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GAS CHROMATOGRAPHIC METHOD FOR THE ANALYSIS OF RELATED COMPOUNDS OF THE PRODUCT

3-CHLORO-N, N-DIMETHYLPROPAN-1-AMINE HYDROCHLORIDE

G.Kalpana*, Srinivasarao.Tumati [1], P.Govindhachowdary [2], D.Rajesh[3], B.Ramana Reddy[4]

* Research scholar Department of chemistry BEST Innovative University, Gownivaripalli, Gorantla, Andhra Pradesh 515231

1. Research supervisor Department of chemistry BEST Innovative University and Associate professor, department of Basic sciences& Humanities (Chemistry), Vignan institute of technology and science, Hyderabad. Corresponding author,prof.tumati@gmail.com

2. Associate professor, department of Basic sciences& Humanities (Chemistry), Vignan institute of technology and science, Hyderabad.

3. Associate professor department of chemistry, Joginpally B.R engineering college, Hyderabad.

4. Assistant professor, department of Basic sciences& Humanities (Chemistry), Vignan institute of technology and science, Hyderabad.

ABSTRACT

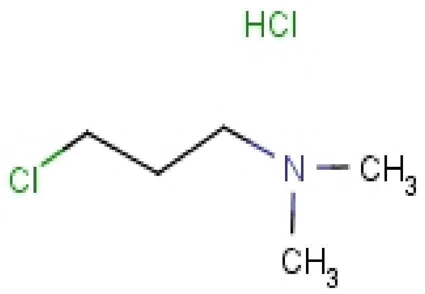
The chemical compound 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride also known as 3-Dimethyl amino propyl chloride hydrochloride. It's molecular formula is $C_5H_{12}ClN.HCl$ and it's molecular weight is 158.07.It is miscible with methanol.it is used as pharmaceutical intermediate and agriculture and chemical intermediate for the manufacture of various agriculture and chemical products and used if various research applications. Gas chromatography method is proposing for the determination of various related substance which are present in the 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride. This method is validated according to ICHQ2 (R2) guideline. The proposed method is simple and convenient for the Routine analysis of related substances which are present in the 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride.

Key words: 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride, miscible, Gas chromatography, ICHQ2 (R2) guideline.

INTRODUCTION

The chemical compound 3-chloro-N, N-Dimethyl propane-1-amine hydrochloride also known as 3-Dimethyl amino propyl chloride hydrochloride. is used mainly as a pharmaceutical intermediate[1] for the synthesis of many types of drugs and as an agricultural chemical intermediate. It is also used as a photographic chemical intermediate and as a biochemical reagent for enzyme and other studies. Its molecular formula is $C_5H_{12}ClN.HCl$ and molecular weight is 158.07.Gas chromatographic method is proposing for the determination of related substance which are present in the 3-chloro-N, N-Dimethyl propane-1-amine hydrochloride. These are Toluene, amino impurity, amino methyl impurity, tetra methyl impurity, unspecified impurity. In gas chromatography, detector used FID has few advantages which include the ease of operation, reliability, simplicity and versatility. FID detector will not detect signal for common carrier gases such as He, Ar, or N_2 or contaminants in such gases such as O_2 and H_2O.[2] FID connected with temperature programming device is easy to handle and is a best detector used for the routine analysis of organic compounds [3]. The main disadvantage of FID is its destructive nature, so it cannot be connected directly to other GC detectors. FID can be combined and used with other detectors if the carrier gas is split between the FID and the other detector [4]. A specific GC method was developed and validated for the determination of related substances. The literature search reveals that no analytical methods were reported for the quantification of impurities of 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride.

Structure of 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride



Determination of related compounds in house Gas chromatography method is proposing, for this used Gas chromatography instrument -make Agilent 7890A

Chemicals and Instruments: All chemicals and reagents used in this process is Analytical grade,

And Instrument is Agilent 7890A, software is Lab solutions. Glass ware is “A” grade

Methodology: Chromatographic conditions are selected based on literature review and trial and error method. Finally following Chromatographic conditions are selected for the analysis of related substances.

Chromatographic conditions

- Apparatus : A gas chromatography system equipped with FID (flame ionization detector)
- Column :DB-624 capillary column or equivalent
- Length : 75 mts
- ID : 0.53mm
- injection temperature: 220°C
- Split ratio :1:10
- Test and method of analysis
- Detector temperature : 260°C(FID)
- carrier gas : helium
- Air flow : 400 mL/min
- Hydrogen flow :40mL/min
- Make up gas flow(Nitrogen) : 30mL/min

- Injection volume :1.0mL
- diluent :Dichloromethane (AR grade)
- pressure :15.0 psi
- sample concentration :100.0mg/mL
- Pressure programming: The pressure is programmed according to following steps.
- 15 psi for 5 minutes, it is decreased to 4.5psi at the rate of 10 psi per minute and hold at 4.5 psi for 39.80 minutes
- Column oven programmed: Column temperature is programmed according to following steps.

Table A.

Rate	Temperature(°C)	Hold time(min)
-----	60	5
8	150	10
25	240	16

Toluene stock solution preparation:

Weigh about 50 mg of Toluene into a 10 ml volumetric flask ,add about 5 mL of diluent ,mix well and then dilute to volume with diluent and mix well.

Tetra methyl impurity stock solution preparation:

Weigh about 50 mg of Tetra methyl impurity into a 10 mL volumetric flask, add about 5 mL of diluent ,mix well and then dilute to volume with diluent and mix well.

Test and method of analysis

Preparation of amino impurity stock solution:

Weight about 50mg of amino impurity and transfer into a 50 ml volumetric flask add 10mL of 0.1N sodium hydroxide solution, shack well for 5minutes and dissolve it.

To this solution add exactly 10 mL of diluent and shake well for 5 minutes. Transfer this entire solution into a separating funnel and separate the organic layer (Lower layer).This organic layer allows standing for 5 minutes and then it will be formed clear solution .Use this clear solution as an amino impurity stock solution.

Amino methyl impurity stock solution preparation:

Weight accurately about 50 mg of amino methyl impurity in to a 50 mL volumetric flask, add 10 mL of 0.1N sodium hydroxide solution, shake well for 5 minutes and dissolve it.

To this solution add exactly 10 mL of diluent and shake well for 5 minutes. Transfer this entire solution in to separating funnel and separate the organic layer (lower layer).This organic layer allows standing for 5 minutes and then it will be formed clear solution. Use this clear solution as amino methyl impurity stock solution.

0.10%SST solution preparation:

Weigh accurately about 500 mg of standard in to a 50 mL volumetric flask, add 5mL of 0.1N sodium hydroxide solution, shake well for 5 minutes and dissolve it. To this solution add exactly and shake well for 5 minutes .transfer this entire solution in to a separating funnel and separate the organic layer (lower layer).Take 3 ml of this organic layer (standard solution) in to 5 mL volumetric flask ,then transfer 100µL of amino impurity stock solution, 100µL of amino methyl impurity stock solution , 100µL of Toluene stock solution and 100µL of tetra methyl impurity stock solution mix well and make up to the mark with same standard solution.

Acceptance criteria for standard solution:

1) Theoretical plates for 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride standard peak not be less than 3000.

2) Resolution between3-chloro-N,N-Dimethyl propan-1-amine hydrochloride and amino methyl impurity should not be less than 1.0

Standard solution preparation

Weigh accurately 500 mg of standard in to a 50 ml volumetric flask, add about 5mL of 0.1N sodium hydroxide solution, shake well for 5 minutes and dissolve it. To this solution add exactly 5 mL of diluent and shack well for 5 minutes .Transfer this entire solution into a separating funnel and separate the organic layer (lower layer).This organic layer allows stand for 5 minutes and then it will be formed clear solution .use this clear solution as a sample solution.

Preparation of sample solution

Weigh accurately 500 mg of test sample into a 50 mL volumetric flask, add about 5 mL of 0.1 N Sodium hydroxide solution, shake well for 5 minutes and dissolve it. To this solution add exactly 5mL of diluent and shake well for 5minutes.Transfer this entire solution into a separating funnel and separate the organic layer (lower layer).This organic layer allows stands for minutes and then it will be formed clear solution .Use this clear solution as a sample solution.

Note: Always use freshly prepared solution where ever required.

Procedure: Set up the Gas chromatographic system with the conditions mentioned and allow it to equilibrate the column.

System suitability:

The system suitability parameters were determined by the following method. Standard solutions were prepared as per the test method and injected into GC system. The system suitability parameters such as tailing factor, Theoretical plate and relative standard deviation for peak response of six replicate injections of standard solution were calculated and found to be within the limits.

Separately inject equal volume of Diluent as blank ,SST solution to test the system suitability teat criteria ,once system suitability test criteria pass , then inject diluent as blank , standard solution , sample solution and SST solution respectively into the gas chromatographic system , record the chromatograms and measure the peak responses.

Based on retention time of standard peak from standard solution, identify the sample peak retention time from sample solution .Calculate the impurities and total purity by area normalization method.

Total purity: 100-Total impurities (related substance by G.C)

Note: Total impurities are obtained from related substance by GC

ORDER OF INJECTIONS: Table-1

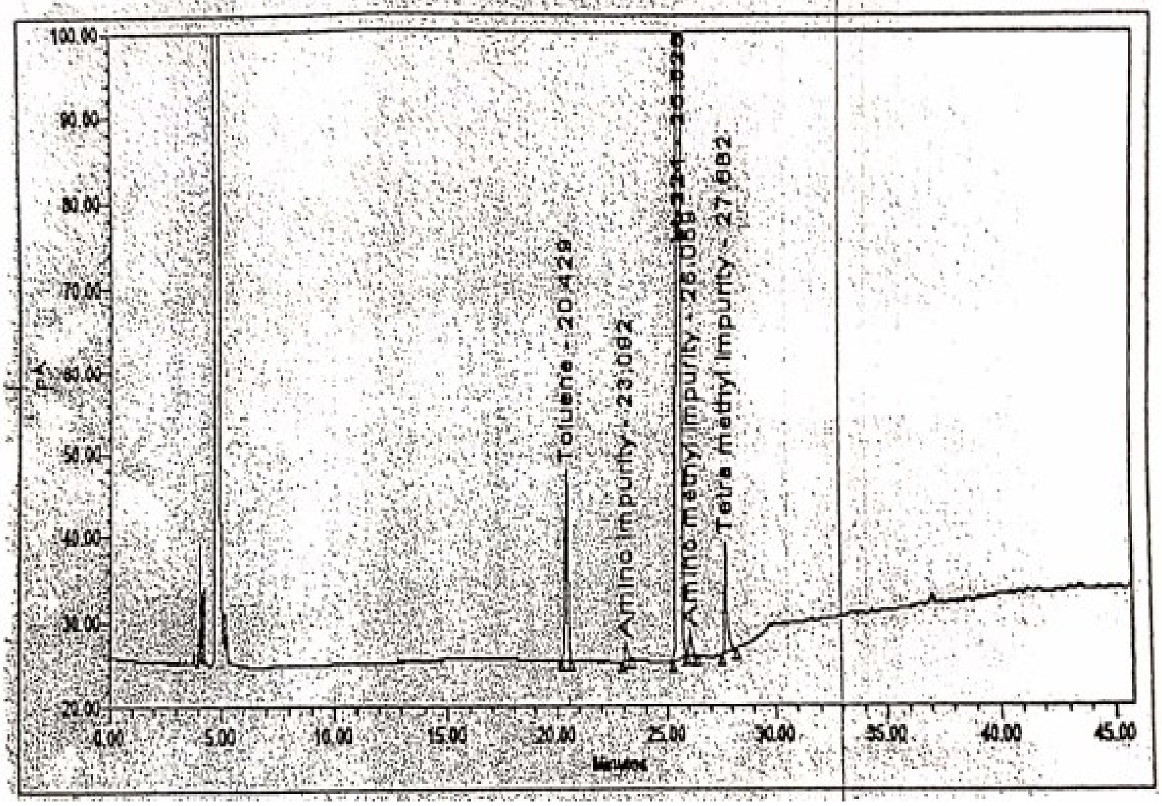
S.NO	SOLUTION NAME	NO OF INJECTIONS
1	Diluent as blank	1
2	SST solution	1
3	Diluent as blank	1
4	standard sample solution	1
5	test sample solution	1
6	SST solution	1

IMPURITY NAME, CHEMICAL NAME, RT, RRT&LOQ, Table-2

S.NO	NAME OF THE IMPURITY	CHEMICAL NAME	RT	RRT	LOQ IN %
1	M-224	3-chloro-N,N-dimethyl propan-1-amine hydrochloride	25.531	1.00	0.03
2	Toluene	Methyl benzene	20.437	0.80	0.002
3	Amino impurity	3-chloro propylamine HCl	23.089	0.90	0.070
4	Amino methyl impurity	N-methyl -3-chloropropyl amine HCl	26.060	1.02	0.041
5	Tetramethyl impurity	N1,N1,N3,N3- tetra methyl propane -1,3 -diamine impurity.	27.678	1.08	0.008

Note: The RRT’s variations can be allowed up to ±10%

TYPICAL CHROMATOGRAM OF M-224 SST SOLUTION



Method validation:

- Method validation is the process of establishing that an analytical procedure is suitable for its intended purpose.
- Method validation have to be performed according to ICH guidelines ICHQ2
- Validation parameters are:-
- Accuracy
- Precision
- Linearity
- LOD(limit of detection)
- LOQ(limit of quantification)
- Specificity
- Range

- Robustness.

Table -3 System suitability parameters. NMT Not more than, NLT not less than

System suitability parameters	Observed value	Acceptance criteria
The % RSD of six replicate standard injections	1.3	NMT 2.0%
The tailing factor for the 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride peak from the first standard injection	1.3	NMT 2.0
The Theoretical plate for the Sodium Valproate peak from the first standard injection	64,806	NLT 3000

Table 4 Precision results for 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride

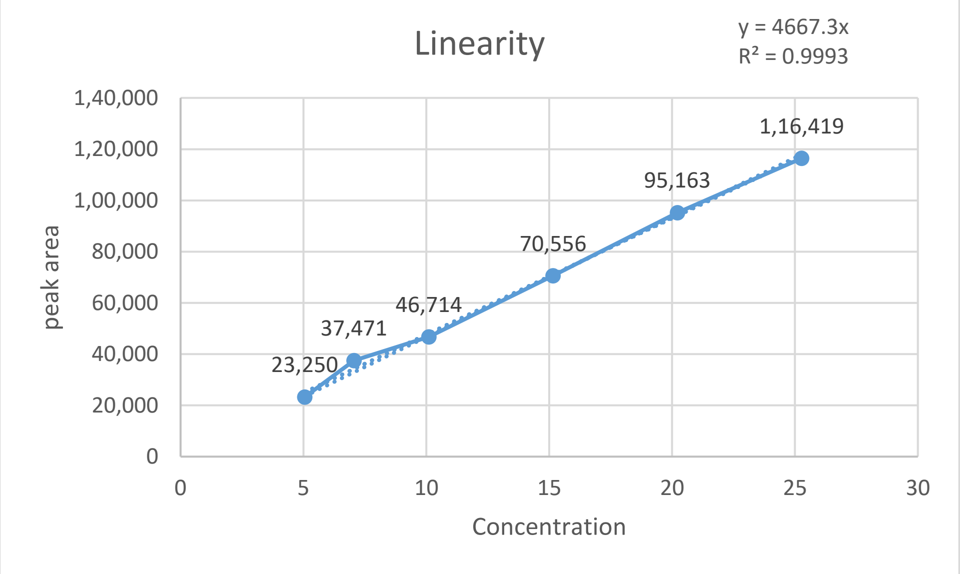
Injection no.	Peak area
01	46,474
02	47,395
03	46,519
04	45,581
05	46,362
06	46,182
Average	46,419
%RSD	1.3

Table 5 Specificity for 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride

Name of the peak	Retention time in minutes
3-chloro-N,N-Dimethyl propan-1-amine hydrochloride	5.3

Table 6 Linearity for 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride

% Level	Concentration in ppm	Area response
LOQ %	5.05	23,250
80%	7.08	37,471
100%	10.11	46,714
150%	15.16	70,556
200%	20.22	95,163
250%	25.27	116,419
Correlation coefficient	0.9963	



Discussion

This work aimed to develop an efficient optimized method for the determination of six process related impurities in 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride solution. Because of volatility, polar and ionic nature of 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride and its impurities, a GC method with FID by following liquid injection method was chosen. Trial experiments were conducted to select the suitable solvent for extraction using Dichloromethane and hence Dichloromethane was selected as extraction solvent. In addition, Dichloromethane is especially suitable for acidic extraction conditions. 0.1 N Sodium hydroxide solution was used to basify the 3-chloro-N,N-Dimethyl propan-1-amine hydrochloride sample solution. Finally, for extraction Dichloromethane was finalized with 0.1 N Sodium hydroxide solution. By using DB-624 capillary column or equivalent elution of analytes was investigated using helium as carrier gas, with the constant column pressure of 15.0 psi and keeping the column oven temperature initially 60 °C is maintained for 5 min and then increased to 150 °C at a rate of 10 °C/min, followed by holding at 240 °C for 16 min. From this experimental trial, it was observed that all analytes were not clearly separated. Satisfactory separation and better peak shapes were achieved within a reasonable time by flushing helium as the carrier gas with a constant pressure of 15psi and initial column oven temperature of 60 °C is maintained for 5 min and then increased to 150 °C at a rate of 10 °C/min, followed by holding at 240 °C for 16 min. The validation protocols such as accuracy, precision, linearity, specificity, sensitivity and robustness were observed to be within the acceptance limit. The correlation coefficient was within the acceptance criteria in the range of 0.9963**.** The evaluated concentrations for Sodium Valproate were in the ranges of 5.05–25.27 ppm. The average recovery values were in the range of 92.32– 101.48%. The validation parameters such as % RSD of six replicate standard injections found to be 1.3% was observed to be within the limit. The tailing factor for the 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride peak from the first standard injection was observed as 5.3 and was within the acceptance limit. The Theoretical plate for the 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride peak from the first standard injection was found to be 64,806 and was observed to be within the limit. Finally, a new novel optimized method was developed and validated, with better peak shape and satisfactory separation was achieved on chromatographic conditions.

Conclusion:

This proposed in house analytical method is simple, highly sensitive, cost effective, very convenient and validated. It is useful for the determination five related substances of the 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride using gas chromatography with FID. This method is use full for the routine analysis of determination of related substances and impurity profiles of 3-chloro-N, N-Dimethyl propane -1-amine hydrochloride, it is important reaction intermediate in various active pharmaceutical ingredients synthesis

Abbreviations:

GC: Gas Chromatography;

FID: Flame Ionization Detector;

RT: Retention time

RRT: Relative Retention time

LOQ: Limit of quantification;

RS: Related Substance;

ICH: International Council for Harmonization;

HCl: Hydrochloric acid;

% RSD: Relative Standard Deviation.

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Authors' contributions

All the authors have equally contributed to the article. All authors read and

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Availability of data and materials

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Declarations: Here with i am submitting research paper entitled

"GAS CHROMATOGRAPHIC METHOD FOR THE ANALYSIS OF RELATED COMPOUNDS OF THE PRODUCT3-CHLORO-N, N-DIMETHYLPROPAN-1-AMINE HYDROCHLORIDE" for publishing in your journal, this work is original, and this work is not incorporated / not published any journal, book, magazine

Corresponding Author; Dr.Srinivasarao.Tumati (On behalf of all authors)

Competing interest: I/We declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable

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