Synthesis of Trimetazidine Hydrochloride impurity by conventional method

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ABSTRACT
The aim of work was to synthesis (2,3,4-trimethoxyphenyl)methanol i.e. Impurity D of Trimetazidine hydrochloride, Impurity was synthesized in a very conventional method and structural interpretations was done by IR, Mass, NMR and HPLC.

Keywords: Reduction, Impurity.

INTRODUCTION
Trimetazidine hydrochloride is a coronary vasodilator, Anti-anginal drugs. Drugs used in this class are nitrates and beta blocker, Trimetazidine hydrochloride comes in the class of nitrated. Drug which are used to abort anginal attacks that have occurred while longer acting nitrates are used in the prophylactic management.

Impurities in pharmaceuticals are unwanted chemicals that remain with active pharmaceutical ingredients (API). The presence of these unwanted chemicals in small amount may influence the efficacy of the API or formulation. Different pharmacopeias. Have incorporated limits for this known impurities [1]. Thus International conference on Harmonization (ICH) has formulated a workable guideline regarding the control of impurities [3]

EXPERIMENTAL SECTION
Purity of the compound was monitored on silica gel 60 F254 purchased from Merck and solvent from Aldrich chemical Co Ltd. Anhydrous silica gel 60 was used as solid support after dehydration in oven at 100°C for 5 minutes. Structural interpretation was done by performing Mass spectra, Infra red spectroscopy, P-NMR and HPLC which was compared with reference standard.
General process for synthesizing the Impurity D:
Preparation of (2,3,4-trimethoxyphenyl)methanol i.e. Impurity D of Trimetazidine hydrochloride was carried out by reduction reaction[2].

In clean and dry reactor, methanol 150ml and 2,3,4-trimethoxy benzaldehyde 25gm were charged at room temperature under stirring. Reaction mass was chilled to 10-15°C and gradually solution B was added. (i.e15gms of NaOH + 20 ml water + 4gms sodium borohydride). Addition was carried out maintaining temperature of the reaction mass between 10-15°C. Reaction mass was then maintained for 5 hrs at 10-15°C for completion of reduction reaction. Reaction completion was checked on TLC.. After completion of reaction, methanol was distilled off under vacuum below 50°C and degassed at 50°C for 1 hr under vacuum to obtain the residue. Residue was cooled to room temperature and dissolved in Methylene dichloride and stirred for 30 mins at room temperature, organic layer was washed with water till neutral pH was obtained. Sodium Sulphide treatment was given to the organic layer to remove traces of water, then methylene dichloride was distilled off below 45°C under vacuum and degassed for 1 hr at 45°C under vacuum. Oily mass obtained was (2,3,4-trimethoxyphenyl)methanol, i.e. Impurity D of Trimetazidine hydrochloride.
Yield = 18gm, Density 1.151g/ml at RT, Boiling point 105.0°C, Purity 99.76%, CAS No : 71989-96-3.

RESULT AND DISCUSSION
Elemental Analysis was carried out to match with standard impurity D of Trimetazidine hydrochloride by Mass spectroscopy[fig 8] , Infrared spectroscopy[Fig 6], proton NMR[fig 7]. H.P.L.C. analysis [fig1-5] was also carried out by BP 2009 method [4] to check the retention time and purity of the impurity.
Fig 1

Sample Id: Trimetazidine HCl
Injection volume: 10 ul
Analyst: SSP
Sample: Diluent
Chromatogram: Trimetazidine HCl 01
Date Time: 12-09-2010 8.00 am

Fig 2

Sample ID: Trimetazidine HCl
Injection Volume: 10 ul
Analyst: SSP
Sample: Trimetazidine HCl WS
Chromatogram: Trimetazidine HCl 02
Date Time: 12-09-2010 8.55 am
Fig 3

Sample ID: Trimetazidine HCl
Injection Volume: 10ul
Analyst: DNT
Sample: Impurity D (210 ppm) WS
Chromatogram: Trimetazidine HCl 03
Date & Time: 12-09-2010 / 10:00 am

![Chromatogram Image]

Result Table (Uncal - Trimetazidine HCl 03)

<table>
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<th>Retain Time [min]</th>
<th>Area [mV.s]</th>
<th>Height [mV]</th>
<th>Area [%]</th>
<th>Height [%]</th>
<th>W65 [min]</th>
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<tr>
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<td>118.065</td>
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Fig 4

Sample ID: Trimetazidine HCl
Injection volume: 10ul
Analyst: SNT
Sample: USP Impurity D
Chromatogram: Trimetazidine HCl 04
Date & Time: 12-09-2010 / 11:00 am

![Chromatogram Image]

Result Table (Uncal - Trimetazidine HCl 04)

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Fig 5

![Chromatogram](image)

**Sample ID**: Trimetazidine HCl  
**Injection Volume**: 10 µl  
**Analyst**: DNT  
**Sample**: Trimetazidine HCl + Impurity D  
**Chromatogram**: Trimetazidine HCl 06  
**Date & Time**: 12-09-2010 / 12.50 pm

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<th>Height [mV]</th>
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<th>Height [%]</th>
<th>WOS [min]</th>
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</table>

Fig 6: IR of (2,3,4- Trimethoxyphenyl) methanol

![IR Spectrum](image)

- ~1660-1600, C=C (cis/vinyl strong; trans weak)  
- ~1600 (narrow), aromatic ring C=C  
- ~1475 (narrow), aromatic ring C=C  
- ~3000 (broad), C-H
CONCLUSION

Synthesized compound can be used as impurity standard (purity 99.76%) of Trimetazidine hydrochloride, which can be further studied in various aspects.
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REFERENCES