Midodrine Hydrochloride Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	18-Nov-2022
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 2

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 2 Expert Committee intends to revise the Midodrine Hydrochloride Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Midodrine Hydrochloride Tablets monograph to add *Dissolution Test 2*. Labeling Information has been incorporated to support the inclusion of *Dissolution Test 2*.

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 Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@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

Midodrine Hydrochloride Tablets

DEFINITION

Midodrine Hydrochloride Tablets contain NLT 90.0% and NMT 105.0% of the labeled amount of Midodrine Hydrochloride ($C_{12}H_{18}N_2O_4 \cdot HCl$).

IDENTIFICATION

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

  Sample specimen: Weigh a quantity, from finely powdered Tablets (NLT 20), equivalent to 15 mg of midodrine hydrochloride, into a 50-mL disposable centrifuge tube. Add 20 mL of water, and stir for 2 min using a vortex mixer. Pass the mixture through filter paper into a 50-mL beaker, and boil it until about 2 mL of the solution is left. Evaporate the final solution in an oven at 105° for 1 h.

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

ASSAY

- **Procedure**

  Buffer: 13.6 g/L of monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 4.00 ± 0.05.

  Mobile phase: Acetonitrile and *Buffer* (3:22)

  Standard solution: 0.05 mg/mL of USP Midodrine Hydrochloride RS in *Mobile phase*

  Sample solution: 0.05 mg/mL of midodrine hydrochloride in *Mobile phase* from NLT 5 Tablets (for 10-mg Tablet strength) or NLT 10 Tablets (for 5-mg and 2.5-mg Tablet strength). Initially add *Mobile phase* up to 80% of the volume of the flask. Sonicate for 10 min, stir for 15 min, and then dilute to volume, mix, and let stand for 10 min. Pass through a suitable PVDF filter of 0.45-µm pore size, and discard the first 5 mL.

  Chromatographic system

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

  Mode: LC

  Detector: UV 290 nm

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

  Flow rate: 1.0 mL/min

  Injection size: 20 µL

  System suitability

  Sample: *Standard solution*

  Suitability requirements

  Column efficiency: NLT 3000 theoretical plates

  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 midodrine hydrochloride ($C_{12}H_{18}N_2O_4 \cdot HCl$) 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 the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲**Test 1**▲ (TBD)

Medium: 0.1 N hydrochloric acid; 900 mL, deaerated

Apparatus 2: 50 rpm

Time: 15 min

Buffer: Proceed as directed in the *Assay*.

Mobile phase: Acetonitrile and *Buffer* (3:17)

Standard solution: L/900 mg/mL of USP Midodrine Hydrochloride RS in *Medium*, where L is the label claim in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

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

Flow rate: 1.0 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 2000 theoretical plates

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of midodrine hydrochloride dissolved:

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

r_U = peak area from the *Sample solution*

r_S = peak area from the *Standard solution*

C_S = concentration of 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 midodrine hydrochloride is dissolved.

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

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 15 min

Buffer: Dissolve 13.6 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 50% (v/v) of phosphoric acid in water to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (15:85)

Standard solution: (*L*/500) mg/mL of USP Midodrine Hydrochloride RS in *Medium*, where *L* is the label claim in mg/Tablet. Sonicate to dissolve if necessary.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 290 nm

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

Flow rate: 1 mL/min

Injection volume: 50 µL

Run time: NLT 2.1 times the retention time of midodrine

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 midodrine hydrochloride ($C_{12}H_{18}N_2O_4 \cdot HCl$) dissolved:

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

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

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

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

V = volume of *Medium*, 500 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of midodrine hydrochloride ($C_{12}H_{18}N_2O_4 \cdot HCl$) is dissolved.▲ (TBD)

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

IMPURITIES

• Organic Impurities

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

Standard stock solution 1: 25 µg/mL of USP Midodrine Hydrochloride RS in *Mobile phase*

Standard stock solution 2: 25 µg/mL of USP Midodrine Related Compound A RS in *Mobile phase*

Standard solution: 1.25 µg/mL each of USP Midodrine Hydrochloride RS and USP Midodrine Related Compound A RS from *Standard stock solution 1* and *Standard stock solution 2* in *Mobile phase*

Sample solution: 0.25 mg/mL in *Mobile phase* from NLT 5 Tablets (for 10-mg Tablet strength) and NLT 10 Tablets (for 5-mg and 2.5-mg Tablet strength). Initially add *Mobile phase* to about 80% of the volume of the flask. Sonicate for 10 min, stir for 15 min, and then dilute to volume. Pass through a suitable PVDF filter of 0.45-µm pore size, and discard the first 5 mL.

Chromatographic system

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

Proceed as directed in the *Assay* except for the following:

Injection volume: 40 µL

System suitability

Sample: *Standard solution*

Suitability requirements

[Note—The relative retention times for midodrine related compound A and midrodrine hydrochloride are 0.83 and 1, respectively.]

Resolution: NLT 2.0 between midodrine hydrochloride and midodrine related compound A

Column efficiency: NLT 2000 theoretical plates for the midodrine peak

Tailing factor: NMT 2.0 for the midodrine peak

Relative standard deviation: NMT 2.0% for the midodrine peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of midodrine related compound A in the portion of Tablets taken:

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

r_U = peak response of midodrine related compound A from the *Sample solution*

r_S = peak response of midodrine related compound A from the *Standard solution*

C_S = concentration of USP Midodrine Related Compound A RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of midodrine hydrochloride in the *Sample solution* (µg/mL)

Calculate the percentage of any other unknown impurity in the portion of Tablets taken:

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

r_U = peak response of any other unknown impurity from the *Sample solution*

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

C_S = concentration of USP Midodrine Hydrochloride RS in the *Standard solution* (µg/mL)

C_U = nominal concentration of midodrine hydrochloride in the *Sample solution* (µg/mL)

Acceptance criteria

Individual impurities: NMT 0.5% of midodrine related compound A; NMT 0.2% of any other individual impurity

Total impurities: NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.

Add the following:

▲● **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

- **USP Reference Standards** ⟨11⟩

USP Midodrine Hydrochloride RS

USP Midodrine Related Compound A RS

1-(2,5 Dimethoxyphenyl)-2-aminoethanol.

$C_{10}H_{15}NO_3$ 197.23

Page Information:

Not Applicable

Current DocID: