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Research Article

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Synthesis of trimetazidine hydrochloride impurity B by conventional method

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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; there fore 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. There fore 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

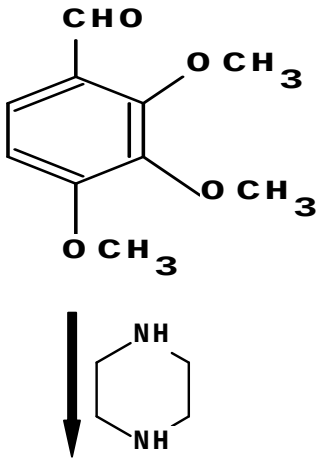
Purity of the compound was monitored on silica gel 60 F_{254} purchased from Merck and solvent from Aldrich chemical Co Ltd. Anhydrous silica gel 60 was used as solid support after dehydration in oven at 100°C for 5 minutes. Structural interpretation was done by performing Mass spectra, Infra red spectroscopy, 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.

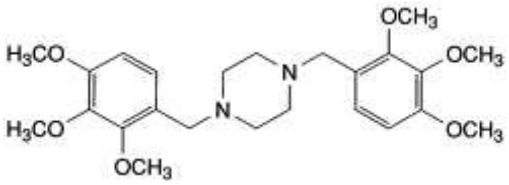
Crude impurity B was charged in 50 ml of methanol, heated to dissolve, 2 g activated charcoal was added and stirred for 15 min and finally hot solution was filtered through Hyflo. Clear filtrate was concentrated, cooled to room temperature and then chilled to 15° C . The solid obtained was filtered, 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



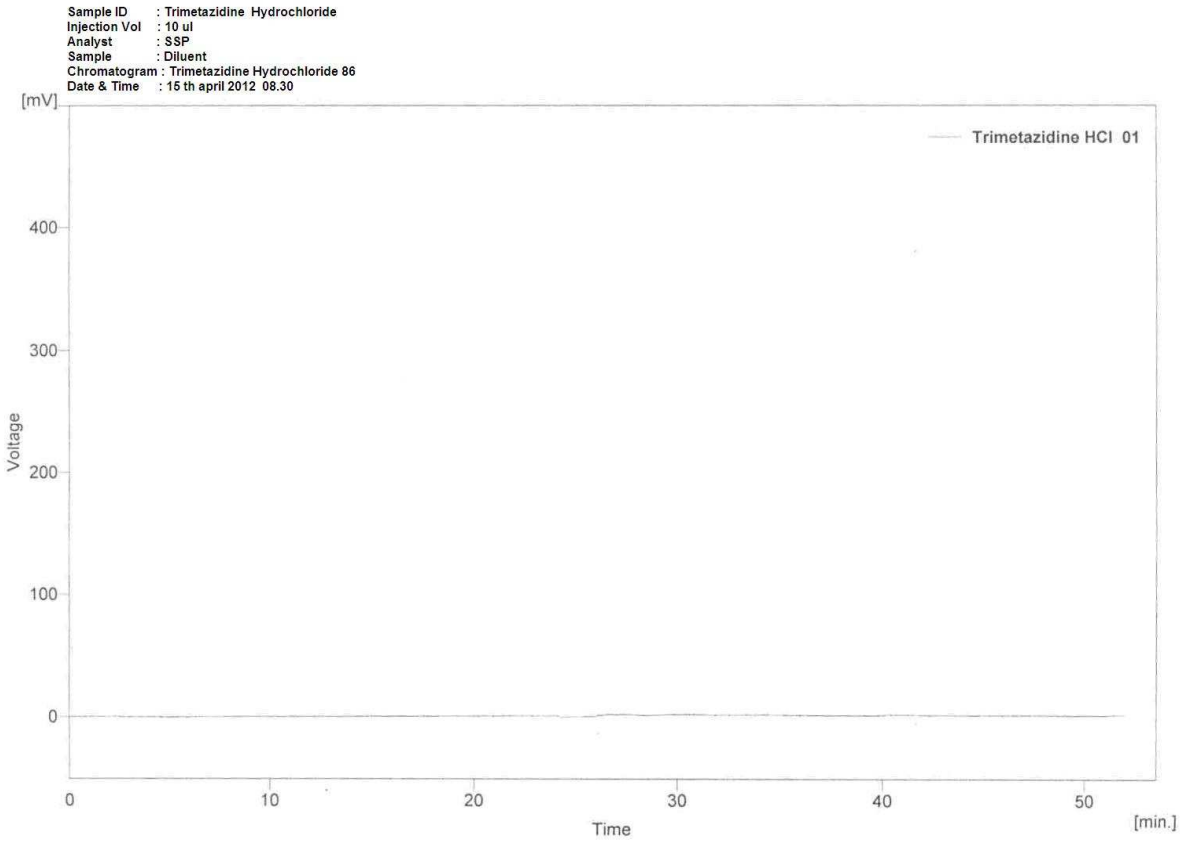
Formic acid



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.

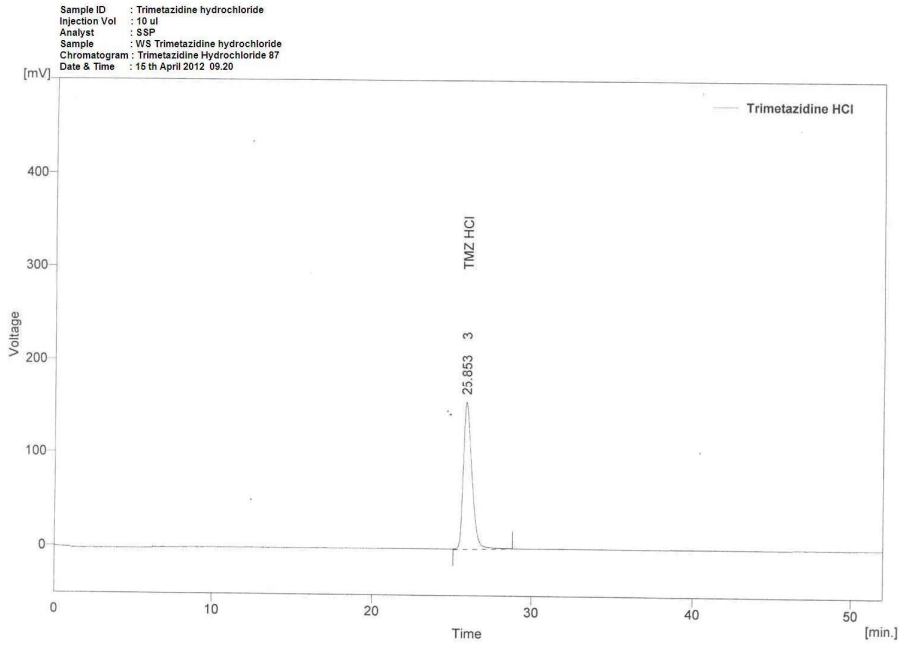
Fig 1:Blank



Result Table (Uncal - Trimetazidine HCl 01)

Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
No peak to report					

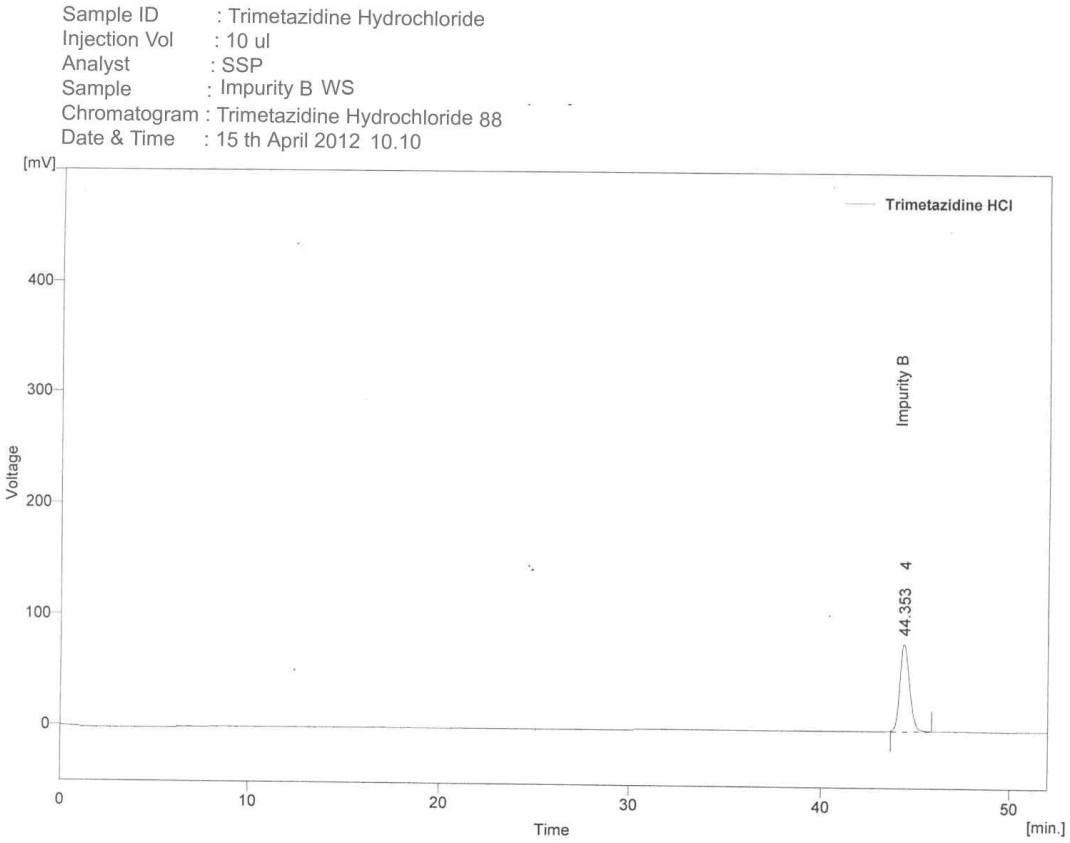
Fig 2: WS Trimetazidine Hydrochloride



Result Table (Uncal - Trimetazidine HCl 05)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	25.853	5893.479	156.483	100.0	100.0	0.57
Total		5893.479	156.483	100.0	100.0	

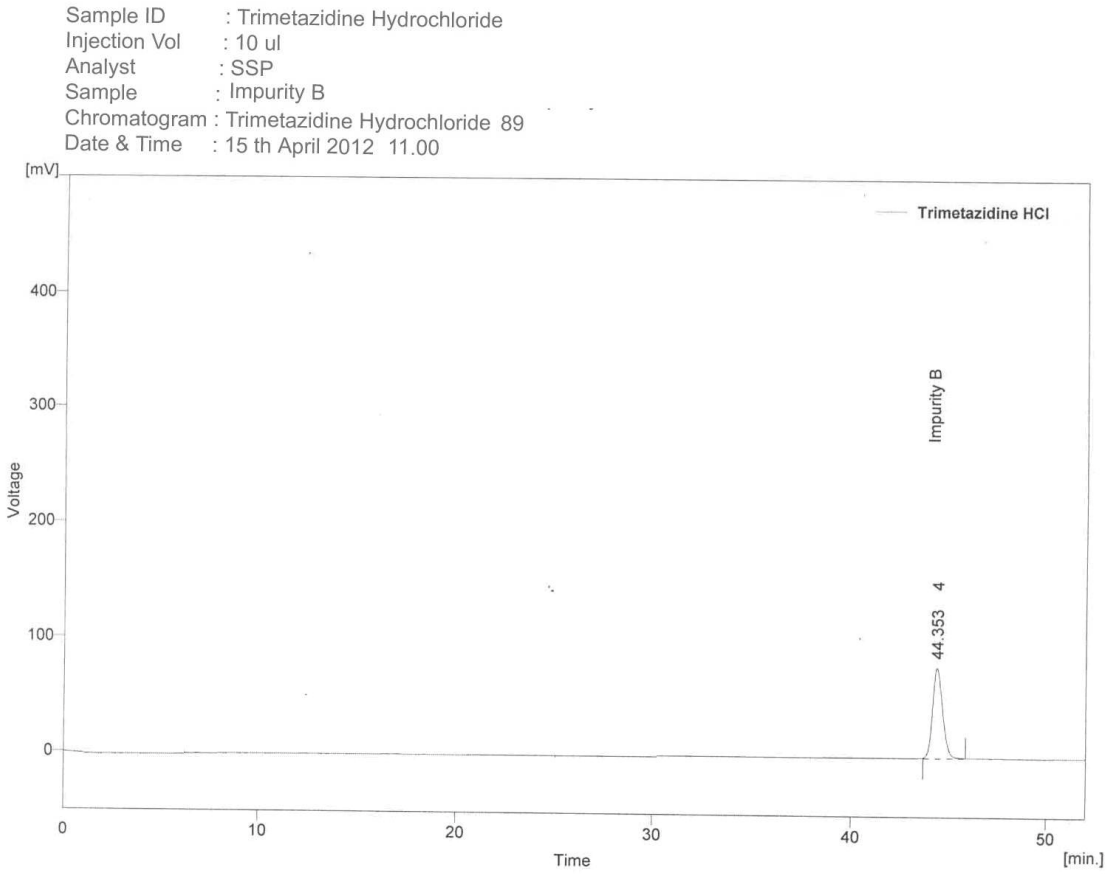
Fig 3: WS of Impurity B



Result Table (Uncal - Trimetazidine HCl 05)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	44.353	2776.977	77.874	100.0	100.0	0.55
	Total	2776.977	77.874	100.0	100.0	

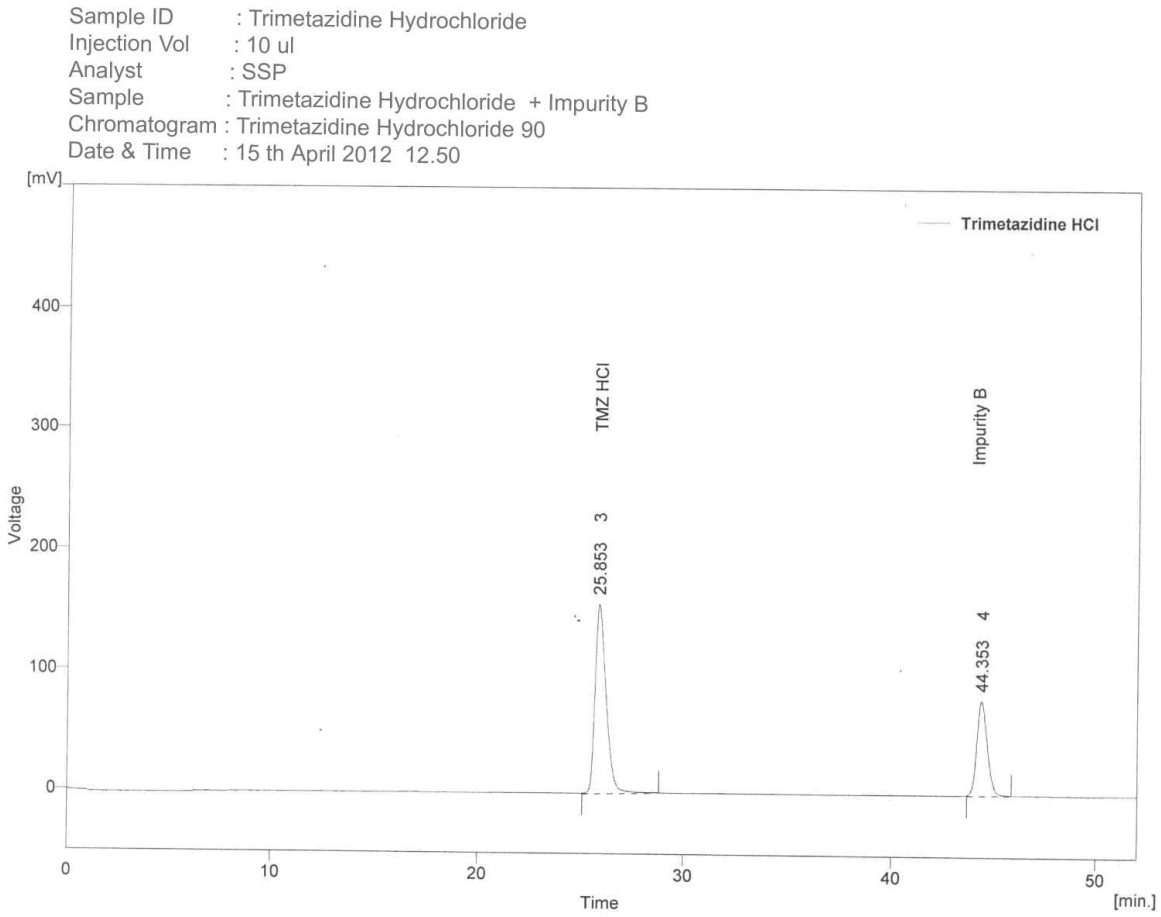
Fig 4: Impurity B



Result Table (Uncal - Trimetazidine HCl 05)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	44.353	2756.971	77.824	100.0	100.0	0.55
	Total	2756.971	77.824	100.0	100.0	

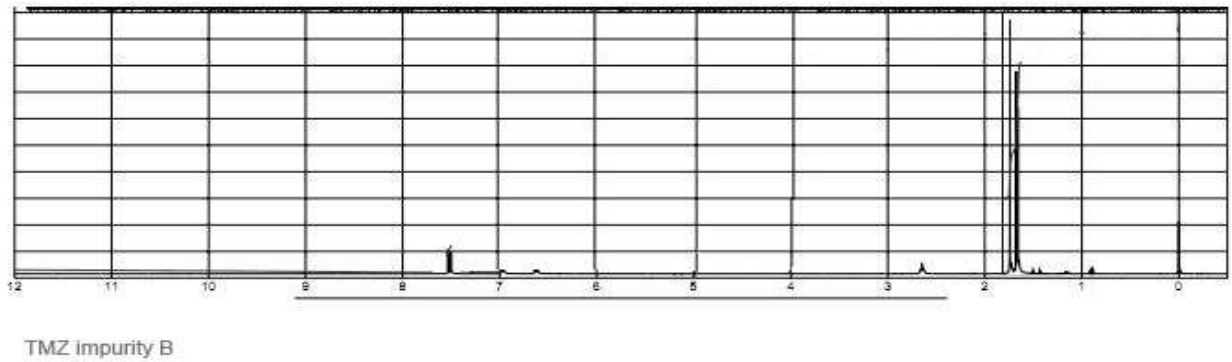
Fig 5: Trimetazidine hydrochloride + Impurity B



Result Table (Uncal - Trimetazidine HCl 05)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	25.853	5813.479	156.483	67.8	66.8	0.57
2	44.353	2756.971	77.824	33.2	33.2	0.55
	Total	8570.465	234.309	32.2	100.0	

Fig 6: NMR of Impurity B



TMZ 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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