Status: Currently Official on 15-Feb-2025
Official Date: Official as of 01-Dec-2023
Document Type: USP Monographs
DocId: GUID-0893D017-21E9-4D1E-963D-8CE50EF8B4C6_4_en-US
DOI: https://doi.org/10.31003/USPNF_M54049_04_01
DOI Ref: 560t2

Midodrine Hydrochloride Tablets

To view the Notice from the Expert Committee that posted in conjunction with this accelerated revision, please click www.uspnf.com/rb-midodrine-hcl-tabs-20231117.

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**▲ (RB 1-Dec-2023)

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.▲ (RB 1-Dec-2023)

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

IMPURITIES

Organic Impurities

- **Procedure**

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 in *Mobile phase* from *Standard stock solution 1* and *Standard stock solution 2*

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.▲ (RB 1-Dec-2023)

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Midodrine Hydrochloride RS

USP Midodrine Related Compound A RS

▲2-Amino-1-(2,5 Dimethoxyphenyl)ethanol.▲ (CN 1-Dec-2023)

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

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

Topic/Question	Contact	Expert Committee
MIDODRINE HYDROCHLORIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 36(2)

Current DocID: GUID-0893D017-21E9-4D1E-963D-8CE50EF8B4C6_4_en-US

DOI: https://doi.org/10.31003/USPNF_M54049_04_01

DOI ref: 560t2