



ISSN No: 0975-7384  
CODEN(USA): JCPRC5

*J. Chem. Pharm. Res.*, 2010, 2(6):154-160

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## **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.

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### **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**

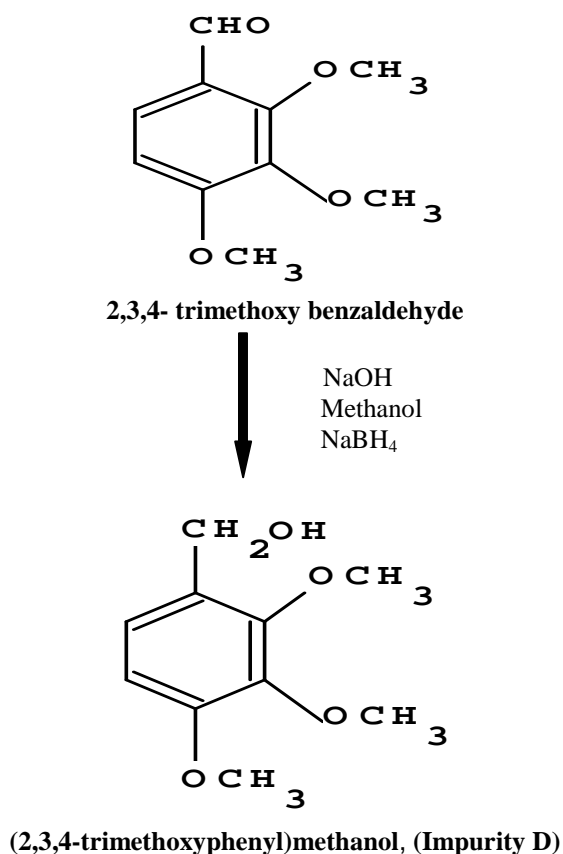
Purity of the compound was monitored on silica gel 60 F<sub>254</sub> purchased from Merck and solvent from Aldrich chemical Co Ltd . Anhydrous silica gel 60 was used as solid support after dehydration in oven at 100°C for 5 minutes. Structural interpretation was done by performing Mass spectra, Infra 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.e.15gms 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.

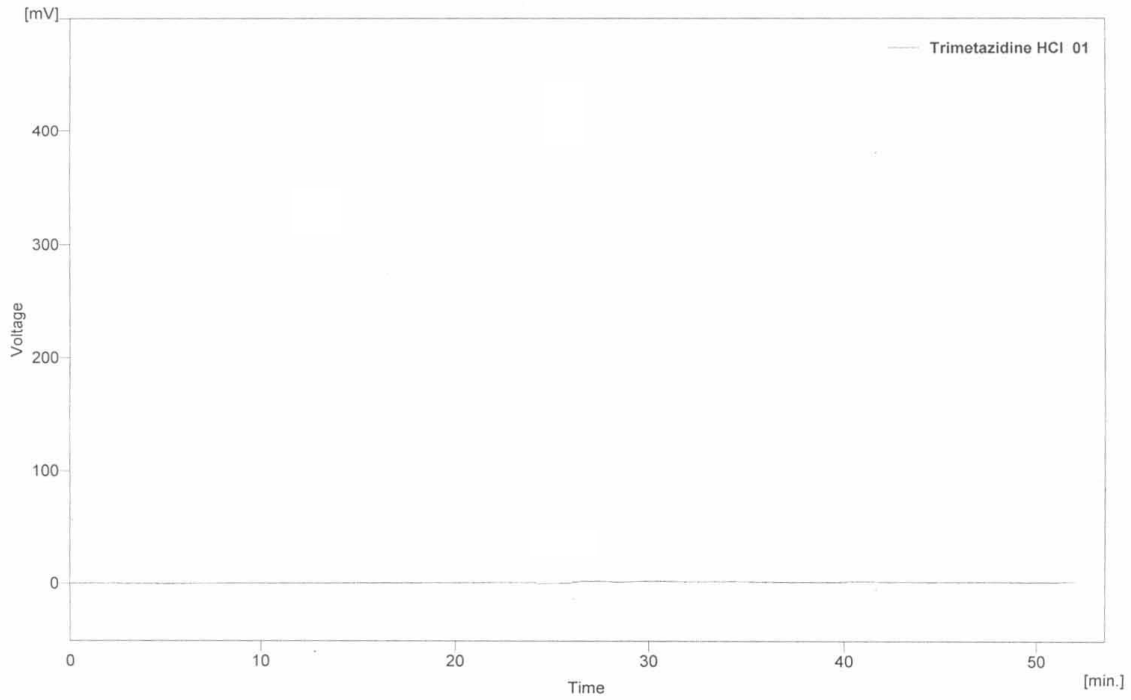
Yield = 18gm, Density 1.151g/ml at RT, Boiling point 105.0°C, Purity 99.76%, CAS No : 71989-96-3.

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

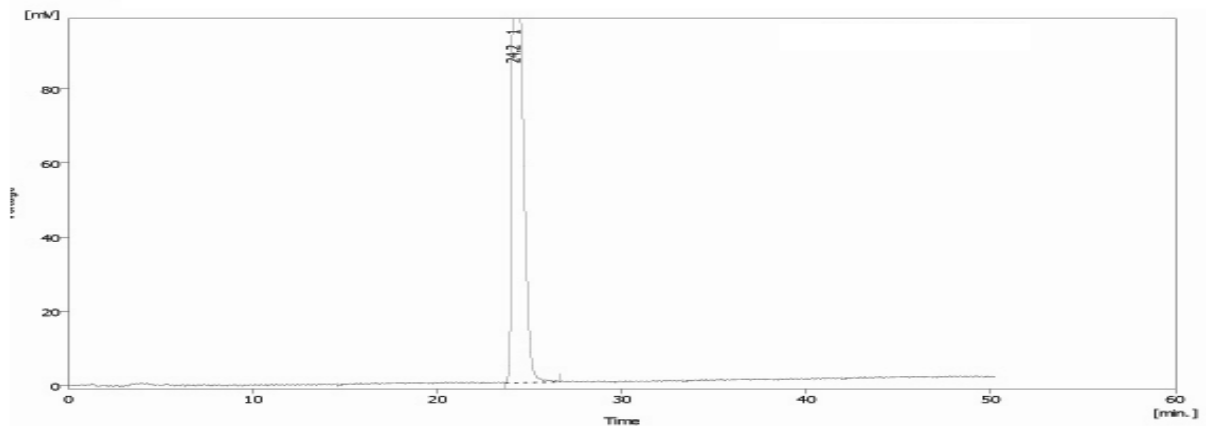


Result Table (Uncal - Trimetazidine HCl 01)

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

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

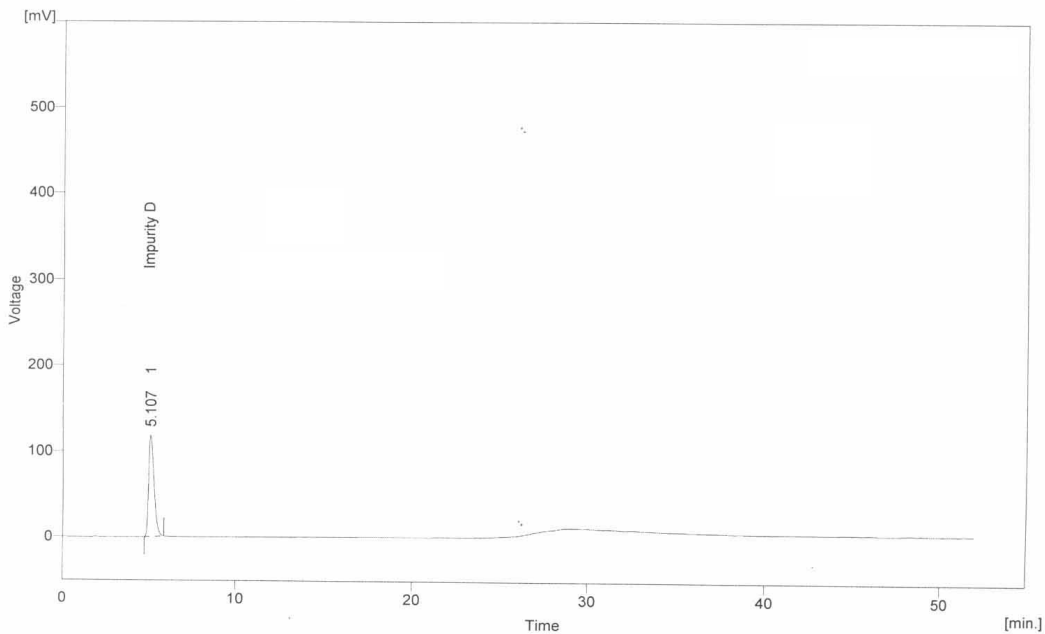


Result Table (Uncal - TMZ DI HCL 151)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	24.193	5494.531	149.892	100.0	100.0	0.58
Total		5494.531	149.892	100.0	100.0	

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

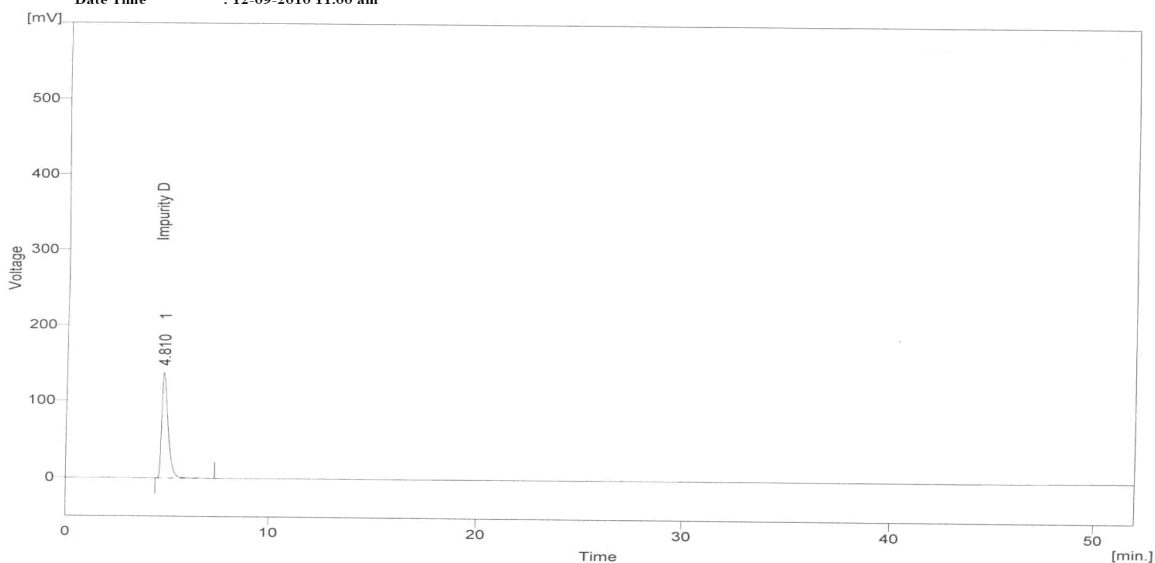


Result Table (Uncal - Trimetazidine HCl 70)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	5.107	2546.525	118.065	100.0	100.0	0.34
	Total	2546.525	118.065	100.0	100.0	

Fig 4

Sample ID : Trimetazidine HCl  
 Injection volume : 10 ul  
 Analyst : SSP  
 Sample : TS of Impurity D  
 Chromatogram : Trimetazidine HCl 04  
 Date Time : 12-09-2010 11.00 am



Result Table (Uncal - Trimetazidine HCl 84)

	Reten. Time [min]	Area [mV.s]	Height [mV]	Area [%]	Height [%]	W05 [min]
1	4.810	2999.720	136.956	100.0	100.0	0.33
	Total	2999.720	136.956	100.0	100.0	

Fig 5

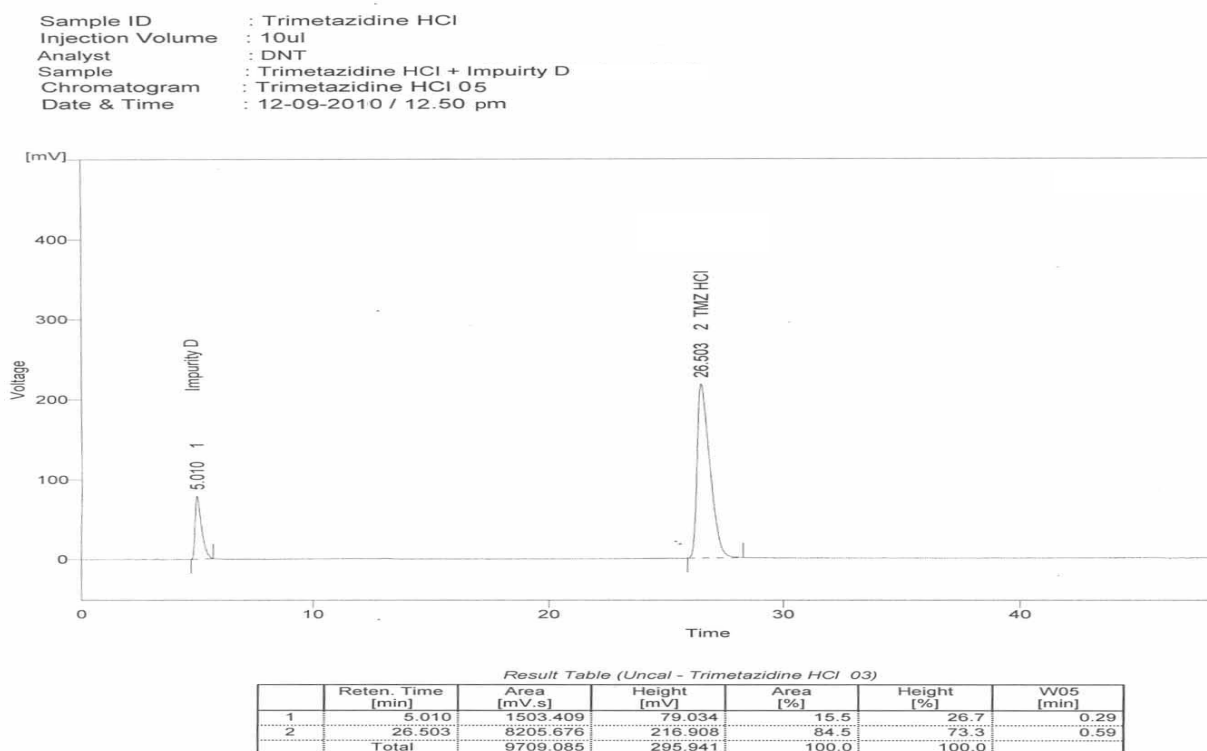
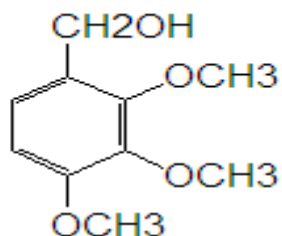
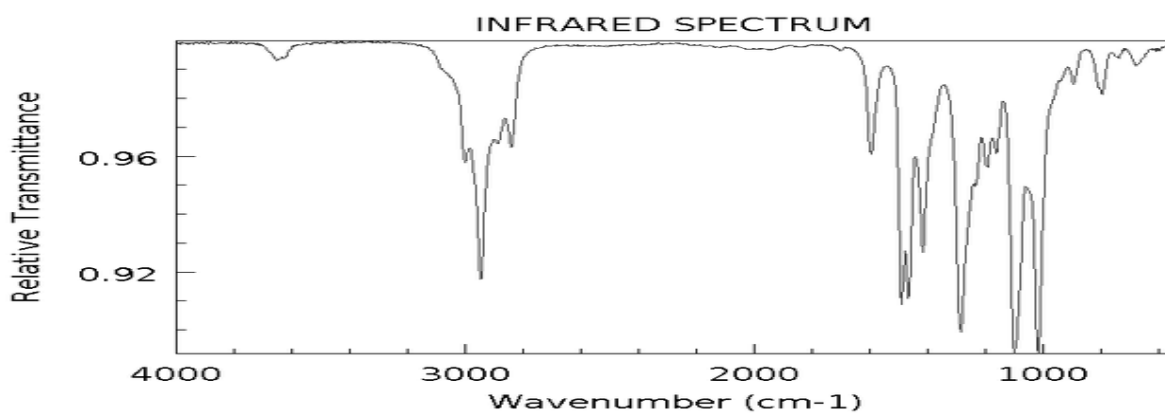


Fig 6: IR of (2,3,4- Trimethoxyphenyl) methanol



- ~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

Fig 7: Proton NMR of (2,3,4- Trimethoxyphenyl) methanol

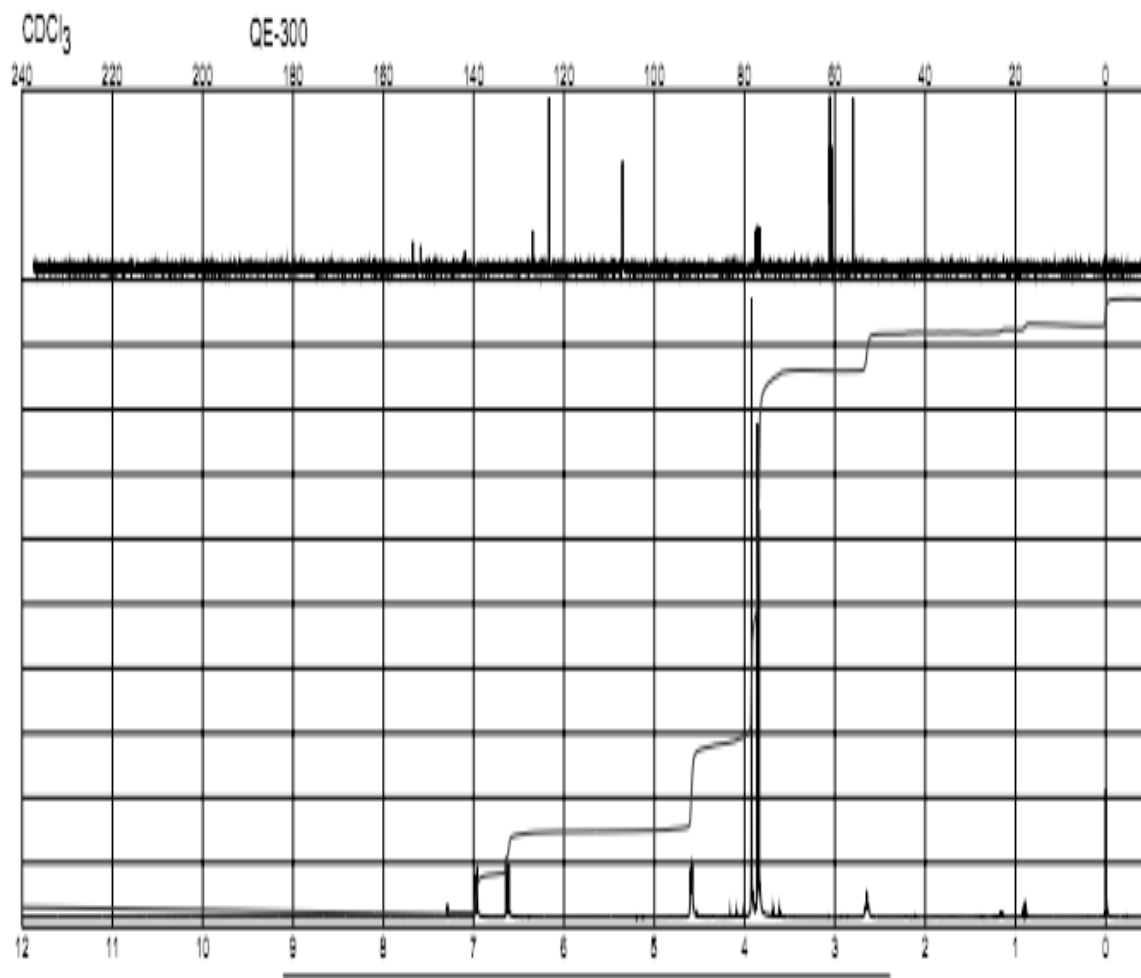
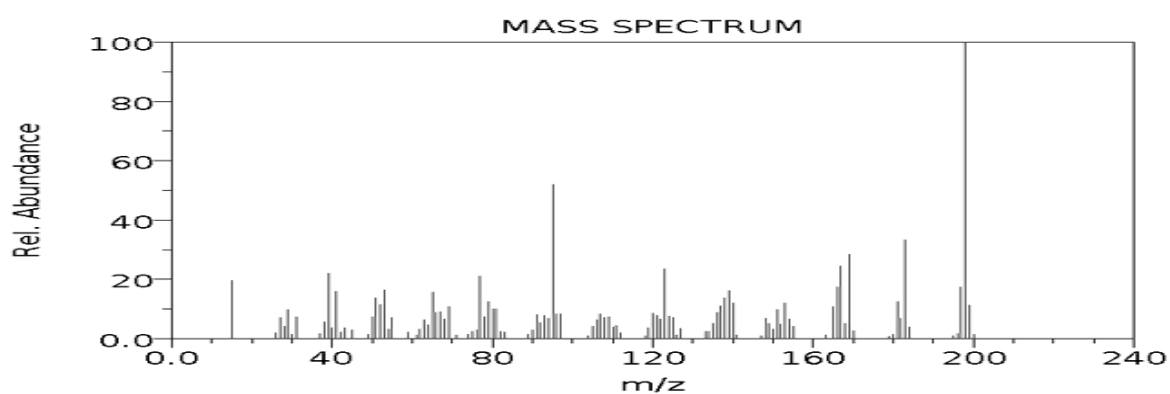


Fig 8: Mass Spectra of (2,3,4- Trimethoxyphenyl) methanol



### CONCLUSION

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

**Acknowledgements**

I am thankful to Ultratech India Ltd. and D. G. Ruparel College for providing all the necessary analytical details of the compound, required support and co-operation for executing this project. I am also thankful to Mr. Deepak U. Shanbhag for his support.

**REFERENCES**

- [1] International Conference on Harmonisation tripartite guideline (ICH), Impurities In New Drug Substances Q3A(R2), Current Step 4 version dated 25 October **2006**.
- [2] Arun Bahal, B. S . Bahl, *A Textbook of Organic Chemistry*
- [3] *Indian Journal of chemistry* Vol 48B may **2009**,pp741-745
- [4] BP, British Pharmacopoeia (**2009**).
- [5] [www.rxlist](http://www.rxlist)
- [6] [www.pharmatext.org](http://www.pharmatext.org)
- [7] <http://www.wipo.int/pctdb/en/>
- [8] <http://www.daviddarling.info/encyclopedia/alphindexv.html>