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Ramipril Tablets

DEFINITION
Ramipril Tablets contain NLT 90.0% and NMT 105.0% of the labeled amount of ramipril ($C_{23}H_{32}N_2O_5$).

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Infrared Spectroscopy*: 197A or 197K▲ (CN 1-May-2020)

Sample: Finely powder a suitable number of Tablets and transfer a portion of the powder, equivalent to 100 mg of ramipril, to a suitable beaker. Add 25 mL of methanol, shake to dissolve, and pass through the filter. Evaporate the solution in air and heat to complete dryness at 105° for 1 h.

Acceptance criteria: Meet the requirements

• **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**

Solution A: 2 g of sodium perchlorate in a mixture of 0.5 mL of triethylamine and 800 mL of water. Adjust with phosphoric acid to a pH of 3.6, and add 200 mL of acetonitrile.

Solution B: 2 g of sodium perchlorate in a mixture of 0.5 mL of triethylamine and 300 mL of water. Adjust with phosphoric acid to a pH of 2.6, and add 700 mL of acetonitrile.

Mobile phase: *Solution A* and *Solution B* (60:40)

Diluent: 6.8 g of monobasic sodium phosphate in 500 mL of water. Add 1000 mL each of methanol and acetonitrile. Adjust with phosphoric acid to a pH of 5.5.

Standard solution: 0.1 mg/mL of USP Ramipril RS in *Diluent*

Sample stock solution: Nominally 0.25 mg/mL of ramipril from NLT 10 Tablets prepared as follows. Add 50% of the final volume of *Diluent* to the flask and sonicate to disperse the Tablets. Sonicate for an additional 30 min and dilute with *Diluent* to volume.

Sample solution: Nominally 0.1 mg/mL of ramipril from the *Sample stock solution* in *Diluent*. Pass through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 50°

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 15 min

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 ramipril ($C_{23}H_{32}N_2O_5$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 90.0%–105.0%

PERFORMANCE TESTS

• **Dissolution** ⟨711⟩

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Time: 30 min

Standard stock solution: 0.25 mg/mL of USP Ramipril RS in methanol

Standard solution: (*L*/500) mg/mL of USP Ramipril RS in *Medium* from the *Standard stock solution* where *L* is the label claim of ramipril in mg/Tablet

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Solution A, Solution B, Mobile phase, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay* except for the *Injection volume*.

Injection volume: 100 µL

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of ramipril ($C_{23}H_{32}N_2O_5$) dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

V = volume of *Medium*, 500 mL

L = label claim for ramipril (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of ramipril ($C_{23}H_{32}N_2O_5$) is dissolved.

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

IMPURITIES

• **Organic Impurities**

Solution A and **Solution B:** Prepare as directed in the *Assay*.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	70	30
6	70	30
30	30	70
40	30	70
45	70	30

Time (min)	Solution A (%)	Solution B (%)
50	70	30

System suitability solution: 50 µg/mL each of USP Ramipril RS, USP Ramipril Related Compound A RS, and USP Ramipril Related Compound D RS in *Solution B*

Sensitivity solution: 1 µg/mL of USP Ramipril RS in *Solution B*

Standard solution: 0.005 mg/mL of USP Ramipril RS in *Solution B*

Sample solution: Nominally 1 mg/mL of ramipril prepared as follows. Finely powder NLT 20 Tablets and transfer a portion of the powder to an appropriate volumetric flask. Add about 60% of the flask volume of *Solution A*, and sonicate for 30 min with intermittent shaking to dissolve. Dilute with *Solution A* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.0-mm × 25-cm; 3-µm packing L1

Column temperature: 65°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between ramipril related compound A and ramipril, *System suitability 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 degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product from the *Sample solution*

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

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

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

F = relative response factor (see *Table 2*)

Acceptance criteria: See *Table 2*. Disregard any peak less than 0.04%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria for 1.25-mg Tablets, NMT (%)	Acceptance Criteria for 2.5-, 5-, and 10-mg Tablets, NMT (%)
Ramipril related compound A[a]	0.71	—	—	—
Ramipril	1.0	—	—	—
Ramipril isopropyl ester[a,b]	1.31	—	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria for 1.25-mg Tablets, NMT (%)	Acceptance Criteria for 2.5-, 5-, and 10-mg Tablets, NMT (%)
Hexahydroramipril[a,c]	1.63	—	—	—
Ramipril related compound D[d]	1.92	0.91	8.0	6.0
Any unspecified degradation product	—	1.0	0.2	0.2
Total degradation products	—	—	1.0	1.0

[a] This is a process impurity monitored in the drug substance that is for identification only. It is not included in the total degradation products.

[b] (2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)-1-(Methylethoxy)carbonyl-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

[c] Ethyl (2*S*)2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-1*H*-cyclopenta[*e*]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenyl-butanoate.

[d] Not included in the total degradation products.

ADDITIONAL REQUIREMENTS

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

• **USP Reference Standards** ⟨11⟩

USP Ramipril RS

USP Ramipril Related Compound A RS

(2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)-1-(Methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid.

$C_{22}H_{30}N_2O_5$ 402.48

USP Ramipril Related Compound D RS

Ethyl (2*S*)2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-1*H*-cyclopenta[*e*]pyrrolo[1,2-*a*]pyrazin-2-yl]-4-phenyl-butanoate.

$C_{23}H_{30}N_2O_4$ 398.50

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

Topic/Question	Contact	Expert Committee
RAMIPRIL TABLETS	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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