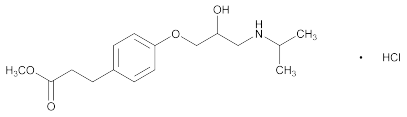
Esmolol Hydrochloride



$C_{16}H_{25}NO_4 \cdot HCl$ 331.83

Benzenepropanoic acid, 4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]-, methyl ester, hydrochloride, (±);
(±)-Methyl *p*-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate hydrochloride [81161-17-3].

DEFINITION

Esmolol Hydrochloride contains NLT 98.0% and NMT 102.0% of esmolol hydrochloride ($C_{16}H_{25}NO_4 \cdot HCl$), calculated on the anhydrous basis.

IDENTIFICATION

- **A. Infrared Absorption** ⟨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.*

ASSAY

- **Procedure**

Buffer: Dissolve 3.0 g of potassium dihydrogen phosphate in 650 mL of water.

Mobile phase: Acetonitrile, methanol, and *Buffer* (150:200:650)

System suitability stock solution: 1 mg/mL of esmolol hydrochloride prepared as follows. Transfer a suitable quantity of USP Esmolol Hydrochloride RS to a suitable volumetric flask, and dissolve in and dilute with 1 N hydrochloric acid to volume. Allow the contents to stand for at least 30 min. [Note—This results in the partial degradation of the esmolol resulting in the production of esmolol free acid (see *System suitability* for the relative retention time).]

System suitability solution: 0.2 mg/mL in water from *System suitability stock solution*

Standard solution: 200 µg/mL of USP Esmolol Hydrochloride RS in water

Sample solution: 200 µg/mL of Esmolol Hydrochloride in water

Chromatographic system

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

Mode: LC

Detector: UV 222 nm

Column: 3.9-mm × 30-cm; 10-µm packing L1

Flow rate: 2 mL/min

Injection volume: 20 µL

System suitability

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

[Note—The relative retention times for esmolol free acid and esmolol are 0.41 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 4.0 between esmolol free acid and esmolol, *System suitability solution*

Tailing factor: NMT 2.0 for the esmolol peak, *System suitability solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of esmolol hydrochloride ($C_{16}H_{25}NO_4 \cdot HCl$) in the portion of the sample taken:

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

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

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

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

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

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

IMPURITIES

- **Heavy Metals** ⟨231⟩

Standard solution: Into a 50-mL color-comparison tube pipet 2 mL of *Standard Lead Solution* (20 µg of Pb), and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Sample solution: Into a 50-mL color-comparison tube dissolve 1 g of the sample in water, and dilute with water to 25 mL. Using a pH meter or short-range pH indicator paper as external indicator, adjust with 1 N acetic acid to a pH between 3.0 and 4.0, dilute with water to 40 mL, and mix.

Analysis

Samples: *Standard solution* and *Sample solution*

To each of the tubes add 10 mL of hydrogen sulfide TS, and mix. Allow to stand for 2 min. View downward into the tube over a white background.

Acceptance criteria: The color of the *Sample solution* is not darker than the color of the *Standard solution* (NMT 20 ppm).

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

Change to read:

- **Organic Impurities**

Buffer and **System suitability solution:** Prepare as directed in the *Assay*.

Solution A: Methanol

Solution B: Prepare as directed for *Mobile phase* in the *Assay*.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	0	100
20	0	100
25	25	75
35	25	75
36	0	100
40	0	100

Sample solution: 1 mg/mL of Esmolol Hydrochloride in water

Chromatographic system: Proceed as directed in the *Assay*, except include a column temperature of 30°.

System suitability
Sample: *System suitability solution*
Suitability requirements
Resolution: NLT 4.0 between esmolol free acid and esmolol
Tailing factor: NMT 2.0 for the esmolol peak
Analysis
Sample: *Sample solution*
Calculate the percentage of each individual impurity in the portion of Esmolol Hydrochloride taken:

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

r_U = peak response of each individual impurity from the *Sample solution*
r_T = sum of all the peak responses from the *Sample solution*
Acceptance criteria: See *Table 2*.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Esmolol free acid[a]	0.43	●0.4● (RB 1-Apr-2013)
●Esmolol isopropylamide analog[b] (if present)● (RB 01-Apr-2013)	●0.65● (RB 1-Apr-2013)	●0.25● (RB 01-Apr-2013)
●● (RB 01-Apr-2013)	●● (RB 1-Apr-2013)	●● (RB 1-Apr-2013)
N-Ethyl esmolol[c] (if present)	●0.84● (RB 1-Apr-2013)	0.15
Esmolol	1.0	—
Esmolol dimer[d]	6.5	●0.5● (RB 1-Apr-2013)
Any other individual unspecified impurity	—	0.10
Total impurities[e]	—	●1.0● (RB 1-Apr-2013)

[a] 3-{4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl}propanoic acid.
●[b] 3-{4-[2-Hydroxy-3-(isopropylamino)propoxy]phenyl}-*N*-isopropylpropionamide.● (RB 1-Apr-2013)
[c] Methyl 3-{4-[3-(ethylamino)-2-hydroxypropoxy]phenyl}propionate.
[d] Methyl 3-{4-[2-hydroxy-3-(3-{4-[2-hydroxy-3-(isopropylamino)propoxy]phenyl}-*N*-isopropylpropanamido)propoxy]phenyl}propanoate.
[e] Disregard any peak below 0.05%.

SPECIFIC TESTS

- **pH** ⟨**791**⟩**:** 3.0–5.0
- **Water Determination,** *Method Ia* ⟨**921**⟩**:** NMT 1.0%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Protect from freezing, and store at controlled room temperature.
- **USP Reference Standards** ⟨**11**⟩

USP Esmolol Hydrochloride RS
Benzenepropanoic acid, 4-[2-hydroxy-3-[(1-methylethyl)-amino]propoxy]-, methyl ester, hydrochloride, (±)-.
$C_{16}H_{25}NO_4 \cdot HCl$ 331.83