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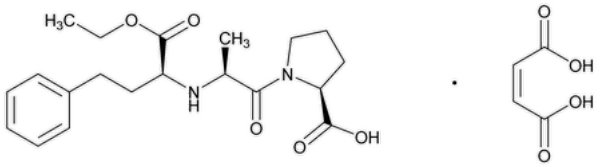
Enalapril Maleate



$C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$ 492.52

L-Proline, 1-[*N*-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-, (*S*)-, (*Z*)-2-butenedioate (1:1);
1-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline, 1'-ethyl ester, maleate (1:1) CAS RN®: 76095-16-4; UNII: 9O25354EPJ.

DEFINITION

Enalapril Maleate contains NLT 98.0% and NMT 102.0% of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$), calculated on the dried basis.

IDENTIFICATION

Change to read:

• **A.** ▲Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: ⟨197M⟩ or ⟨197A⟩▲ (USP 1-Dec-2019)

• **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

Change to read:

• **Procedure**

Buffer 1: 2.8 g of sodium phosphate, monobasic in 900 mL of water in a 1000-mL volumetric flask. Adjust with a 9 M sodium hydroxide solution to a pH of ▲▲ (USP 1-Dec-2019) 6.8, and dilute with water to volume.

Buffer 2: 2.8 g of sodium phosphate, monobasic in 900 mL of water in a 1000-mL volumetric flask. Adjust with phosphoric acid to a pH of ▲▲ (USP 1-Dec-2019) 2.5, and dilute with water to volume.

Solution A: Acetonitrile and *Buffer 1* (5:95)

Solution B: Acetonitrile and *Buffer 1* (66:34)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	40	60
25	40	60
26	95	5
30	95	5

Diluent: Acetonitrile and *Buffer 2* (5:95)

Standard solution: 0.3 mg/mL of USP Enalapril Maleate RS in *Diluent*

▲▲ (USP 1-Dec-2019)

Sample solution: 0.3 mg/mL of Enalapril Maleate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.1-mm × 15-cm; ▲5-µm▲ (USP 1-Dec-2019) packing L21

Column temperature: 70°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution* ▲▲ (USP 1-Dec-2019)

Suitability requirements

▲**Tailing factor:** NMT 2.0▲ (USP 1-Dec-2019)

Relative standard deviation: NMT ▲0.73%▲ (USP 1-Dec-2019)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of enalapril maleate ($C_{20}H_{28}N_2O_5 \cdot C_4H_4O_4$) in the portion of Enalapril Maleate 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 = concentration of Enalapril Maleate in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.2%

Change to read:

• **Organic Impurities**

▲**Buffer:** 0.14 g/L of potassium phosphate, monobasic in water. Adjust with phosphoric acid to a pH of 2.0.

Solution A: Acetonitrile and *Buffer* (10:90)

Solution B: Acetonitrile and *Buffer* (80:20)

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
21	80	20
30	15	85
40	100	0
50	100	0

Diluent: Acetonitrile and *Buffer* (20:80)

System suitability solution: 1 mg/mL of USP Enalapril Maleate RS and 3 µg/mL of USP Moexipril Related Compound F RS in *Diluent*. Sonicate to dissolve as needed.

Standard solution: 0.01 mg/mL of USP Enalapril Maleate RS in *Diluent*

Sensitivity solution: 0.5 µg/mL of USP Enalapril Maleate RS in *Diluent* from the *Standard solution*

Sample solution: 1 mg/mL of Enalapril Maleate in *Diluent*. Sonicate to dissolve as needed.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Temperatures

Autosampler: 20°

Column: 70°

Flow rate: 1.5 mL/min

Injection volume: 50 µL

System suitability

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

[NOTE—See *Table 3* for the relative retention times.]

Suitability requirements

Resolution: NLT 1.0 between moexipril related compound F and enalapril, *System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Enalapril Maleate taken:

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

r_U = peak response of each impurity 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 = concentration of Enalapril Maleate in the *Sample solution* (mg/mL)

F = relative response factor (see *Table 3*)

Acceptance criteria: See *Table 3*. The reporting threshold is 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Maleic acid[a]	0.13	—	—
Enalaprilat[b]	0.55	1.41	0.3
Moexipril related compound F	0.93	0.85	0.3
Enalapril	1.00	—	—
Enalapril cyclohexyl analog[c]	1.33	0.45	0.3
Enalapril related compound D[d]	1.48	1.27	0.3
Any unspecified impurity	—	1.00	0.10
Total impurities	—	—	2.0

[a] This peak is due to the counterion and is not to be reported or included in the total impurities.

[b] 1-[*N*-[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl]-L-proline.

[c] 1-{*N*-[(*S*)-1-Ethoxycarbonyl-3-cyclohexylpropyl]-L-alanyl}-L-proline.

[d] (*S*)-Ethyl 2-[(3*S*,8a*S*)-3-methyl-1,4-dioxohexahydropyrrolo[1,2-α]pyrazin-2(1*H*)-yl]-4-phenylbutanoate.

▲ (USP 1-Dec-2019)

SPECIFIC TESTS

• **OPTICAL ROTATION** ⟨781S⟩, *Procedures*, *Specific Rotation*

Sample solution: 10 mg/mL in methanol

Acceptance criteria: −41.0° to −43.5°

• **Loss on Drying** ⟨731⟩

Analysis: Dry under vacuum at a pressure not exceeding 5 mm of mercury at 60° for 2 h.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature.

Change to read:

• **USP Reference Standards** ⟨11⟩

USP Enalapril Maleate RS

▲ USP Moexipril Related Compound F RS

(*S*)-2-[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoic acid;
Also known as *N*-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]-L-alanine.

$C_{15}H_{21}NO_4$ 279.33

▲ (USP 1-Dec-2019)

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

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

Chromatographic Database Information: Chromatographic Database

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