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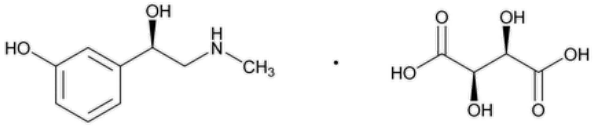
Phenylephrine Bitartrate



$C_9H_{13}NO_2 \cdot C_4H_6O_6$ 317.29

Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1) (salt);

(*R*)-(-)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrogen tartrate CAS RN®: 17162-39-9; UNII: 27O3Q5ML57.

DEFINITION

Phenylephrine Bitartrate contains NLT 98.0% and NMT 102.0% of phenylephrine bitartrate ($C_9H_{13}NO_2 \cdot C_4H_6O_6$), calculated on the dried basis.

IDENTIFICATION

Change to read:

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

• **B.** Identification Tests—General, *Tartrate* ⟨191⟩

Sample: The alkaline filtrate from the test for *Optical Rotation* ⟨781S⟩, *Specific Rotation*

Acceptance criteria: The *Sample* responds positively to the test for *Tartrate* in *Identification Tests—General* ⟨191⟩.

C. 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 3.25 g of 1-octanesulfonic acid sodium salt monohydrate in 1 L of water, and adjust with 3 M phosphoric acid to a pH of 2.8.

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

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

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	93	7
10	70	30
10.1	93	7
18	93	7

Diluent: *Solution A* and *Solution B* (80:20)

Standard solution: 0.6 mg/mL of USP Phenylephrine Hydrochloride RS in *Diluent*

Sample solution: 0.9 mg/mL of Phenylephrine Bitartrate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4.0-mm × 5.5-cm; 3-µm packing L1

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 4 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.9

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of phenylephrine bitartrate ($C_9H_{13}NO_2 \cdot C_4H_6O_6$) in the portion of Phenylephrine Bitartrate taken:

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

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

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

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

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

M_{r1} = molecular weight of phenylephrine bitartrate, 317.29

M_{r2} = molecular weight of phenylephrine hydrochloride, 203.67

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

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

Buffer, Solution A, Solution B, Mobile phase, and **Diluent:** Proceed as directed in the *Assay*.

System suitability solution: 1.0 mg/mL of USP Phenylephrine Hydrochloride RS and 0.9 µg/mL each of USP Norphenylephrine Hydrochloride RS and USP Phenylephrine Related Compound C RS in *Diluent*

Standard solution: 0.001 mg/mL each of USP Phenylephrine Hydrochloride RS, USP Norphenylephrine Hydrochloride RS, USP Phenylephrine Related Compound C RS, USP Phenylephrine Related Compound D RS, and USP Phenylephrine Related Compound E RS in *Diluent*

Blank: 0.8 mg/mL of L(+)-tartaric acid in *Diluent*

Sample solution: 1.56 mg/mL of Phenylephrine Bitartrate in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 215 nm

Column: 4-mm × 5.5-cm; 3-µm packing L1

Column temperature: 45°

Flow rate: 1.5 mL/min

Injection volume: 4 µL

System suitability

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

Suitability requirements

Resolution: NLT 1.5 between norphenylephrine and phenylephrine and NLT 1.5 between phenylephrine and phenylephrine related compound C, *System suitability solution*

Relative standard deviation: NMT 5% for norphenylephrine, phenylephrine, phenylephrine related compound C, phenylephrine related compound D, and phenylephrine related compound E, *Standard solution*

Analysis

Samples: *Standard solution*, *Blank*, and *Sample solution*

Examine the chromatogram of the *Blank* for the peaks, and disregard any corresponding peaks observed in the chromatogram of the *Sample solution*.

Calculate the percentage of norphenylephrine as free base in the portion of Phenylephrine Bitartrate taken:

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

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

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

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

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

M_{r1} = molecular weight of norphenylephrine as free base, 153.18

M_{r2} = molecular weight of norphenylephrine as hydrochloride salt, 189.64

Calculate the percentage of phenylephrine related compound C as free base in the portion of Phenylephrine Bitartrate taken:

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

r_U = peak response of phenylephrine related compound C from the *Sample solution*

r_S = peak response of phenylephrine related compound C from the *Standard solution*

C_S = concentration of USP Phenylephrine Related Compound C RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of phenylephrine related compound C as free base, 165.19

M_{r2} = molecular weight of phenylephrine related compound C as hydrochloride salt, 201.65

Calculate the percentage of phenylephrine related compound D in the portion of Phenylephrine Bitartrate taken:

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

r_U = peak response of phenylephrine related compound D from the *Sample solution*

r_S = peak response of phenylephrine related compound D from the *Standard solution*

C_S = concentration of USP Phenylephrine Related Compound D RS in the *Standard solution* (mg/mL)

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

Calculate the percentage of phenylephrine related compound E as free base in the portion of Phenylephrine Bitartrate taken:

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

r_U = peak response of phenylephrine related compound E from the *Sample solution*

r_S = peak response of phenylephrine related compound E from the *Standard solution*

C_S = concentration of USP Phenylephrine Related Compound E RS in the *Standard solution* (mg/mL)

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

M_{r1} = molecular weight of phenylephrine related compound E as free base, 255.31

M_{r2} = molecular weight of phenylephrine related compound E as hydrochloride salt, 291.77

Calculate the percentage of any individual unspecified impurity in the portion of Phenylephrine Bitartrate taken:

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

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

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

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

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

M_{r1} = molecular weight of phenylephrine bitartrate, 317.29

M_{r2} = molecular weight of phenylephrine hydrochloride, 203.67

Acceptance criteria: See *Table 2*. Disregard any peaks below 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Norphenylephrine	0.9	0.2
Phenylephrine	1.0	—
Phenylephrine related compound C	1.2	0.1
Phenylephrine related compound D	2.9	0.2
Phenylephrine related compound E	3.1	0.1
Any individual unspecified impurity	—	0.1
Total impurities	—	0.5

SPECIFIC TESTS

- **Optical Rotation,** *Specific Rotation* ⟨781S⟩

  Sample solution: Prepare a solution of about 240 mg/mL of Phenylephrine Bitartrate in water. Make the solution slightly alkaline by adding concentrated ammonium hydroxide dropwise. Rub the wall of the vessel with a glass rod so that the base precipitates out. Filter the base under suction, wash with a little water and acetone, and dry at 105° for 2 h. Prepare and measure a 50-mg/mL solution of base precipitate in 1 M hydrochloric acid.

  Acceptance criteria: −53° to −57°

- **pH** ⟨791⟩

  Sample solution: 10% w/v aqueous solution

  Acceptance criteria: 3.0–4.0

- **Loss on Drying** ⟨731⟩

  Analysis: Dry at 105° to a constant weight.

  Acceptance criteria: NMT 0.5%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight, light-resistant containers. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

  USP Norphenylephrine Hydrochloride RS

  3-(2-Amino-1-hydroxyethyl)phenol hydrochloride.

  $C_8H_{11}NO_2 \cdot HCl$ 189.64

  USP Phenylephrine Bitartrate RS

  USP Phenylephrine Hydrochloride RS

  USP Phenylephrine Related Compound C RS

  1-(3-Hydroxyphenyl)-2-(methylamino)ethan-1-one hydrochloride.

  $C_9H_{11}NO_2 \cdot HCl$ 201.65

  USP Phenylephrine Related Compound D RS

  (*R*)-3-{2-[Benzyl(methyl)amino]-1-hydroxyethyl}phenol.

  $C_{16}H_{19}NO_2$ 257.33

USP Phenylephrine Related Compound E RS
2-[Benzyl(methyl)amino]-1-(3-hydroxyphenyl)ethan-1-one hydrochloride.
$C_{16}H_{17}NO_2 \cdot HCl$ 291.77

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

Topic/Question	Contact	Expert Committee
PHENYLEPHRINE BITARTRATE	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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