 Small Molecules 4

Chromatographic Database Information: Chromatographic Database

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