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Enalapril Maleate and Hydrochlorothiazide Tablets

DEFINITION

Enalapril Maleate and Hydrochlorothiazide Tablets contain NLT 90.0% and NMT 110.0% of the labeled amounts of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

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* for *Enalapril Maleate*.

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

ASSAY

• **Enalapril Maleate**

Buffer: 136 mg/L of monobasic potassium phosphate in water. Initially add water to 80% of the total volume, adjust with phosphoric acid to a pH of 2.0, and dilute with water to volume. Adjust the pH before makeup to final volume.

Mobile phase: Acetonitrile and *Buffer* (400:600)

Standard solution: 0.2 mg/mL of USP Enalapril Maleate RS prepared as follows. Dissolve a suitable amount of USP Enalapril Maleate RS in about 25% of the total volume with methanol, and dilute to volume with *Buffer*.

Sample solution: Transfer a portion of the powder from NLT 20 Tablets, equivalent to 40 mg of enalapril maleate, to a 200-mL volumetric flask. Add 50 mL of *Buffer*, and sonicate for 15 min. Add 50 mL of methanol, sonicate for an additional 15 min, dilute with *Buffer* to volume, and filter.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 65°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 700 theoretical plates

Tailing factor: NMT 3.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

• **Hydrochlorothiazide**

Buffer: Prepare as directed in the *Assay* for *Enalapril Maleate*.

Mobile phase: Acetonitrile and *Buffer* (100:900)

Standard solution: 0.1 mg/mL of USP Hydrochlorothiazide RS prepared as follows. Dissolve a suitable quantity of USP Hydrochlorothiazide RS in 25% of the total volume of methanol, and dilute with *Buffer* to volume.

Sample solution: Transfer a portion of the powder from NLT 20 Tablets, equivalent to 20 mg of hydrochlorothiazide, to a 200-mL volumetric flask. Add 50 mL of *Buffer*, and sonicate for 15 min. Add 50 mL of methanol, sonicate for an additional 15 min, dilute with *Buffer* to volume, and filter.

Chromatographic system

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

Mode: LC

Detector: UV 310 nm

Column: 4.6-mm × 20-cm; 10-µm packing L7

Column temperature: 30°

Flow rate: 2.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Tailing factor: NMT 2.0

Capacity factor, k': NLT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

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⟩**

Enalapril maleate

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: USP Enalapril Maleate RS in *Medium*

Sample solution: Sample per *Dissolution ⟨711⟩*. Dilute with *Medium* to a concentration similar to that of the *Standard solution*.

Analysis: Determine the percentage of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) dissolved, using the test for *Uniformity of Dosage Units*, *Procedure for content uniformity of enalapril maleate*.

Hydrochlorothiazide

Medium: Water; 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Detector: UV 320 and 360 nm

Cell size: 1 cm

Standard solution: USP Hydrochlorothiazide RS dissolved in 20 mL of methanol and diluted with *Medium*

Sample solution: Sample per *Dissolution ⟨711⟩*. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

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

A_U = difference in absorbances ($A_{320} - A_{360}$) at the wavelengths indicated for the *Sample solution*

A_S = difference in absorbances ($A_{320} - A_{360}$) at the wavelengths indicated for the *Standard solution*

C_S = concentration of hydrochlorothiazide in the *Standard solution* (mg/mL)

L = label claim of hydrochlorothiazide (mg/Tablet)

V = volume of *Medium*, 900 mL

D = dilution factor of the *Sample solution*

Tolerances: NLT 80% (Q) of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) and NLT 60% ($Q$) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) are dissolved.

Change to read:

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

Procedure for content uniformity of enalapril maleate

Buffer: 136 g/L of monobasic potassium phosphate in water. Initially add water to 80% of the total volume, adjust with phosphoric acid to a pH of 4.0, and then dilute to volume with water.

Solution A: *Buffer* and water (10:490)

Mobile phase: Acetonitrile, water, and *Buffer* (150:340:10)

Standard solution: 100 µg/mL of USP Enalapril Maleate RS in *Solution A*

Sample solution: Transfer 1 finely powdered Tablet to a 50-mL volumetric flask, add 30 mL of *Solution A*, and sonicate for 15 min. Shake by mechanical means for 30 min, dilute with *Solution A* to volume, sonicate for 30 min, mix, and filter, discarding the first portion of the filtrate. Dilute a portion of the filtrate with *Solution A* to obtain a solution containing about 100 µg/mL.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 20-cm; 10-µm packing L7

Column temperature: 80°

Flow rate: 2 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 1000 theoretical plates

Tailing factor: NMT 2.0

Capacity factor, k': NLT 2.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) in the Tablet taken:

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

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

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

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

C_U = nominal concentration of enalapril maleate in the *Sample solution* (µg/mL)

Acceptance criteria: Meet the requirements

Procedure for content uniformity of hydrochlorothiazide

Buffer and **Solution A:** Prepare as directed in *Procedure for content uniformity of enalapril maleate*.

Standard stock solution: 0.25 mg/mL of USP Hydrochlorothiazide RS prepared as follows. Dissolve a suitable amount of USP Hydrochlorothiazide RS in 10% of the total volume of methanol, and dilute with *Solution A* to volume.

Standard solution: 50 µg/mL of USP Hydrochlorothiazide RS in *Solution A* from *Standard stock solution*

Sample stock solution: Transfer 1 Tablet to a volumetric flask of a suitable size such that, when the hydrochlorothiazide is dissolved from the Tablet, a solution having a concentration of about 250 µg/mL is obtained. Add a volume of *Solution A* equal to about half the capacity of the flask, and sonicate with occasional shaking for 15 min. Shake by mechanical means for 30 min, dilute with *Solution A* to volume, and sonicate for 30 more min. Filter, and discard the first portion of the filtrate.

Sample solution: Transfer 5.0 mL of the clear filtrate to a 25-mL volumetric flask, and dilute with *Solution A* to volume.

Instrumental conditions

Mode: UV-Vis

Analytical wavelength: 320 and 360 nm

Cell: 1 cm

Blank: *Solution A*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amounts of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the Tablet taken:

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

A_U = difference in absorbances ($A_{320} - A_{360}$) at the wavelengths indicated for the *Sample solution*

A_S = difference in absorbances ($A_{320} - A_{360}$) at the wavelengths indicated for the *Standard solution*

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

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

▲▲ (CN 1-Aug-2023)

IMPURITIES

• **Organic Impurities**

Buffer, Mobile phase, and **Sample solution:** Proceed as directed in the *Assay* for *Enalapril Maleate*.

Enalaprilat stock solution: 0.4 mg/mL of USP Enalaprilat RS in water

Enalapril diketopiperazine solution: Carefully place 20 mg of USP Enalapril Maleate RS in a 100-mL beaker to form a mound on the bottom of the beaker. Place the beaker on a hot plate at about one-half the maximum hot plate temperature setting. Heat for about 5–10 min until the solid is melted. Immediately remove the beaker from the hot plate, and allow to cool. To the cooled residue in the beaker add 50 mL of acetonitrile, and sonicate for a few min to dissolve. The solution typically contains between 0.2 and 0.4 mg/mL of enalapril diketopiperazine. [Note—Avoid overheating to prevent heat-induced degradation, which gives rise to a brown color.]

Standard solution: Transfer about 40 mg of USP Enalapril Maleate RS, accurately weighed, to a 200-mL volumetric flask, and dissolve with about 50 mL of methanol. Pipet 1 mL each of *Enalaprilat stock solution* and *Enalapril diketopiperazine solution* into the volumetric flask, and dilute with *Buffer* to volume.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 25-cm; 5-µm packing L7

Column temperature: 65°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

[Note—The relative retention times for enalaprilat, enalapril diketopiperazine, and enalapril are 0.3, 0.4, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.3 between enalapril and any peak

Column efficiency: NLT 700 theoretical plates for enalapril, NLT 1500 for enalaprilat, and NLT 1500 for enalapril diketopiperazine

Tailing factor: NMT 3.5

Relative standard deviation: NMT 5.0% for enalaprilat and enalapril diketopiperazine, and NMT 2.0% for enalapril

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of enalaprilat in the portion of Tablets taken:

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

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

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

C_S = concentration of enalaprilat in the *Standard solution* (mg/mL)

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

Calculate the percentage of enalapril diketopiperazine in the portion of Tablets taken:

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

r_U = peak response of enalapril diketopiperazine from the *Sample solution*

r_S = peak response of enalapril diketopiperazine from the *Standard solution*

C_S = concentration of enalapril diketopiperazine in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 5.0% of total impurities

ADDITIONAL REQUIREMENTS

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

USP Enalapril Maleate RS

USP Enalaprilat RS

L-Proline, 1-[*N*-(1-carboxy-3-phenylpropyl)-L-alanyl]-, dihydrate (*S*)-.

$C_{18}H_{24}N_2O_5 \cdot 2H_2O$

USP Hydrochlorothiazide RS

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

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

Chromatographic Database Information: Chromatographic Database

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