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# Haloperidol Tablets

**DEFINITION**
Haloperidol Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of haloperidol ($C_{21}H_{23}ClFNO_2$).

**IDENTIFICATION**

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

***Add the following:***

▲• **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

**ASSAY**

***Change to read:***

• **Procedure**

▲**Buffer:** Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water.▲ (USP 1-May-2021)

**Mobile phase:** Methanol and ▲*Buffer*▲ (USP 1-May-2021) (60:40). Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 4.0.

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

**Sample solution:** Nominally 0.1 mg/mL of haloperidol ▲from Tablets▲ (USP 1-May-2021) prepared as follows. Transfer an equivalent of about 10 mg of haloperidol from finely powdered Tablets (NLT 20) to a 100-mL volumetric flask. Add 60 mL of *Mobile phase*, sonicate ▲with occasional shaking for 30 min. Dilute with *Mobile phase* to volume. Pass the solution through a filter of suitable pore size, discarding the first 1 mL of the filtrate.▲ (USP 1-May-2021)

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

**Mode:** LC

**Detector:** UV 254 nm. ▲For *Identification B*, use a diode array detector in the range of 200–400 nm.▲ (USP 1-May-2021)

**Column:** ▲4.6-mm × 25-cm; 5-µm▲ (USP 1-May-2021) packing L1

▲**Column temperature:** 30°▲ (USP 1-May-2021)

**Flow rate:** 1 mL/min

**Injection volume:** 15 µL

▲**Run time:** NLT 2 times the retention time of haloperidol▲ (USP 1-May-2021)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

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

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

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

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

$r_U$ = peak response of the *Sample solution*

$r_S$ = peak response of the *Standard solution*

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

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

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

***Change to read:***

• **Dissolution** ⟨711⟩

**Medium:** Simulated gastric fluid TS without enzyme; 900 mL

**Apparatus 1:** 100 rpm

**Time:** 60 min

▲**Buffer** and▲ (USP 1-May-2021) **Mobile phase:** Prepare as directed in the *Assay*.

**Standard solution:** A known concentration of USP Haloperidol RS in *Medium*

**Sample solution:** Pass a portion of the solution under test through a suitable filter. Dilute with *Medium*, if necessary, to a concentration that is similar to that of the *Standard solution*.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 254 nm

**Column:** ▲4.6-mm × 25-cm; 5-µm▲ (USP 1-May-2021) packing L1

▲**Column temperature:** 30°▲ (USP 1-May-2021)

**Flow rate:** 1 mL/min

**Injection volume:** 50 µL

▲**Run time:** NLT 2 times the retention time of haloperidol▲ (USP 1-May-2021)

**System suitability**

**Sample:** *Standard solution*

**Suitability requirements**

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT ▲1.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of haloperidol ($C_{21}H_{23}ClFNO_2$) dissolved:

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

$r_U$ = peak response from the *Sample solution*

$r_S$ = peak response from the *Standard solution*

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

$L$ = label claim (mg/Tablet)

$V$ = volume of *Medium* (900 mL)▲ (USP 1-May-2021)

**Tolerances:** NLT 80% ($Q$) of the labeled amount of haloperidol ($C_{21}H_{23}ClFNO_2$) is dissolved.

***Change to read:***

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

▲▲ (USP 1-May-2021)

**IMPURITIES**

***Add the following:***

▲• **Organic Impurities**

**Solution A:** 0.1% (v/v) perchloric acid in water

**Solution B:** Acetonitrile

**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 70 | 30 |
| 5 | 70 | 30 |
| 25 | 50 | 50 |
| 33 | 30 | 70 |
| 35 | 30 | 70 |
| 36 | 70 | 30 |
| 40 | 70 | 30 |

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

**System suitability solution:** 1 mg/mL of USP Haloperidol RS, 0.02 mg/mL of USP Haloperidol Related Compound A RS, and 0.003 mg/mL of USP Haloperidol Related Compound B RS in *Diluent*

**Sensitivity solution:** 0.001 mg/mL of USP Haloperidol RS in *Diluent*

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

**Sample solution:** Nominally 1.0 mg/mL of haloperidol in *Diluent* prepared as follows. Transfer Tablets (NLT 20) to a suitable volumetric flask. Add 50%–75% of the flask volume of *Diluent* and sonicate for NLT 15 min. Then stir for about 15 min. Allow the solution to cool.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 230 nm

**Column:** 4.6-mm × 10-cm; 3.5-µm packing L1

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**System suitability**

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

[NOTE—See *Table 2* for the relative retention times. The peak eluting at a relative retention time of 1.37 is *cis*-haloperidol-*N*-oxide. Its IUPAC name is 4-[*cis*-4-(4-chlorophenyl)-4-hydroxy-1-oxido-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone.]

**Suitability requirements**

**Peak-to-valley ratio:** NLT 50 for the ratio of the height of the haloperidol related compound B peak to the height of the valley between the haloperidol related compound B and haloperidol peaks, *System suitability solution*

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

**Signal-to-noise ratio:** NLT 10, *Sensitivity solution*

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

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

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

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

$r_S$ = peak response from the *Standard solution*

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

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

**Acceptance criteria:** See *Table 2*. The reporting threshold is 0.05%.

**Table 2**

| Name | Relative Retention Time | Acceptance criteria, NMT (%) |
|---|---|---|
| 4-(4-Chlorophenyl)-4-hydroxypiperidine[a,b] | 0.19 | — |
| 4-Fluorobenzoic acid[a] | 0.47 | — |
| Haloperidol related compound B[a] | 0.96 | — |
| Haloperidol | 1.0 | — |
| Haloperidol *N*-oxide[c] | 1.15 | 0.2 |
| Haloperidol related compound A[a] | 1.95 | — |
| 4-Chloro-4'-fluorobutyrophenone[a,d] | 2.20 | — |
| Any unspecified degradation product | — | 0.2 |
| Total degradation products | — | 1.0▲ (USP 1-May-2021) |

[a] Process impurity controlled in drug substance and not included in the total degradation products.

[b] 4-(4-Chlorophenyl)piperidin-4-ol.

[c] 4-[4-(4-Chlorophenyl)-4-hydroxy-1-oxido-1-piperidinyl]-1-(4-fluorophenyl)-1-butanone.

[d] 4-Chloro-1-(4-fluorophenyl)butan-1-one.

**ADDITIONAL REQUIREMENTS**

***Change to read:***

• **Packaging and Storage:** Preserve in tight, light-resistant containers. ▲Store at controlled room temperature.▲ (USP 1-May-2021)

***Change to read:***

• **USP Reference Standards** ⟨11⟩

USP Haloperidol RS

▲ USP Haloperidol Related Compound A RS

4,4'-Bis[4-*p*-chlorophenyl)-4-hydroxypiperidino]butyrophenone.

$C_{32}H_{36}Cl_2N_2O_3$ 567.56

USP Haloperidol Related Compound B RS

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

$C_{21}H_{23}ClFNO_2$ 375.86▲ (USP 1-May-2021)

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

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

**Chromatographic Database Information:** Chromatographic Database

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