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METHOD DEVELOPMENT AND VALIDATION OF N, N-DIMETHYLAMINOPROPYL CHLORIDE (DMPC) CONTENT IN CLOMIPRAMINE HYDROCHLORIDE DRUG SUBSTANCE BY GC-MS/MS

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ABSTRACT

A GC-MS/MS method was developed for determination of N, N-Dimethylaminopropyl chloride (DMPC) in Clomipramine Hydrochloride drug substanceusingDB-624column (30m X 0.25mm X 1.4µm) and a mobile phase of Helium gas with gradient GC oven temperature programming, at flow rate of 1.0ml/min with MS detector. The mass of N, N-Dimethylaminopropyl chloride (DMPC) were found 121, 58 and 42 respectively. The retention time was found 8.5 minutes. The proposed method was validated for System suitability, Specificity, Linearity, LOD and LOQ determination, Recovery, Precision, and Range. All the parameters were found within the acceptable limits. The Linearity of N, N-Dimethylaminopropyl chloride (DMPC) was in the range of 0.026µg/gm (LOQ) to 0.129µg/gm (200%) of specification limit. This GC-MS/MS method was specific, accurate, precise and suitable for the analysis of N, N-Dimethylaminopropyl chloride (DMPC) in Clomipramine Hydrochloride drug substance.

KEYWORDS

Gas chromatography with mass spectrometry (GC-MS/MS), Genotoxic impurity, ICH guideline and Method Validation.

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INTRODUCTON

Genotoxic impurities are undesirable chemicals, have no beneficial for health and are potentially harmful for direct DNA damage. Therefore, they need to be controlled in Active pharmaceutical ingredient and Drug products. Genotoxic impurities are those substances which impact DNA by means of transformations. Mutations can be chromosomal breaks, rearrangements, covalent binding or insertion into DNA during replication. Mutations may also occur indirectly by activating a cell to produce genotoxic substances. The focus of this

study is on reactive substances they have a potential to directly cause DNA damage when present low levels lading to mutations and there for potentially causing cancer. Because of this, it is important to identify genotoxic substances followed by monitoring and control at very low levels to ensure safety to the public.

The source of genotoxic impurities in pharmaceuticals (API and DP) can come from many places including starting materials, by products, reagents, intermediates, degradation products, ligands and catalysts, solvents or unwanted side reactions from the Active pharmaceutical ingredient synthetic process that get carried forward into the final product. In addition, the Active pharmaceutical ingredient itself can decompose to form genotoxic substances or they can form in the final product by reaction between excipients or containers and the Active pharmaceutical ingredient.

The use of these substances within the synthetic procedure is logical as these compounds are reactive fragment that come together to form complex drug substances.

Impurity guidelines have mainly been developed by international Conference on Harmonization (ICH). ICH Q3A regulates impurities in new drug substances with thresholds for reporting, identifying, and qualifying impurities. ICH Q3B is the equivalent guideline for impurities in new drugs. ICH Q3C controls residual solvent, and is the first time the ICH applied substance specific limits. Depending on their potential risk to human health. At this time ICH Q3D is developed and included elements and limits for heavy metal impurities. At present the ICH guidelines for genotoxic impurity limits are not suitable. The genotoxins material considered unsafe at any level. The limit for a genotoxin with an understood toxicity can be calculated based upon the know PDE. The limit for the genotoxin without sufficient information must determine based upon TTC of 6.0µg/day.

METHOD DEVELOPMENT

Instrument, Chemicals and Reagents

The following reagents and chemicals were used during the evaluation studies:

Instrumentation

A Shimadzu Gas chromatography system (GC 201 Plus) with mass spectrometer (GCMS TQ8050) equipped with an auto sampler with Real time analysis software. Column was employed in the method was Restek DB-624 (30m X 0.25mm X 1.4µm). The flow rate selected was 1.0ml/min. All the weighing in the experiments was done with Mattlertole do electronic balance capable of measuring with an accuracy of 0.01mg.

Glassware

All the volumetric glassware used in the study was grade a quality Borosil.

Preparation of Diluent

Use Di-isopropyl ether as a Diluent-I.

Prepare a homogeneous mixture of ethyl acetate and di-isopropyl ether in the ratio of 15:85% v/v. Label this solution as Diluent-II.

Preparation of Blank

Use Diluent-II as blank.

Preparation of 4% Sodium Hydroxide Solution

Accurately weigh and transfer about 4.0gm of sodium hydroxide into clean and dry 100mL volumetric flask. Add about 20.0mL water, sonicate to dissolve the content and dilute to the volume with water.

Preparation of Standard Solution

Transfer approximately 10mL of Diluent-I into 50.0mL volumetric flask. Tare to zero. Add about 30.0mg of free base DMPC working/reference standard, record the weight and dilute to volume with Diluent-I.

Transfer 0.5mL of this solution into clean and dry 100.0mL volumetric flask and dilute to the volume with the diluent-II.

Further transfer 1.0mL of this solution of this clean and dry 50.0mL volumetric flask and dilute to the volume with diluent-II.

Transfer 10mL of this solution into clean and dry 100.0mL separating funnel. Add 5mL of 4% sodium hydroxide solution and shake well, so that two layers are formed.

Take the solvent (upper) layer into suitable 20ml vial (Headspace) and dry by adding about 2.0g sodium sulphate. Label this solution as Label this solution as STD-Sol.

Transfer 1.0ml of STD-Sol into a GC vial and inject on GC-MS/MS system.

Preparation of Test Solution

Accurately weigh and transfer about 100mg of test sample into clean and dry 100mL separating funnel. Add 5mL of 4% sodium hydroxide solution and shake well, then add 10mL of diluent- II and shake well so that two layers are formed.

Take the solvent (upper) layer into suitable 20ml vial (Headspace) and dry by adding about 2.0g sodium sulphate. Label this solution as Test Solution.

Transfer 1.0ml of Test Solution into a GC vial and inject on GC-MS/MS system.

Validation Parameters

Specificity

The specificity is defined as the ability to assess and ensure that theimpurities, degradation product and diluent do not affect the sample analyzed.

Inject the Blank (as Diluent), Standard solution, sample solution, and spike sample of N,N-Dimethylaminopropyl chloride at specification level. Check the interference and mass at the retention time analyte. Results are given below in Table No.1.

No peak was observed in blank and sample at the retention time of N, N-Dimethylaminopropyl chloride. There is no interference observed in blank and other components presents in sample matrix with analyte peak. Hence method is specific.

Limit of detection (LOD) and Limit of quantitation (LOQ)

It is the smallest amount or concentration of an analyte that can be estimated with acceptable reliability. The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

The limit of detection is determined by establishing the signal to noise ratio. Inject the blank and standard solutions at lower concentration and calculate the signal to noise ratio.

A signal-to-noise ratio between 3:1 estimating the detection limit.

The detection limit and quantitation limit for N, N-Dimethylaminopropyl chloride in Clomipramine Hydrochloride Drug substance1.2mcg/g and 2.4mcg/g respectively. For details, refer Table No.2.

Precision at detection limit and Limit of quantitation

The N, N-Dimethylaminopropyl chloride peak is detected reliably in six replicate injections at DL level. Hence obtained concentration can be considered DL level for N, N-Dimethylaminopropyl chloride. The %RSD of area for peak N, N-Dimethylaminopropyl chloride should be less than 33%.

%RSD of peak area of N, N-Dimethylaminopropyl chloride in six replicate injections of LOD precision solution was found 8.1%. For details, refer Table No.3.

The Quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

The limit of quantification is determined by establishing the signal to noise ratio. Inject the blank sample and the spiked sample at LOQ level in six replicates and calculate signal to noise ratio and the % RSD at LOQ level. The % RSD of peak area for six replicated injections of LOQ precision solution for N, N-Dimethylaminopropyl chloride should not be more than 15.0%.

%RSD of peak area of N, N-Dimethylaminopropyl in six replicate injections of LOQ precision solution was found 1.6%. For details, refer Table No.4.

Precision

System precision

System precision was determined by injecting blank and six replicates of standard preparation. %RSD was calculated for Epichlorohydrin area response.

Prepared blank and standard solution as per description of analytical method.

Injected blank, standard solution, and checked the acceptance criteria for system suitability. For details, refer Table No.5.

Method Precision

Method precision was determined by analyzing six sample preparations as per the method representing a single batch.

Determined the results of these samples and evaluate the precision of the method by computing the %RSD results for N, N-Dimethylaminopropyl. The %RSD for N, N-Dimethylaminopropyl from six set of test preparation (above LOQ) should be NMT 20.0

Prepared blank and standard solution as per description of analytical method. %RSD for result for N, N-Dimethylaminopropyl of six sample is not applicable as it was found not detected hence it will not consider for evaluation. For details, refer Table No.6.

Since results of N, N-Dimethylaminopropyl was found not detected, then performed the spiked test repeatability by spiking N, N-Dimethylaminopropyl at specification level in the sample and injected in six replicates. N, N-Dimethylaminopropyl content was calculated. %RSD for result of N, N-Dimethylaminopropyl of six spiked sample was found 9.8%. For details, refer Table No.7.

Intermediate Precision

Intermediate precision was determined by analyzing six sample preparations as per the method representing a single batch by different analyst on different day. % RSD for N, N-Dimethylaminopropyl results were calculated.

Since results of N, N-Dimethylaminopropyl observed not detected in all test preparation during method precision study, then six individually test sample spiked with N, N-Dimethylaminopropyl at specification level was analyzed in intermediate precision.

Prepared blank, standard solution and sample solution as per description of analytical method and injected. Results of intermediate precision refer Table No.8.

Linearity

A linear relationship should be evaluated across the range of the analytical procedure. It may be demonstrated directly on the analyte by dilution of a standard stock solution using the proposed procedure. Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods by calculation of a regression line. The correlation coefficient, y-intercept, slope of the regression line should be calculated.

The total number of seven concentration LOQ to 200% of specification levels considered and inject the duplicate injection of each concentration level to define a calibration graph. The acceptable value of the correlation coefficient (r2) should be more than 0.99 for N, N-Dimethylaminopropyl.

Correlation coefficient for the linearity curve of N, N-Dimethylaminopropyl in Clomipramine Hydrochloride drug substance found >0.99. The method is found linear from LOQ to 200% of sample Concentration, for details, refer Table No.9.

Recovery

Recovery means the percentage of the true concentration of a substance recovered during the analytical procedure.

Recovery assessed using a minimum of 3preparations over a minimum of 3 concentration levels (3 concentrations/3 replicates each level). % Recovery was calculated for each level.

Acceptable limits for a recovery result during validation should be within the range of 70% - 130%. However, the lower recovery may be acceptable if the results are consistent (i.e. good precision).

Prepared blank, sample and standards solution as per methodology. Injected blank, sample and standards solution and checked the acceptance criteria for system suitability. Accuracy was carried out for N, N-Dimethylaminopropyl at QL level, 100% and 150% of specification level.% Accuracy for each level was found within acceptance criteria refer Table No.10.

Range

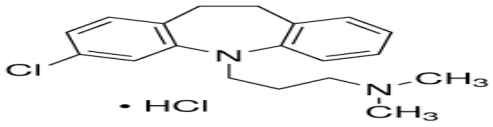
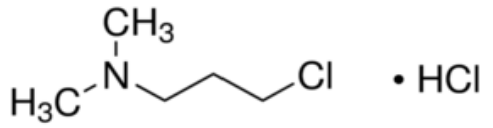
Range of N, N-Dimethylaminopropyl content in Clomipramine Hydrochloride drug substance are linear, precise, and accurate from LOQ to 150% of specification level.

DISCUSSION

A chromatographic method involves demonstrating specificity, which is the ability of the method to accurately measure the N, N-Dimethylaminopropyl response in the presence of all potential sample

components. The chromatographic and mass spectroscopy parameters were fixed and GC-MS/MS system was studied for suitability of residual analysis. The developed method was performed for linearity, precision, Accuracy, specificity, range, LOD and LOQ.

Chemical Structure of Ranolazine and 2-[(2-Methoxyphenoxy) methyl] oxirane

Clomipramine Hydrochloride **Chemical Name*:*** 3-Chloroimipramine hydrochloride **Molecular weight*:*** 314.86 g/mol **Molecular Formula:** $C_{19}H_{23}ClN_2$	
N, N-Dimethylamino propyl chloride **Chemical Name:** 3-Chloro-N, N-dimethylpropylamine hydrochloride **Molecular weight:** 158.07g/mol **Molecular Formula:** $(CH_3)_2N(CH_2)_3Cl\cdot HCl$	

The following reagents and chemicals were used during the evaluation studies

S.No	Name of the materials	Grade	Make
1	Water	HPLC	Merck
2	Ethyl Acetate	HPLC	Merck
3	Sodium Hydroxide	Emplura	Merck
4	Sodium Sulphate	Emplura	Merck
5	Di-Isopropyl ether	AR	Spectrochem
6	N, N-Dimethylaminopropyl chloride	NA	Mankind
7	Clomipramine Hydrochloride	NA	Mankind

Chromatographic Conditions for GC

S.No	Parameters	Description
1	Carrier Gas	Helium
2	Flow control mode	Linear velocity
3	Linear velocity	36.1cm/sec
4	Split ratio	1:5
5	Flow rate	1.0mL/min
6	Injector Temperature	290°C
GC Oven program for Standard		
7	Initial Temp	40°C, hold for 0.0 min
8	Ramp 1	10°C/min to 150°C, hold for 0.00 min
9	Ramp 2	30°C/min to 250°C, hold for 2.67 min
9	Run time	17.0 minutes
GC Oven program for Sample		
10	Initial Temp	40°C, hold for 0.0 min
11	Ramp 1	10°C/min to 150°C, hold for 0.00 min
12	Ramp 2	30°C/min to 250°C, hold for 65.67 min
13	Run time	80.0 minutes
14	Injection volume	1.0µL

MS Conditions

Ion Source temperature	230.0°C	
Interface temperature	250.0°C	
Solvent cut time	6.0 min	
Detector gain Voltage	Relative to the tuning result	
Detector gain	+ 0.40kV	
Acquisition Mode	SIM	
Start Time	7.00 minutes	
End Time	11.0 minutes	
Ion (m/z)	Target-Ion	58
	Reference-Ion	42
	Reference-Ion	121

Auto Sampler Parameters (ALS-20S+i)

# of Rinse with solvent (Pre Run)	5
# of Rinse with solvent (Post Run)	5
# of Rinse with sample	5
Plunger speed (suction)	High
Plunger speed (injection)	High
Syringe Insertion speed	High
Viscosity Comp. Time	0.2 Seconds
Injection mode	Normal

Table No.1

S.No	Solution	Peak Name	RT (min.)	Target Ion	Reference Ion-1	Reference Ion-2
1	Blank	N, N-Dimethylaminopropyl chloride	ND	ND	ND	ND
2	Standard solution	N, N-Dimethylaminopropyl chloride	8.5	58	42	121
3	Test solution	N, N-Dimethylaminopropyl chloride	ND	ND	ND	ND
4	Spiked test solution	N, N-Dimethylaminopropyl chloride	8.5	58	42	121

Table No.2

S.No	Compound	LOD Level (ppm)		LOQ Level (ppm)	
		Standard Conc.	W.R.T test	Standard Conc.	W.R.T test
1	N, N-Dimethylaminopropyl chloride	0.012	1.2	0.024	2.4

Table No.3

S.No	No. of injections	1	2	3	4	5	6	%RSD
1	Peak Area of N, N-Dimethylaminopropyl chloride	167228	142870	143373	165522	152817	138240	8.1

Table No.4

S.No	No. of injections	1	2	3	4	5	6	%RSD
1	Peak Area of N, N-Dimethylaminopropyl chloride	299950	318271	294946	300671	296861	291987	3.1

Table No.5

S.No	Parameter	Result	Acceptance criteria
1	The % relative standard deviation of six replicate injections of standard solution for N, N-Dimethylaminopropyl chloride	5.8	Should not be more than 15.0%.

Table No.6

S.No	Sample Result (in ppm)									
	Sample preparations	1	2	3	4	5	6	Mean	SD	%RSD
1	N, N-Dimethylaminopropyl	BDL	BDL	BDL	BDL	BDL	BDL	NA	NA	NA

Table No.7

S.No	Sample Result after spiking N, N-Dimethylaminopropyl at specification level (in ppm)									
	Sample preparations	1	2	3	4	5	6	Mean	SD	%RSD
1	N, N-Dimethylaminopropyl	6.02	7.38	7.87	7.99	7.77	7.42	7.40	0.72	9.8

Table No.8

S.No	Result of intermediate precision at specification level of N, N-Dimethylaminopropyl (in ppm)									
	Sample preparations	1	2	3	4	5	6	Mean	SD	%RSD
1	N, N-Dimethylaminopropyl	6.31	7.81	7.22	7.73	7.79	8.12	7.49	0.649	8.7

Table No.9

S.No	Linearity Conc. level	N, N-Dimethylaminopropyl (DMPC)	
		Conc. (ppm)	Mean area
1	LOQ level	0.026	349013
2	50% level	0.032	480061
3	75% level	0.048	806510
4	100% level	0.064	1112784
5	125% level	0.081	1447247
6	150% level	0.097	1845881
7	200% level	0.129	2560347
8	Correlation coefficient		0.9992
9	Squared Correlation coefficient		0.99841
10	Slope		21296217.45
11	Y-Intercept		-222350.389
12	Residual sum of square		5902560140
13	Linearity plot for N, N-Dimethylaminopropyl		

Table No.10

S.No	Level (%)	Sample ID	Amount added (ppm W.R.T. Sample)	Amount recovered (ppm W.R.T. Sample)	Recovery (%)	Average Recovery (%)
1	LOQ	Injection-1	2.3188	2.8502	122.91	120.7
		Injection-2	2.3188	2.7853	120.11	
		Injection-3	2.3188	2.7623	119.12	
2	100	Injection-1	5.9047	5.3312	90.28	101.7
		Injection-2	5.9047	6.0368	102.23	
		Injection-3	5.9047	6.6440	112.52	
3	150	Injection-1	8.8571	9.0735	102.44	100.5
		Injection-2	8.8571	8.9678	101.24	
		Injection-3	8.8571	8.6585	97.75	
4	Recovery (Overall)			**Mean**	**STDEV**	**%RSD**
				107.6	11.406	10.6

Chromatograms of study

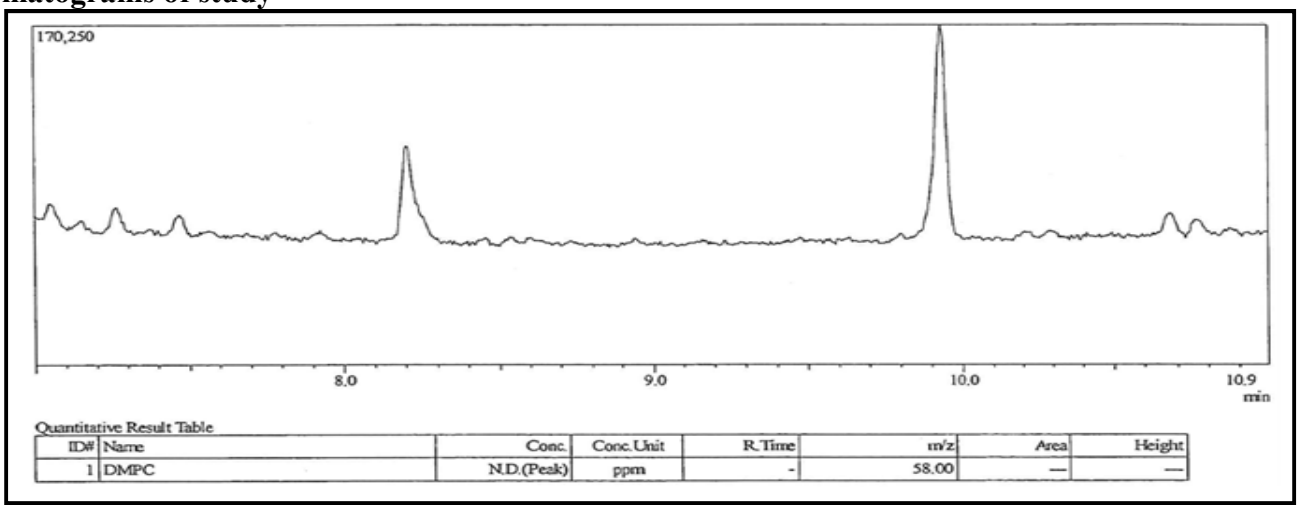


Figure No.1: Blank Chromatogram

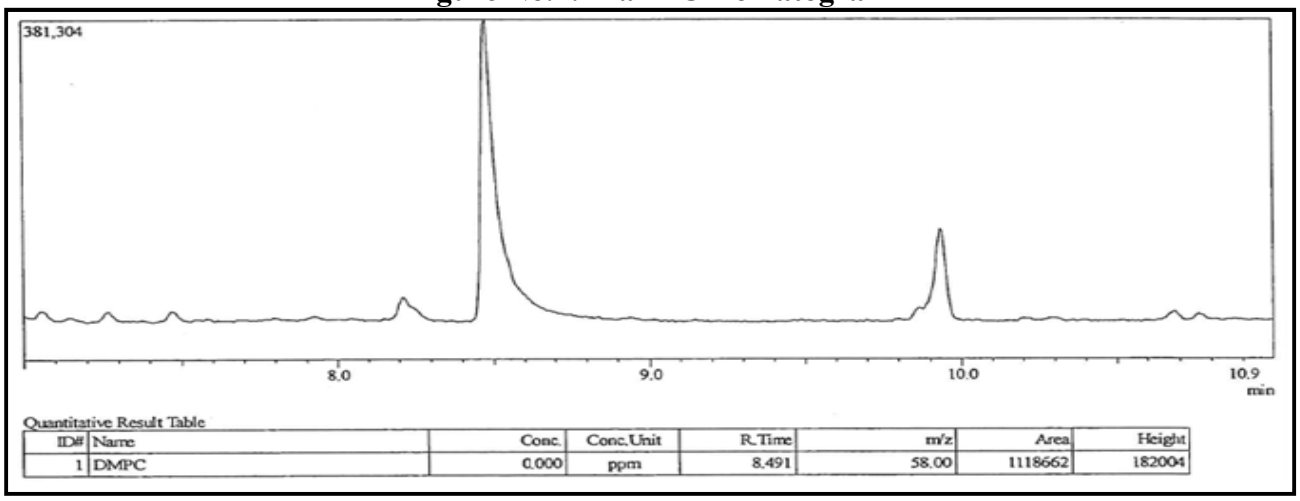
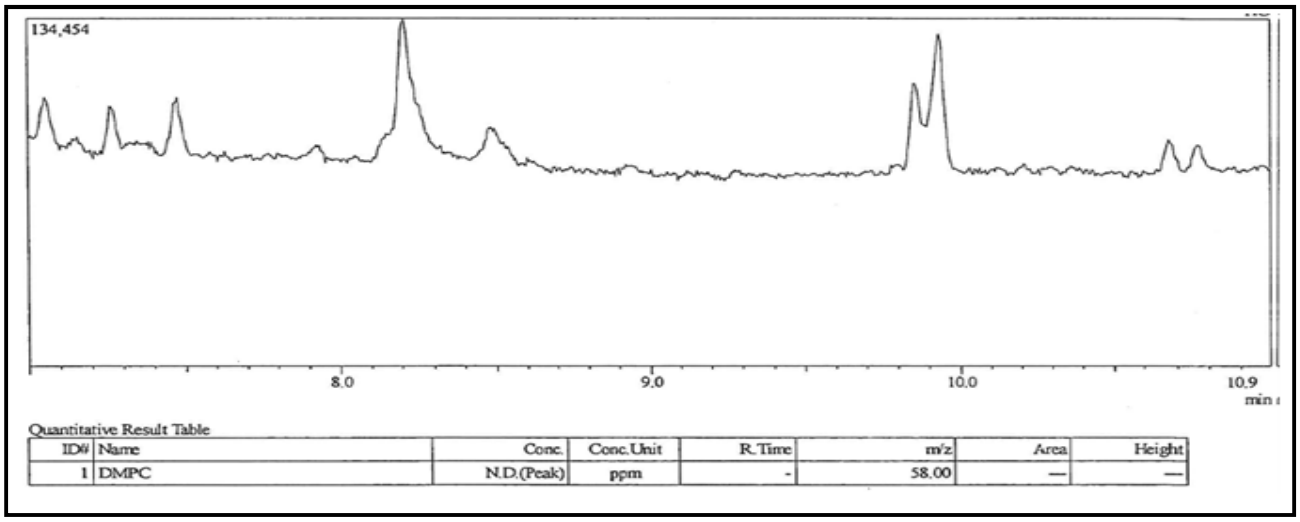


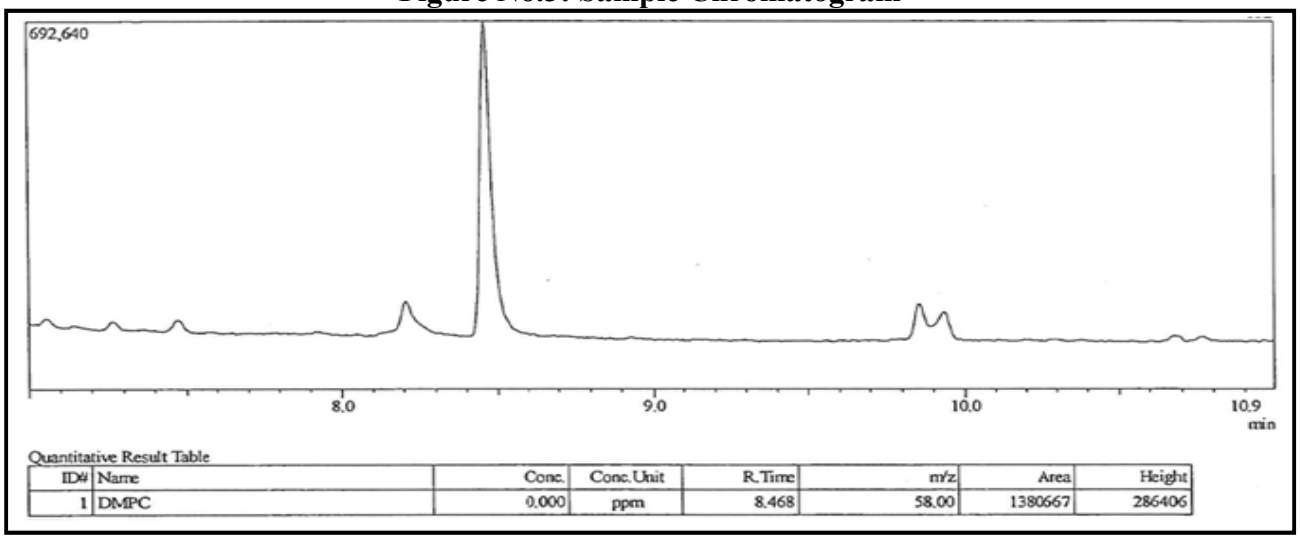
Figure No.2: Standard Chromatogram



Quantitative Result Table

ID#	Name	Conc.	Conc.Unit	R.Time	m/z	Area	Height
1	DMPC	N.D.(Peak)	ppm	-	58.00	—	—

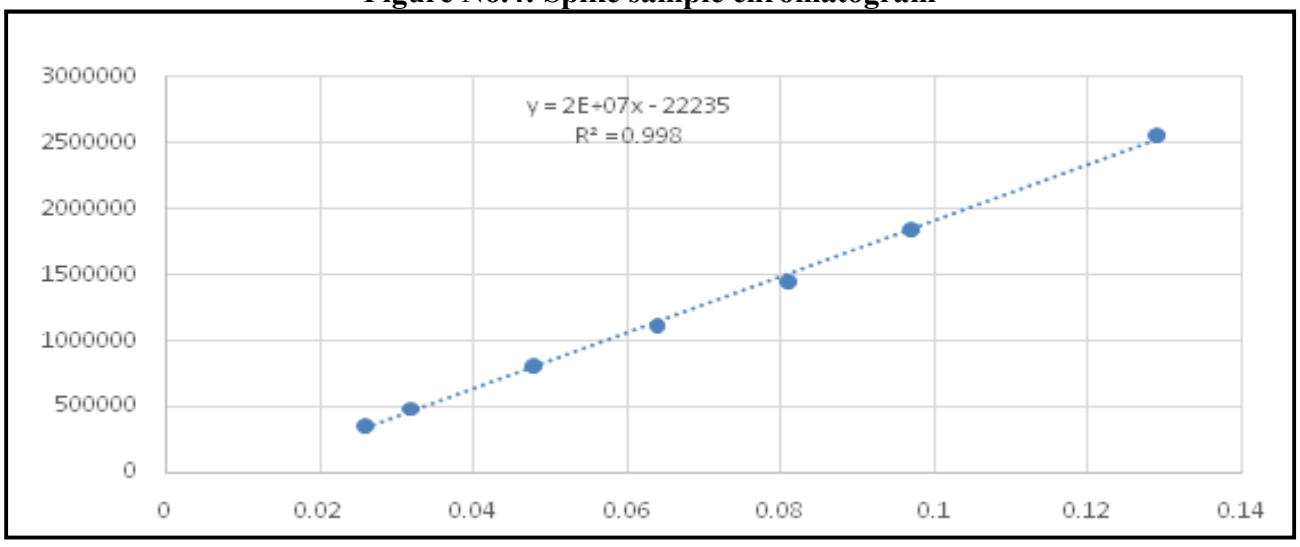
Figure No.3: Sample Chromatogram



Quantitative Result Table

ID#	Name	Conc.	Conc.Unit	R.Time	m/z	Area	Height
1	DMPC	0.000	ppm	8.468	58.00	1380667	286406

Figure No.4: Spike sample chromatogram



CONCLUSION

A simple and sensitive method for the determination N, N-Dimethylaminopropyl (DMPC) content in Clomipramine Hydrochloride drug substance by using GC-MS/MS was developed, validated and applied for the analysis of Clomipramine Hydrochloride drug substance samples. The sample of Clomipramine Hydrochloride drug substance was prepared with diluent. The present method was validated to secure the feasibility of the applied method for its application in day to day analysis. The limit of quantification observed by this technique were lower than the specification limit (TTC) of N, N-Dimethylaminopropyl (DMPC).

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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