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Ramipril Capsules

DEFINITION

Ramipril Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of $C_{23}H_{32}N_2O_5$.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests** ⟨197⟩, *Ultraviolet-Visible Spectroscopy*: **197U**▲ (CN 1-May-2020)

Phosphoric acid solution: 30 mL/L of phosphoric acid in water

Diluent: Acetonitrile and *Phosphoric acid solution* (2:3)

Standard solution: 0.2 mg/mL of USP Ramipril RS in *Diluent*. Sonicate for 1 min, if necessary, for complete dissolution.

Sample solution: Use the *Sample solution* prepared as directed in the *Assay*.

Wavelength range: 200–400 nm

Path length: 0.1-cm cell

• **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**

Buffer: Dissolve 17 g of monobasic potassium phosphate and 11.2 g of sodium perchlorate in 750 mL of water in a 1-L flask. Dilute with water to volume. Adjust with phosphoric acid to a pH of 2.3.

Solution A: Acetonitrile, *Buffer*, and water (1:2:2). [Note—Do not filter *Solution A*.]

Solution B: Acetonitrile, *Buffer*, and water (9:10:6). [Note—Do not filter *Solution B*.]

Phosphoric acid solution and **Diluent:** Prepare as directed in *Identification* test *A*.

Mobile phase: Use the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	100	0
5	100	0
50	0	100
51	0	100
51.1	100	0
60	100	0

Standard solution: 0.2 mg/mL of USP Ramipril RS and 0.002 mg/mL of USP Ramipril Related Compound A RS in *Diluent*

Sample stock solution: Transfer the contents of 8 Capsules into each of the flasks as described in *Table 1*. Add Capsule shells into the flasks. Add acetonitrile per *Table 1*, and swirl to agitate the contents. Sonicate for 15 min, and mechanically shake for 10 min. Dilute with acetonitrile to volume for Capsule strengths 5.0 and 10 mg only. For 1.25- and 2.5-mg Capsules, use the solution as is without further dilution. [Note—Extracts from the vial cap may result in extraneous peaks.]

Table 1

Strength of Capsule (mg)	Volumetric Flask Size (mL)	Acetonitrile (mL)
1.25	50	25
2.5	100	50
5.0	100	70
10	200	140

Sample solution: Nominally 0.2 mg/mL of ramipril in *Phosphoric acid solution* from the *Sample stock solution*. Pass through a nylon filter of 0.20-µm pore size, and discard the first 2 mL of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1 with a guard column, packing L1

Temperature: 60°

Flow rate: 1.5 mL/min

Injection size: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.5 between ramipril and ramipril related compound A

Tailing factor: NMT 2.5 for the ramipril peak

Relative standard deviation: NMT 2.0% for the ramipril peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{23}H_{32}N_2O_5$, based on the label claim, in the portion of Capsules 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 ramipril in the *Standard solution* (mg/mL)

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: 0.1 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm, with sinkers. [Note—A suitable sinker is catalog number CAPWHT-02 available from *www.QLA-LLC.com*.]

Time: 30 min

Standard solution: 0.01 mg/mL of USP Ramipril RS in *Medium*

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

Phosphoric acid solution: Prepare as directed in *Identification* test *A*.

Mobile phase: Acetonitrile and *Phosphoric acid solution* (2:3)

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

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

Temperature: 30°

Flow rate: 1 mL/min

Injection size: 25 µL

Suitability requirements

Sample: *Standard solution*

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of ramipril dissolved:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

L = label claim (mg/Capsule)

V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amount of ramipril is dissolved.

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

Procedure for content uniformity

Phosphoric acid solution: Prepare as directed in *Identification* test *A*.

Mobile phase: Acetonitrile and *Phosphoric acid solution* (2:3). Pass through a nylon filter of 0.45-µm pore size.

Standard solution: 0.03 mg/mL of USP Ramipril RS in *Mobile phase*. Sonicate for 1 min, if not dissolved completely.

Sample solution: Transfer the contents of 1 Capsule into a suitable flask as described in *Table 2*. Add *Mobile phase* (about 50% of total volume), and sonicate for 25 min. Mechanically shake for 10 min, and dilute with *Mobile phase* to volume. Further dilute the solution from the 10-mg strength Capsule with *Mobile phase*, as shown in *Table 2*. Pass through a nylon filter of 0.20-µm pore size, and discard the first 2 mL of filtrate.

Table 2

Strength of Capsule (mg)	Volumetric Flask Size (mL)	Dilution Volume (mL)	Volumetric Flask (mL)
1.25	50	—	—
2.5	100	—	—
5.0	200	—	—
10	50	6.0	50

Chromatographic system: Proceed as directed in the test for *Dissolution*.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of $C_{23}H_{32}N_2O_5$, based on the label claim, in the portion of Capsules 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 ramipril in the *Standard solution* (mg/mL)

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

IMPURITIES

Organic Impurities

- **Procedure**

Buffer, Solution A, Solution B, Phosphoric acid solution, Diluent, Standard solution, and **Sample solution:** Proceed as directed in the *Assay*.

Sensitivity solution: 0.1 µg/mL of ramipril in *Diluent* from the *Standard solution*

Chromatographic system: Prepare as directed in the *Assay*.

Suitability requirements

Samples: *Standard solution* and *Sensitivity solution*

Resolution: NLT 2.5 between ramipril and ramipril related compound A, *Standard solution*

Tailing factor: NMT 2.5 for the ramipril peak, *Standard solution*

Relative standard deviation: NMT 2.0% for the ramipril peak, *Standard solution*

Signal-to-noise ratio: NLT 10 for the ramipril peak, *Sensitivity solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Tablets taken:

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

r_U = peak response of each individual impurity from the *Sample solution*

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

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

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

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

Acceptance criteria

Individual impurities: See *Impurity Table*.

Total impurities: NMT 8.0% for Capsule strength 1.25 mg, NMT 7.0% for Capsule strength 2.5 mg, and NMT 6.0% for Capsule strengths 5 mg and 10 mg. [Note—Total impurities include the sum of individual specified and unspecified degradants. Disregard any peak below 0.1%.]

Impurity Table

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%) for 1.25-mg Capsules	Acceptance Criteria, NMT (%) for 2.5-mg Capsules	Acceptance Criteria, NMT (%) for 5-mg and 10-mg Capsules
Ramipril diacid	0.24	0.41	1.0	1.0	1.0
Ramipril related compound A[a]	0.72	—	—	—	—
Ramipril diacid impurity[a]	0.85	—	—	—	—
Ramipril	1	—	—	—	—
Ramipril related compound B[a]	1.31	—	—	—	—

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%) for 1.25-mg Capsules	Acceptance Criteria, NMT (%) for 2.5-mg Capsules	Acceptance Criteria, NMT (%) for 5-mg and 10-mg Capsules
Ramipril related compound C[a]	1.68	—	—	—	—
Ramipril related compound D[b]	1.84	1	8.0	5.5	5.0
Any other individual unspecifed degradant	—	—	0.2	0.2	0.2

[a] Disregard this impurity as it is process related and is controlled in the drug substance.

[b] Ethyl (2*S*)-2-[(3*S*,5a*S*,8a*S*,9a*S*)-3-methyl-1,4-dioxodecahydro-2*H*-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-2-yl]-4-phenylbutanoate (Ramipril diketopiperazine).

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

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

Topic/Question	Contact	Expert Committee
RAMIPRIL CAPSULES	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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