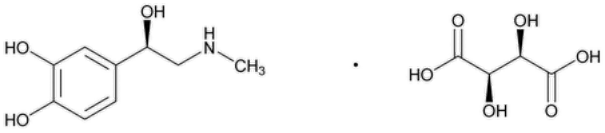
Status: Currently Official on 14-Feb-2025
Official Date: Official as of 01-May-2021
Document Type: USP Monographs
DocId: GUID-C2644E82-34AC-47BD-B4D8-A82A95938114_3_en-US
DOI: https://doi.org/10.31003/USPNF_M29610_03_01
DOI Ref: vdx4k

Epinephrine Bitartrate



$C_9H_{13}NO_3 \cdot C_4H_6O_6$ 333.29

1,2-Benzenediol, 4-[1-hydroxy-2-(methylamino)ethyl]-, (*R*)-, [*R*-(*R**,*R**)]-2,3-dihydroxybutanedioate (1:1) (salt);

(-)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol (+)-tartrate (1:1) salt CAS RN®: 51-42-3.

UNII: 30Q7KI53AK

Change to read:

DEFINITION

Epinephrine Bitartrate contains NLT 97.0% and NMT ▲103.0%▲ (USP 1-May-2021) of Epinephrine Bitartrate ($C_9H_{13}NO_3 \cdot C_4H_6O_6$), calculated on the dried basis.

IDENTIFICATION

Delete the following:

▲• **Procedure**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 20 mL of water containing 100 mg of sodium bisulfite. Add 6 N ammonium hydroxide until the solution has a distinct odor of ammonia, and allow to stand in a refrigerator for 1 h. Filter the precipitate, wash it with three 2-mL portions of cold water, then with 5 mL of cold alcohol, and finally with 5 mL of cold ether, and dry in vacuum over silica gel for 3 h. To 5 mL of pH 4.0 acid phthalate buffer, add 0.5 mL of a slightly acid solution of above obtained Epinephrine (1 in 1000) and 1.0 mL of 0.1 N iodine, and allow to stand for 5 min. Add 2 mL of sodium thiosulfate solution (1 in 40). (See *Reagents, Indicators, and Solutions–Buffer Solutions*.)

Acceptance criteria: A deep red color is produced.▲ (USP 1-May-2021)

Add the following:

▲• **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K▲ (USP 1-May-2021)

Add the following:

▲• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.▲ (USP 1-May-2021)

ASSAY

Change to read:

• **Procedure**

▲Protect the *Standard solution* and *Sample solution* from light.

Buffer: 5.0 g/L of potassium dihydrogen phosphate and 2.6 g/L of sodium octanesulfonate in water. Adjust with phosphoric acid to a pH of 2.8. Dilute with water to volume.

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

Solution B: Acetonitrile and *Buffer* (45:55)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
20	50	50

Time (min)	Solution A (%)	Solution B (%)
21	50	50
23	95	5
30	95	5

Standard solution: 0.91 mg/mL of USP Epinephrine Bitartrate RS in *Solution A*

Sample solution: 0.91 mg/mL of Epinephrine Bitartrate in *Solution A*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 10-cm; 3-µm packing L1

Temperatures

Autosampler: 4°

Column: 50°

Flow rate: 1.2 mL/min

Injection volume: 5 µL

Run time: NLT 5.6 times the retention time of epinephrine

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.1%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of epinephrine bitartrate ($C_9H_{13}NO_3 \cdot C_4H_6O_6$) in the portion of Epinephrine Bitartrate taken:

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

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

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

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

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

Acceptance criteria: 97.0%–103.0% on the dried basis▲ (USP 1-May-2021)

IMPURITIES

Change to read:

• **Residue on Ignition ⟨281⟩:** ▲NMT 0.1%▲ (USP 1-May-2021)

Delete the following:

▲• **Limit of Adrenalone**

Sample: 4 mg/mL of Epinephrine Bitartrate in dilute hydrochloric acid (1 in 200)

Instrument conditions

Mode: UV

Analytical Wavelength: 310nm

Cell: 1cm

Analysis: Determine absorptivity.

Acceptance criteria: NMT 0.2▲ (USP 1-May-2021)

Delete the following:

▲• **Limit of Norepinephrine Bitartrate**

Standard stock solution A: 200 mg/mL of USP Epinephrine Bitartrate RS in water

Standard solution A: 20 mg/mL of USP Epinephrine Bitartrate RS in methanol, from *Standard stock solution A*

Standard stock solution B: 8.0 mg/mL of USP Norepinephrine Bitartrate RS in water

Standard solution B: 0.80 mg/mL of USP Norepinephrine Bitartrate RS in methanol, from *Standard stock solution B*

Sample solution: 20 mg/mL of Epinephrine Bitartrate in a mixture of methanol and water (90:10)

Chromatographic system

(See *Chromatography ⟨621⟩, Thin-Layer Chromatography*.)

Mode: TLC

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture

Application volume: 5 µL

Spray reagent: Folin-Ciocalteu Phenol TS, followed by sodium carbonate solution (1 in 10)

Developing solvent system: *n*-Butanol, water, and formic acid (70:20:10)

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Spray the plate. The R_F value of the principal spot of the *Sample solution* corresponds to that of *Standard solution A*. Any spot of the *Sample solution* is not larger nor more intense than the spot with the same R_F value of *Standard solution B*.

Acceptance criteria: NMT 4.0% of norepinephrine▲ (USP 1-May-2021)

Add the following:

▲• **Organic Impurities**

Protect the *Standard solution* and *Sample solution* from light.

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

Standard stock solution: 1.5 mg/mL of USP Epinephrine Bitartrate RS in a mixture of 0.1 M hydrochloric acid and *Solution A* (10:90). [Note—If necessary, sequentially add 0.1 M hydrochloric acid to 10% of the flask volume, then dilute with *Solution A*, to aid in complete dissolution.]

System suitability solution: 15 µg/mL each of USP Norepinephrine Bitartrate RS, USP Adrenalone Hydrochloride RS, and USP Epinephrine Bitartrate RS, prepared as follows. Transfer a suitable amount of USP Norepinephrine Bitartrate RS and USP Adrenalone Hydrochloride RS into a suitable volumetric flask. Add a suitable volume of *Standard stock solution* into the volumetric flask. Dilute with *Solution A* to volume.

Standard solution: 1.5 µg/mL of USP Epinephrine Bitartrate RS. Dilute with *Solution A* from the *Standard stock solution*.

Sensitivity solution: 0.75 µg/mL of USP Epinephrine Bitartrate RS in *Solution A* from the *Standard solution*

Sample solution: 1.5 mg/mL of Epinephrine Bitartrate in a mixture of 0.1 M hydrochloric acid and *Solution A* (10:90). [Note—If necessary, sequentially add 0.1 M hydrochloric acid to 10% of the flask volume, then dilute with *Solution A*, to aid in complete dissolution.]

Chromatographic system: Proceed as directed in the *Assay*, except for the *Injection volume*.

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between norepinephrine and epinephrine, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each specified or any unspecified impurity in the portion of Epinephrine Bitartrate taken:

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

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

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

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

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

Acceptance criteria: See *Table 2*. The reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Norepinephrine[a]	0.8	0.15
Epinephrine	1.0	—
Adrenalone[b]	1.3	0.2
Unidentified impurity peak 1[c]	3.2	0.3

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Any unspecified impurity	—	0.10
Total impurities	—	0.6▲ (USP 1-May-2021)

[a] (*R*)-4-(2-Amino-1-hydroxyethyl) benzene-1,2-diol.

[b] 3',4'-Dihydroxy-2-(methylamino)acetophenone.

[c] Unknown structure, and identified based on relative retention time.

Add the following:

▲• **Enantiomeric Purity**

Protect the *Standard solution* and *Sample solution* from light.

Buffer: Dissolve 1.2 g of monobasic sodium phosphate in 900 mL of water and adjust with dilute sodium hydroxide to a pH of 5.8. Dilute with water to 1000 mL. Add 18.6 mg of EDTA disodium salt dihydrate and mix.

Mobile phase: Isopropyl alcohol and *Buffer* (5:95)

Standard stock solution A: 1.8 mg/mL of USP Epinephrine Bitartrate RS in 1 N hydrochloric acid and *Mobile phase* (2:98)

Standard stock solution B: 0.96 mg/mL of USP Racepinephrine Hydrochloride RS in *Mobile phase*

System suitability solution: 1.8 mg/mL of USP Epinephrine Bitartrate RS and 0.072 mg/mL of USP Racepinephrine Hydrochloride RS prepared as follows. Transfer a suitable amount of USP Epinephrine Bitartrate RS into a suitable volumetric flask. Add *Standard stock solution B* to 7.5% of the flask volume and 1 N hydrochloric acid to 2% of the flask volume. Dilute with *Mobile phase* to volume.

Standard solution: 0.054 mg/mL of USP Epinephrine Bitartrate RS in *Mobile phase* from *Standard stock solution A*

Sample solution: 1.8 mg/mL of Epinephrine Bitartrate in a mixture of 1 N hydrochloric acid and *Mobile phase* (2:98)

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.0-mm × 10-cm; 5-µm packing L108

Autosampler temperature: 4°

Flow rate: 0.9 mL/min

Injection volume: 10 µL

Run time: NLT 10 times the retention time of *S*-epinephrine

System suitability

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

[Note—The relative retention times of *R*-epinephrine and *S*-epinephrine are about 1.0 and 1.25, respectively.]

Suitability requirements

Resolution: NLT 1.5 between *R*-epinephrine and *S*-epinephrine, *System suitability solution*

Relative standard deviation: NMT 2.0% for *R*-epinephrine, *Standard solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of *S*-epinephrine bitartrate in the portion of Epinephrine Bitartrate taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of *S*-epinephrine

r_T = sum of the peak responses of *R*-epinephrine and *S*-epinephrine

Acceptance criteria: NMT 3.0%▲ (USP 1-May-2021)

SPECIFIC TESTS

Delete the following:

▲• **Melting Range or Temperature ⟨741⟩:** 147°–152°, with decomposition▲ (USP 1-May-2021)

Change to read:

• **Loss on Drying ⟨731⟩**

▲**Sample:** 1 g

Analysis: Dry under vacuum for 18 h or until constant weight.

Acceptance criteria: NMT 0.5%▲ (USP 1-May-2021)

Delete the following:

▲• **Optical Rotation, *Specific Rotation*⟨781S⟩:** −50.0° to −53.5°

Sample solution: 20 mg/mL of above obtained epinephrine, in hydrochloric acid solution (1 in 20)▲ (USP 1-May-2021)

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers.

Change to read:

• **USP Reference Standards** ⟨11⟩

▲ USP Adrenalone Hydrochloride RS

3',4'-Dihydroxy-2-(methylamino)acetophenone hydrochloride.

$C_9H_{11}NO_3 \cdot HCl$ 217.65▲ (USP 1-May-2021)

USP Epinephrine Bitartrate RS

USP Norepinephrine Bitartrate RS

▲ USP Racepinephrine Hydrochloride RS

(*RS*)-4-(1-Hydroxy-2-(methylamino)ethyl)benzene-1,2-diol hydrochloride.

$C_9H_{13}NO_3 \cdot HCl$ 219.67▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
EPINEPHRINE BITARTRATE	Documentary Standards Support	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. PF 44(5)

Current DocID: GUID-C2644E82-34AC-47BD-B4D8-A82A95938114_3_en-US

DOI: https://doi.org/10.31003/USPNF_M29610_03_01

DOI ref: vdx4k