Synthesis of trimetazidine hydrochloride impurity B by conventional method

Swapnali S. Patil and Nandini Pai *

ABSTRACT
The aim of work was to synthesis 1,4-bis(2,3,4-trimethoxybenzyl)piperazine, i.e. Impurity B of Trimetazidine hydrochloride. Impurity was synthesized in a very conventional method and structural interpretations were done by NMR and HPLC.

Keywords: Impurity, trimetazidine hydrochloride

INTRODUCTION
Trimetazidine hydrochloride is a coronary vasodilator and an anti-anginal drug. Drugs used in this class are nitrates and they are beta blockers. Trimetazidine hydrochloride comes in the class of nitrated drugs which are used to abort anginal attacks, while longer acting nitrates are used in the prophylactic management.

Today in Pharmaceutical Industries, there is a tremendous upsurge for impurity profiling of pharmaceutical products. Presence of impurities in trace quantity in drug substance or drug product is inevitable; therefore their level should be controlled and monitored. They can reinforce or diminish the pharmacological efficacy of the active pharmaceutical ingredient (API). Sometimes, the effect produced by impurities can be teratogenic, mutagenic or carcinogenic. This can jeopardize the human health by affecting quality, safety and efficacy (QSE) of the product. Therefore there is an ever-increasing interest in controlling and monitoring impurities present in API or pharmaceutical product. Hence, API impurity profiling is essential.

EXPERIMENTAL SECTION
Purity of the compound was monitored on silica gel 60 F 254 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 B:
Preparation of 1, 4-bis (2, 3, 4-trimethoxybenzyl) piperazine: Impurity B [2]. Formic acid(61 ml) was charged at room temperature and 25 g of trimethoxy benzaldehyde was added under stirring stir for 15 min followed by addition of piperazine (55g) at room temperature. The temperature increased to 85°C, reaction mass was heated further to 110 -115 °C and maintained for 14 hr. and checked with TLC for completion of reaction. Reaction mass was cooled to 80°C. Reaction mass was then quenched into 170 g of ice cooled water and stirred for 30 min below 10°C. pH of the reaction mass was adjusted to 9-9.5 by slow addition of 20 % caustic solution and stirred for 1 hr below 10°C. Solid precipitated out which was filtered i.e. crude impurity B.

Crude impurity B was charged in 50 ml of methanol, heated to dissolve, 2 g activated charcoal was added and stirred for 15 min and finally hot solution was filtered through Hyflo. Clear filtrate was concentrated, cooled to room temperature and then chilled to 15° C. The solid obtained was filtered, air dried for 1 hr. and finally dried at 40-50°C under vacuum.
Yield = 5 g 
Purity 99.76% (as on HPLC)

RESULTS AND DISCUSSION

\[ \text{Formic acid} \]

1,4-bis(2,3,4-trimethoxybenzyl) piperazine (Impurity B)

Synthesized impurity B was matched with standard impurity B of trimetazidine hydrochloride by Infrared spectroscopy [1660-1600, C-C (cis/vinyl strong; trans weak) ~1350-1000, C-N ~1600 (narrow), aromatic ring C=C ~1475 (narrow)] and proton NMR[fig 6]. 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: Blank

Fig 2: WS Trimetazidine Hydrochloride

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<th>Injection Volume</th>
<th>Area [mV.s]</th>
<th>Height [mV]</th>
<th>Area [%]</th>
<th>Height [%]</th>
<th>W50 [min]</th>
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<td>156.463</td>
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<td>100.0</td>
<td>0.57</td>
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</tbody>
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No peak to report
Fig 3: WS of Impurity B
Fig 4: Impurity B

Sample ID: Trimetazidine Hydrochloride
Injection Vol: 10 ul
Analyst: SSP
Sample: Impurity B
Chromatogram: Trimetazidine Hydrochloride 89
Date & Time: 15th April 2012 11.00

Result Table (Uncel - Trimetazidine HCl 55)

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<th>Height [mV]</th>
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<tr>
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<td>77.824</td>
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Fig 5: Trimetazidine hydrochloride + Impurity B

Fig 6: NMR of Impurity B
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