Haloperidol Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	31-May-2024
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 4

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Haloperidol Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Haloperidol Tablets monograph to add *Dissolution Test 2*. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2.* Existing references to reagents have been updated for consistency with the reagent entry.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Jasmine McFarland, Scientist III (301-230-6363 or jasmine.mcfarland@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

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*.
● **B.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
● **Procedure**

Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water.

Mobile phase: Methanol and *Buffer* (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 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.

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.

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

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 15 µL

Run time: NLT 2 times the retention time of haloperidol

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 ($C_{21}H_{23}ClFNO_2$) 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⟩

▲Test 1▲ (TBD)

Medium: Simulated gastric fluid TS without enzyme; 900 mL

Apparatus 1: 100 rpm

Time: 60 min

Buffer and **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 packing L1

Column temperature: 30°

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 2 times the retention time of haloperidol

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)

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

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Solution A: Transfer 5 mL of phosphoric acid to a 50-mL volumetric flask and dilute with water to volume.

Medium: Simulated gastric fluid TS without enzyme; 900 mL

Apparatus 1: 100 rpm

Time: 60 min

Buffer: Prepare as directed in the *Assay*.

Mobile phase: Methanol and *Buffer* (70:30). Adjust with 1 N sodium hydroxide or *Solution A* to a pH of 4.0.

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 discarding an appropriate volume of filtrate so that a consistent result can be obtained. 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; 4-µm packing L1

Column temperature: 30°

Flow rate: 0.8 mL/min

Injection volume: 50 µL

Run time: NLT 2 times the retention time of haloperidol

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:

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

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)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*

L = label claim (mg/Tablet)

Tolerances: NLT 70% (*Q*) of the labeled amount of haloperidol ($C_{21}H_{23}ClFNO_2$) is dissolved. ▲ (TBD)

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

IMPURITIES

- **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

[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

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

Add the following:

▲● **LABELING:** The labeling states the *Dissolution* test used only if *Test 1* is not used. ▲ (TBD)

- **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

Page Information:

Not Applicable

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