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Structural identification and characterization of impurities in Esmolol hydrochloride

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ABSTRACT

In the synthesis of Esmolol hydrochloride four prominent process impurities were formed during synthesis. These impurities were detected in gradient HPLC method. These impurities are synthesized in different synthesis methods and characterized as 3-(4-(2-hydroxy-3-(isopropyl amino) propoxy) phenyl)propanoic acid (Esmolol free acid), Methyl 3-{4-[3-(ethyl amino)-2-hydroxy propoxy]phenyl} propionate (Esmolol isopropyl amide analog), 3-(4-(2-hydroxy-3(isopropylamino)propoxy)phenyl)-N-isopropylpropanamide (N-Ethyl Esmolol), Methyl 3-(4-(2-hydroxy-3-(3-(4-(2-hydroxy-3-(isopropylamino) propoxy) phenyl)-N-isopropyl propanamido) propoxy)phenyl)propanoate (Esmolol dimer) by 1H NMR, IR and Mass spectral data. Synthesis and Structural elucidation by spectral data is discussed.

Keywords: Esmolol hydrochloride, Characterization, Spectroscopy, Structure elucidation.
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INTRODUCTION

Esmolol hydrochloride (trade name Brevibloc) is a cardio selective beta$_1$ receptor blocker with Rapid onset, [1] a very short duration of action, and no significant intrinsic sympathomimetic or membrane stabilizing activity at therapeutic dosages. It is a class II antiarrhythmic. [2] Esmolol decreases the force and rate of heart contractions by blocking beta-adrenergic receptors of the sympathetic nervous system, which are found in the heart and other organs of the body. Esmolol prevents the action of two naturally occurring substance: epinephrine and norepinephrine.

The analysis of Esmolol hydrochloride bulk drug revealed the presence of four impurities which were up to 0.1%. As per the stringent regulatory requirements, the impurity profile study has to be carried for any final product so as to to identify and characterize all the unknown impurities that are present in the bulk drug in a concentration of > 0.10%. This paper describes the isolation and characterization of impurities present in the bulk drug of Esmolol hydrochloride. The impurity profile study of Esmolol hydrochloride was not reported to the best of our knowledge.

MATERIALS AND METHODS

Samples

The investigated samples were obtained from synthetic R&D laboratory of MSN Laboratories Private Limited. Bulk actives, Unit-1, Hyderabad, India. The impurities were synthesized in the same Laboratory.

High performance liquid chromatography (analytical)

A liquid chromatograph is equipped with variable wavelength U.V detector was used. The analysis was carried out on µ bondapak C18, 300mmx3.9mm, 10µm particle size (Advanced chromatography technologies ACT) with a mobile phase containing of A: 150 ml acetonitrile 200 ml methanol and 650 ml of Buffer (Buffer: Dissolve 3.0 g of Potassium dihydrogen phosphate in 650 ml of water) and B: Methanol. Program gradient elution was used with UV detector at 222nm at a flow rate of 2.0ml/min. The column temperature was maintained at 30°C.

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

NMR spectroscopy

The ^{1}H NMR spectra was recorded on Bruker AV II spectrometer. The ^{1}H NMR (400MHz) was recorded using TMS as an internal standard.

Mass spectrometry

EI (70eV) and CI mass spectra were recorded on 6150 Quadrapole LCMS spectrometer. The samples were introduced with particle beam interface using LC and reodyne injector. The source manifold and quadrupole temperatures were maintained at 250 and 100°C, respectively. Isobutane was used as a reagent gas for chemical ionization (CI) mode. The APCI and ESI mass spectra were recorded on Agilent 6150 Quadrapole LCMS spectrometer.

IR spectroscopy

The FT-IR spectrum was recorded on Perkin Elmer model spectrum 100 FT-IR as KBr pellet.

Synthesis of Esmolol hydrochloride

The scheme for the synthesis of Esmolol hydrochloride is shown in the fig-1

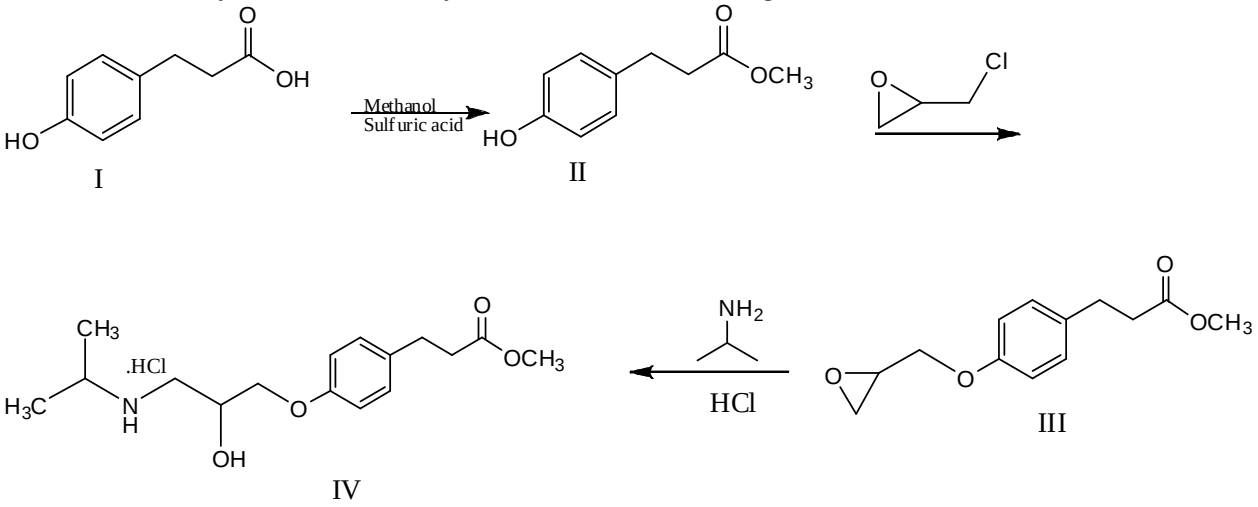


Fig 1. Scheme for the synthesis of Esmolol hydrochloride

RESULTS AND DISCUSSION

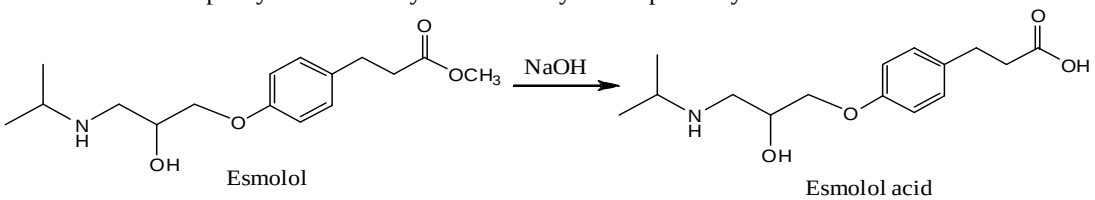
Detection of impurities Esmolol free acid, Esmolol isopropyl amide analog, N-Ethyl Esmolol and Esmolol dimer.

A typical LC-chromatogram of Esmolol hydrochloride bulk drug was recorded using LC-method as described in section 2.2. The target impurities under study were marked as Esmolol free acid, Esmolol isopropyl amide analog,

N-Ethyl Esmolol and Esmolol dimer. Retention times and structures of these impurities and Esmolol hydrochloride are shown in table 1.

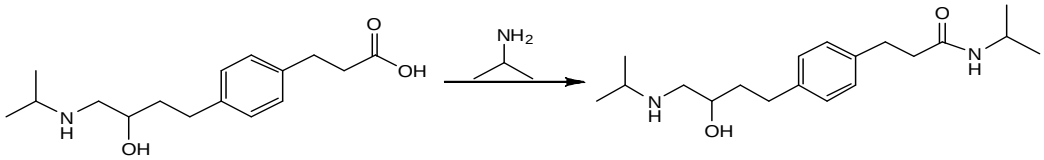
Synthetic pathways by which the impurities of Esmolol were prepared.

1. Esmolol free acid impurity of Esmolol hydrochloride synthetic path way is as follows



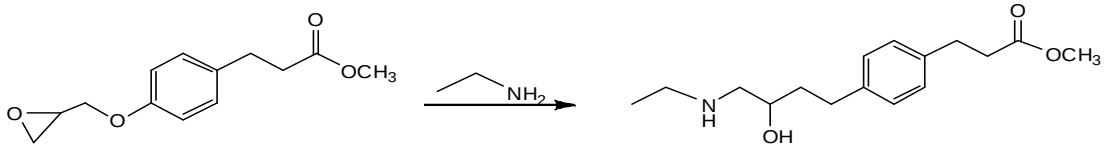
Esmolol Esmolol acid

2. Esmolol isopropyl amide analog impurity of Esmolol hydrochloride synthetic path way is as follows



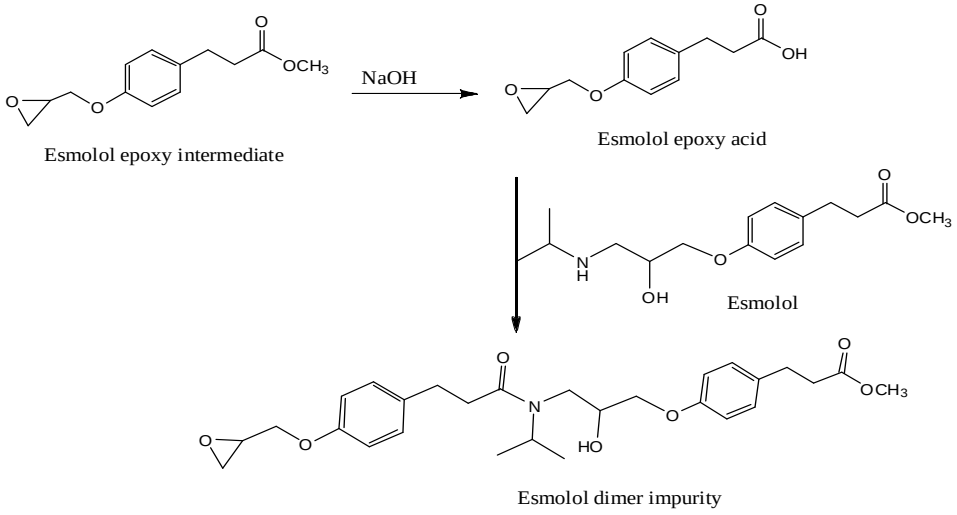
Esmolol acid Isopropyl amide analog impurity

3. N-Ethyl Esmolol impurity of Esmolol hydrochloride synthetic path way is as follows



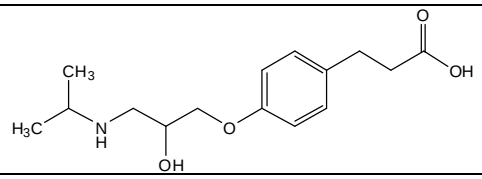
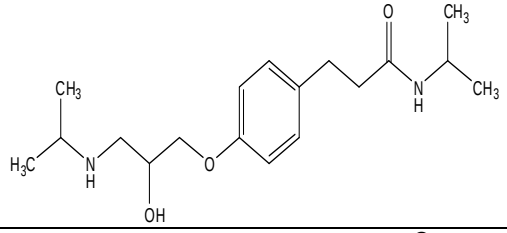
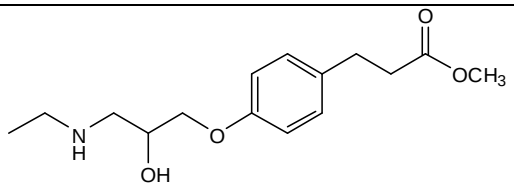
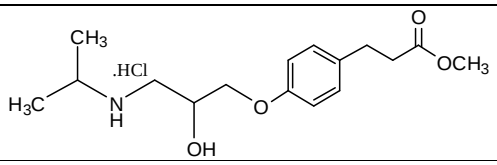
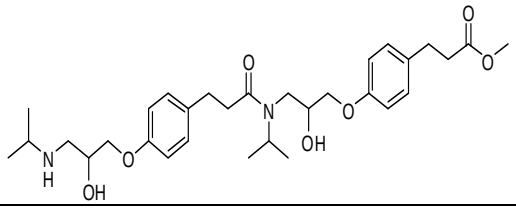
Esmolol epoxy intermediate N-Ethyl Esmolol impurity

4. Esmolol hydrochloride dimer impurity synthetic path way is as follows
5.



Esmolol epoxy intermediate Esmolol epoxy acid Esmolol Esmolol dimer impurity

Table 1: Retention times and structures of these impurities and Esmolol hydrochloride

S. No	Related retention time	Compound	Structure	Nature
01	0.43	Esmolol free acid		Process related and degradation
02	0.65	Esmolol isopropyl amide analog		Process related
03	0.84	N-Ethyl Esmolol		Process related
04	1.0	Esmolol		Esmolol hydrochloride
05	6.5	Esmolol dimer		Process related

STRUCTURAL ELUCIDATION

Structure elucidation of Esmolol free acid

The EI mass spectrum of Esmolol free acid was displayed the molecular ion peak at m/z 282. The CI and APCI (+ve) mass spectra further confirmed this with the presence of protonated molecular ion peak as base peak at m/z 296.4, which is 14 mass units less than that of Esmolol. This can be carboxylic acid of Esmolol. In the IR spectrum of Esmolol free acid, the stretching frequency at 1697.04 and 2944.48 it can be indicated the C=O and OH of carboxylic acid. Further confirmed from the additional singlet signal is absent at 3.648 (3H) in the 1H NMR spectrum.

Based on this data the structure of Esmolol free acid (3-(4-(2-Hydroxy-3-(isopropyl amino) propoxy) phenyl) propanoic acid) was confirmed.

Structural elucidation of Esmolol isopropyl amide analog

The mass spectra of Esmolol isopropyl amide analog displayed the molecular ion at m/z = 323.4, the possibility of amide formation fulfills another isopropyl amine incorporation. In the 1H NMR spectrum four methyl (4CH3) groups in isopropyl amine appear at 0.970-0.74 (6H) and 1.000-1.017 (6H) as doublets. Based on this data the structure of Esmolol isopropyl amide analog (3-(4-(2-hydroxy-3(isopropyl amino) propoxy) phenyl)-N-isopropylpropanamide) was confirmed.

Structural elucidation of N-Ethyl Esmolol
The mass spectra of N-Ethyl Esmolol confirmed the molecular ion at m/z = 323.4, the possibility of amide formation fulfills another isopropyl amine incorporation. In the 1H NMR spectrum four methyl (4CH3) groups in isopropyl amine appear at 0.970-0.74 (6H) and 1.000-1.017 (6H) as doublets. Based on this data the structure of Esmolol isopropyl amide analog (3-(4-(2-hydroxy-3(isopropyl amino) propoxy) phenyl)-N- isopropylpropanamide) was confirmed.

Structural elucidation of Esmolol dimer impurity
The mass spectra of Esmolol dimer confirmed the molecular ion at m/z = 559.4, the possibility of self-condensation fulfills another Esmolol incorporation. In the 1H NMR spectrum four methyl (4CH3) groups in isopropyl amine appear at 1.038-1.105 (6H) as double doublet and 1.163-1.187 (6H) as double doublet and methyl group is appear at 3.586 as singlet. Based on this data the structure of Esmolol dimer (Methyl 3-(4-(2-hydroxy-3-(3-(4-(2-hydroxy-3-(isopropyl amino) propoxy) phenyl)-N-isopropyl propanamido) propoxy) phenyl) propanoate) was confirmed.

The spectral data for the synthesized and isolated impurities were found to be identical. The synthetic standards of impurities Esmolol free acid, Esmolol isopropyl amide analog, N-Ethyl Esmolol and Esmolol dimer were co-eluted on LC with Esmolol hydrochloride.

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REFERENCES

[1]. Baxter. Brevibloc injection (Esmolol hydrochloride) prescribing information (Dated **1998** Jun). In: *Physicians' desk reference.* 54th ed. Montvale NJ: *Medical Economics Company Inc;* **2000**:655-7.
[2]. Du Pont Critical Care. Brevibloc (esmolol HCL) the ultra-short-acting intravenous beta blocker: technical monograph and formulary information. Waukegan, IL., **1987** Feb.
[3]. Angaran DM, Schultz NJ, Tschida VH., *Clin. Pharm*. **1986**, 5:288-303. [IDIS 213788] [PubMed 2871961]
[4]. Covinsky JO., *Drug Intell Clin Pharm.* **1987**, 21:316-21. [IDIS 228570] [PubMed 2882993]
[5]. Benfield P, Sorkin EM., *Drugs*. **1987**, 33:392-412. [IDIS 236763] [PubMed 2885168]
[6]. Erhardt PW, Woo CM, Gorczynski RJ et al., *J Med Chem*. **1982**, 25:1402-7. [PubMed 6130153]
[7]. Erhardt PW, Woo CM, Anderson WG et al., *J Med Chem.* **1982**, 25:1408-12. [PubMed 6130154]
[8]. Sum CY, Yacobi A., *J Pharm Sci*. **1984,** 73:1177-9. [IDIS 188872] [PubMed 6149299]
[9]. Lee YC, Baaske DM, Alam AS., *J Pharm Sci*. **1984**, 73:1660-1. [IDIS 193272] [PubMed 6520778]
[10]. Brevibloc (Esmolol hydrochloride) injection prescribing information. In: PDR.net [database online]. Montvale, NJ: *Thomson Healthcare*; **2004**. Updated (2003 Jun) HID. Trissel LA. *Handbook on injectable drugs.* 17th ed. Bethesda, MD: *American Society of Health-System Pharmacists*; **2013**, 457-61.
[11]. Flaherty J, Wong B, LaFollette G et al., *Clin Pharmacol Ther*. **1986**, 39:192.
[12]. Gorczynski RJ**.,** *Am J Cardiol*. **1985**; 56(Suppl):3-13F.