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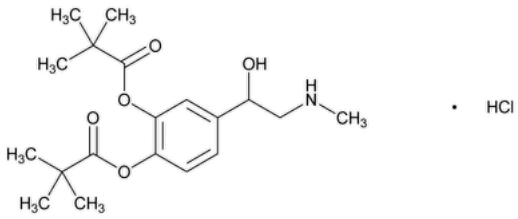
Dipivefrin Hydrochloride



$C_{19}H_{29}NO_5 \cdot HCl$ 387.90

Propanoic acid, 2,2-dimethyl-, 4-[1-hydroxy-2-(methylamino)ethyl]-1,2-phenylene ester, hydrochloride, (±)-;

(±)-3,4-Dihydroxy-α-[(methylamino)methyl]benzyl alcohol 3,4-dipivalate hydrochloride CAS RN®: 64019-93-8; UNII: 5QTH9UHV0K.

DEFINITION

Dipivefrin Hydrochloride contains NLT 98.5% and NMT 101.5% of dipivefrin hydrochloride ($C_{19}H_{29}NO_5 \cdot HCl$), calculated on the dried basis.

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*: 197K**
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay.*
- **C. Identification Tests—General, *Chloride*⟨191⟩**

Sample solution: 10 mg/mL of Dipivefrin Hydrochloride

Acceptance criteria: Meets the requirements

ASSAY

- **Procedure**

Mobile phase: Acetonitrile, 0.014 M sodium dodecyl sulfate, and glacial acetic acid (24:15:1)

Standard solution: 5 mg/mL of USP Dipivefrin Hydrochloride RS in 0.0015 N hydrochloric acid

Sample solution: 5 mg/mL of Dipivefrin Hydrochloride in 0.0015 N hydrochloric acid

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 0.6%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dipivefrin hydrochloride ($C_{19}H_{29}NO_5 \cdot HCl$) in the portion of Dipivefrin Hydrochloride taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

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

Acceptance criteria: 98.5%–101.5% on the dried basis

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.3%

Change to read:

• ▲**Iron ⟨241⟩, *Procedures, Procedure 1*** ▲ (CN 1-Jun-2023)

Standard iron solution: Use the *Standard Iron Solution* prepared as directed in the chapter.

Hydroxylamine solution: 100 mg/mL of hydroxylamine hydrochloride in water

Triazine solution: 1.25 mg/mL of 2,4,6-tri-(2-pyridyl)-*S*-triazine in methanol

Standard solution: Into a 50-mL color-comparison tube pipet 1 mL of *Standard iron solution*, add 42.0 mL of water, and mix.

Sample solution: Into a 50-mL color-comparison tube add 2.0 g of Dipivefrin Hydrochloride, 43.0 mL of water, and mix.

Analysis: To each of the tubes containing the *Standard solution* and the *Sample solution* add 5.0 mL of *Hydroxylamine solution* and 2.0 mL of *Triazine solution*, and mix.

Acceptance criteria: NMT 5 ppm; the color of the solution from the *Sample solution* is not darker than that of the solution from the *Standard solution*.

• **Limits of Epinephrine and Adrenalone**

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

Solution A: 0.1% (v/v) Anhydrous formic acid in water

Solution B: Acetonitrile and methanol (60:40)

Mobile phase: See *Table 1*. Return to the original conditions and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	100	0
3	100	0
5	40	60
10	40	60

Diluent: 0.01 M hydrochloric acid

Standard solution: 0.02 mg/mL of USP Epinephrine Bitartrate RS and 0.01 mg/mL of USP Adrenalone Hydrochloride RS in *Diluent*.

Sample solution 10.0 mg/mL of Dipivefrin Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between epinephrine and adrenalone

Relative standard deviation: NMT 5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of epinephrine in the portion of Dipivefrin Hydrochloride taken:

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

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 Dipivefrin Hydrochloride in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of epinephrine, 183.20

M_{r2} = molecular weight of epinephrine bitartrate, 333.29

Calculate the percentage of adrenalone in the portion of Dipivefrin Hydrochloride taken:

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

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

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

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

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

M_{r1} = molecular weight of adrenalone, 181.19

M_{r2} = molecular weight of adrenalone hydrochloride, 217.65

Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Epinephrine[a,b]	1.0	0.1
Adrenalone[c]	1.4	0.1

[a] 4-1[-Hydroxy-2-(methylamino)ethyl]benzene-1,2-diol.

[b] This impurity is a racemate of epinephrine (also known as racepinephrine or [±] adrenaline).

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

- **Organic Impurities**

Solution A: Acetonitrile and methanol (60:40)

Solution B: 2.7 g/L of ammonium hydroxide, adjusted with 2 M acetic acid to a pH of 10.0

Mobile phase: *Solution A* and *Solution B* (55:45)

Diluent: *Solution A* and 0.01 M hydrochloric acid (55:45)

System suitability solution: 10 mg/mL of USP Dipivefrin Hydrochloride RS and 10 µg/mL of USP Dipivefrin Related Compound E RS in *Diluent*

Standard solution: 10 µg/mL each of USP Dipivefrin Hydrochloride RS and USP Dipivefrin Related Compound E RS in *Diluent*

Sample solution: 10 mg/mL of Dipivefrin Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 260 nm

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

Flow rate: 1 mL/min

Injection volume: 10 µL

Run time: 2.5 times the retention time of dipivefrin

System suitability

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

Suitability requirements

Resolution: NLT 3.0 between dipivefrin and dipivefrin related compound E, *System suitability solution*

Relative standard deviation: NMT 5% for the dipivefrin peak, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of dipivefrin related compound E in the portion of Dipivefrin Hydrochloride taken:

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

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

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

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

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

Calculate the percentage of any other individual impurity in the portion of Dipivefrin Hydrochloride 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 dipivefrin from the *Standard solution*

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

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

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

Acceptance criteria: See *Table 3*. Disregard any impurity peak less than 0.05%.

Table 3

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
5-Pivaloyl racepinephrine[a] and 4-Pivaloyl racepinephrine[b]	0.4[c]	2.0	0.3
Dipivefrin	1.0	—	—
Dipivefrin related compound E[d]	1.3	—	0.1
N-Ethyl dipivefrin[e]	2.0	1.0	0.1
Unspecified impurity	—	1.0	0.10
Total impurities	—	—	0.5

[a] 2-Hydroxy-5-[1-hydroxy-2-(methylamino)ethyl]phenyl pivalate.

[b] 2-Hydroxy-4-[1-hydroxy-2-(methylamino)ethyl]phenyl pivalate.

[c] 5-Pivaloyl racepinephrine and 4-Pivaloyl racepinephrine coelutes.

[d] 4-[(Methylamino)acetyl]-1,2-phenylene dipivalate.

[e] 4-{2-[Ethyl(methyl)amino]-1-hydroxyethyl}-1,2-phenylene dipivalate.

SPECIFIC TESTS

• **Loss on Drying ⟨731⟩**

Analysis: Dry in a suitable vacuum drying tube over phosphorus pentoxide at 60° for 6 h.

Acceptance criteria: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers.

• **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 Dipivefrin Hydrochloride RS

USP Dipivefrin Related Compound E RS
4-[(Methylamino)acetyl]-1,2-phenylene dipivalate hydrochloride.
$C_{19}H_{27}NO_5 \cdot HCl$ 385.88

USP Epinephrine Bitartrate RS $C_9H_{13}NO_3 \cdot C_4H_6O_6$ 333.29

Topic/Question	Contact	Expert Committee
DIPIVEFRIN HYDROCHLORIDE	Documentary Standards Support	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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