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Methyldopa and Hydrochlorothiazide Tablets

DEFINITION

Methyldopa and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of methyldopa ($C_{10}H_{13}NO_4$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A.** The retention times of the two major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.**

Analysis: To 10 mg of methyldopa from a portion of crushed Tablets add 0.15 mL of a solution of ninhydrin in sulfuric acid (1 in 250).

Acceptance criteria: A dark purple color is produced within 5–10 min. The color changes to pale brownish yellow upon adding 0.15 mL of water.

ASSAY

- **Procedure**

Buffer: 11.04 g/L of monobasic sodium phosphate. Initially add 950 mL of water, adjust with phosphoric acid to a pH of 2.8, and then dilute with water to volume.

Mobile phase: Methanol and *Buffer* (5:95)

Standard solution: Transfer a suitable quantity of USP Methyldopa RS to a suitable volumetric flask to prepare a 1-mg/mL solution of anhydrous methyldopa. Add a quantity of USP Hydrochlorothiazide RS that corresponds to the ratio of hydrochlorothiazide to methyldopa in the Tablets. Dissolve in 25% of the total volume a mixture of water, acetonitrile, and 1 N hydrochloric acid (1:1:0.5). Dilute with water to volume.

Sample solution: Transfer an equivalent to 250 mg of methyldopa (NLT 20 Tablets) to a 250-mL volumetric flask, and add 50 mL of water, 25 mL of acetonitrile, and 13 mL of 1 N hydrochloric acid. Shake the flask for 5 min, and dilute with water to volume.

Chromatographic system

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

Mode: LC

Detector: UV 270 nm

Column: 3.9-mm × 30.0-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

[Note—Adjust the flow rate to obtain relative retention times of about 0.38 and 1.0 for methyldopa and hydrochlorothiazide, respectively.]

Suitability requirements

Resolution: NLT 6.0 between methyldopa and hydrochlorothiazide

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of methyldopa ($C_{10}H_{13}NO_4$) in the portion of Tablets taken:

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

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

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

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

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

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Methyldopa

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Solution A: 10 mg/mL of ferrous sulfate, 20 mg/mL of potassium sodium tartrate, and 1 mg/mL of sodium bisulfite in water. [Note—Use a freshly prepared solution.]

Solution B: 50 mg/mL of ammonium acetate in dilute alcohol (1 in 5). Adjust with 6 N ammonium hydroxide to a pH of 8.5.

Standard solution: 0.275 mg/mL of anhydrous methyldopa from USP Methyldopa RS in *Medium*

Sample solution: Filter 35 mL of the solution under test through paper.

Instrumental conditions

Mode: Vis

Analytical wavelength: 520 nm

Cell: 1 cm

Analysis

Samples: *Standard solution* and *Sample solution*

Transfer an aliquot of the *Sample solution* estimated to contain 2–3 mg of methyldopa to a 100-mL volumetric flask. Adjust the final volume, if necessary, with *Medium* to 10 mL. To a second 100-mL volumetric flask add 10.0 mL of *Standard solution*, and to a third 100-mL volumetric flask add 10.0 mL of *Medium* to provide a blank. Pipet 5.0 mL of *Solution A* into each flask, dilute with *Solution B* to volume, and mix. Determine the absorbances of the *Standard solution* and the *Sample solution* at the wavelength of maximum absorbance, using the blank in the reference cell.

Calculate the percentage of the labeled amount of methyldopa ($C_{10}H_{13}NO_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times (C_S/L) \times V \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of anhydrous methyldopa in the *Standard solution* (µg/mL)

L = label claim (mg/Tablet)

V = volume of the medium, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of methyldopa ($C_{10}H_{13}NO_4$) is dissolved.

Hydrochlorothiazide

Medium: 0.1 N hydrochloric acid; 900 mL

Apparatus 2: 50 rpm

Time: 60 min

Instrumental conditions

Mode: Vis

Analytical wavelength: 317 nm

Cell: 1 cm

Standard solution: USP Hydrochlorothiazide RS in *Medium*

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

Tolerances: NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

Change to read:

• **Uniformity of Dosage Units** ⟨905⟩: ▲Meet the requirements▲ (CN 1-Aug-2023)

Procedure for content uniformity: Proceed as directed in the *Assay*, except use the following *Sample solution*.

Sample solution: Transfer 1 Tablet to a 250-mL volumetric flask, add 50 mL of water, and shake gently, if necessary, to disintegrate the Tablet. Do not sonicate. After the Tablet has completely disintegrated, add 25 mL of acetonitrile, and shake by mechanical means for 30

min. Add 13 mL of 1 N hydrochloric acid, and shake by mechanical means for an additional 5 min. Dilute with water to volume.

▲▲ (CN 1-Aug-2023)

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers.
- **USP Reference Standards** ⟨11⟩
  USP Hydrochlorothiazide RS
  USP Methyldopa RS

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

Topic/Question	Contact	Expert Committee
METHYLDOPA AND HYDROCHLOROTHIAZIDE TABLETS	Documentary Standards Support	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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