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Enalapril Maleate Tablets

DEFINITION

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

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*.

ASSAY

• **Procedure**

Buffer: Dissolve 1.38 g of monobasic sodium phosphate in 800 mL of water, adjust with phosphoric acid to a pH of 2.2, and dilute with water to 1000 mL.

Mobile phase: Acetonitrile and *Buffer* (250:750)

Enalapril diketopiperazine solution: 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 one-half the maximum hot plate temperature setting to melt the solid. When melting is observed (after 5–10 min of heating), immediately remove the beaker from the hot plate, and allow it to cool. Avoid overheating beyond the melting initially observed to prevent heat-induced degradation, which would give rise to a brown color.

To the cooled residue in the beaker add 50 mL of acetonitrile, and sonicate for a few min to dissolve the residue. The solution typically contains between 0.2 and 0.4 mg/mL of enalapril diketopiperazine.

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

Standard solution: 0.2 mg/mL of USP Enalapril Maleate RS and 0.002 mg/mL of USP Enalaprilat RS in *Buffer* prepared as follows. To a suitable amount of USP Enalapril Maleate RS in a suitable volumetric flask add an appropriate amount of *Enalaprilat stock solution* to the flask, and add 50% of the total volume of *Buffer* to dissolve. Sonicate if necessary, then dilute with *Buffer* to volume.

System suitability solution: Dilute 0.5 mL of *Enalapril diketopiperazine solution* with *Standard solution* to a final volume of 25 mL.

Sample solution: Nominally 0.2 mg/mL of enalapril maleate in *Buffer* prepared as follows. Transfer NLT 10 Tablets to a volumetric flask of capacity such that when filled to volume it will produce a 0.2-mg/mL solution. Add a volume of *Buffer* that is about one-half the nominal volume of the flask, sonicate for 15 min, and shake by mechanical means for 30 min. Dilute with *Buffer* to volume, shake well, and sonicate for another 15 min. Pass the solution through a suitable filter of 0.45-µm pore size, and discard the first portion of the filtrate.

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: 50°

Flow rate: 2 mL/min

Injection volume: 50 µL

System suitability

Samples: *Standard solution* and *System suitability solution*

[Note—The relative retention times for maleic acid, enalaprilat, enalapril, and enalapril diketopiperazine are about 0.3, 0.5, 1.0, and 1.5, respectively, *System suitability solution*. A peak response for a heat-induced degradation product of enalapril diketopiperazine (if present with a relative retention time of about 1.2) is NMT 15% of the response for enalapril diketopiperazine.]

Suitability requirements

Resolution: NLT 2.0 between maleic acid and enalaprilat; NLT 2.0 between enalaprilat and enalapril; NLT 2.0 between enalapril and enalapril diketopiperazine, *System suitability solution*

Column efficiency: NLT 1000 theoretical plates for enalaprilat; NLT 300 theoretical plates for enalapril; NLT 2500 theoretical plates for enalapril diketopiperazine, *System suitability solution*

Tailing factor: NMT 2.0 for enalapril, *System suitability solution*

Relative standard deviation

Enalapril peak: NMT 2.0%, *Standard solution*

Enalaprilat peak: Responses agree within 5%, *Standard solution*

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 from the *Sample solution*

r_S = peak response 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%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: pH 6.8 phosphate buffer (see *Reagents, Indicators, and Solutions—Buffer Solutions*); 900 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard solution: 0.1 mg/mL of USP Enalapril Maleate RS in *Medium*. Sonicate if necessary. Dilute in *Medium* per *Table 1*.

Table 1

Tablet Strength (mg)	Volume of Standard solution (mL)	Volumetric Flask Size (mL)
2.5	5	200
5	10	200
10	10	100
20	10	50
40	10	25

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

Analysis: Determine the amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) dissolved as directed in *Uniformity of Dosage Units ⟨905⟩*.

Tolerances: NLT 80% (*Q*) of the labeled amount of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) is dissolved.

Change to read:

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

Procedure for content uniformity

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

Standard solution: 0.1 mg/mL of USP Enalapril Maleate RS in *Buffer*

Sample solution: 0.1 mg/mL of enalapril maleate from 1 Tablet in *Buffer*. Add a volume of *Buffer* that is one-half the nominal volume of the flask, sonicate for 15 min, and shake by mechanical means for 30 min. Dilute with *Buffer* to volume, shake well, and sonicate for an additional 15 min. Pass through a suitable filter of 0.45-µm pore size, and discard the first portion of the filtrate.

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: 50°

Flow rate: 2 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Column efficiency: NLT 300 theoretical plates

Tailing factor: NMT 2.0

Capacity factor, *k'*: NLT 1.5

Relative standard deviation: NMT 2.0%

[NOTE—The enalapril peak tailing factor may be minimized by controlling the column temperature between 45° and 50° and by raising the pH of the aqueous component of the *Mobile phase* from 2.2 to 2.6; the capacity factor may be increased by decreasing the amount of acetonitrile in the *Mobile phase*.]

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 from the *Sample solution*

r_S = peak response 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)

▲▲ (CN 1-Aug-2023)

IMPURITIES

• **ORGANIC IMPURITIES**

Buffer, Mobile phase, Enalapril diketopiperazine solution, Standard solution, System suitability solution, Sample solution, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Diluted standard solution: Dilute 1.0 mL of *Standard solution* with *Buffer* to 100 mL.

Analysis

Samples: *Buffer*, *Standard solution*, *Sample solution*, and *Diluted standard solution*

Measure the responses for all of the peaks in the *Sample solution* greater than 0.1% of the response of the enalapril peak that are not observed in the *Buffer*.

Calculate the percentage of anhydrous enalaprilat (as enalapril maleate) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

M_{r1} = molecular weight of enalapril maleate, 492.52

M_{r2} = molecular weight of anhydrous enalaprilat, 348.39

Calculate the percentage of enalapril diketopiperazine (as enalapril maleate) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times 100$$

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

r_S = peak response of enalapril from the *Diluted standard solution*

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

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

F = relative response factor of enalapril diketopiperazine, 1.25

M_{r1} = molecular weight of enalapril maleate, 492.52

M_{r2} = molecular weight of enalapril diketopiperazine, 358.44

Calculate the percentage of the sum of all other individual impurities in the portion of Tablets taken:

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

r_T = sum of the responses of all other individual impurities other than maleic acid, enalapril, enalaprilat, and enalapril diketopiperazine from the *Sample solution*

r_S = peak response of enalapril maleate from the *Diluted standard solution*

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

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

Acceptance criteria: NMT 5.0% for the sum of all impurities including those from enalaprilat and enalapril diketopiperazine

ADDITIONAL REQUIREMENTS

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

USP Enalaprilat RS
USP Enalapril Maleate RS

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

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

Chromatographic Database Information: Chromatographic Database

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