GCMS IMPURITY PROFILING OF METHYLENE CHLORIDE - A SOLVENT WIDELY USED IN PHARMACEUTICAL, ENVIRONMENTAL AND CHEMICAL INDUSTRIES

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ABSTRACT

- (GCMS) has gained broad usage in pharmaceutical. research because the technique supports qualitative and quantitative mits of detection. Methylene chloride is commonly used as an extraction inalvsis of organic molecules by GCMS. Production of ultrapure methylene chloride enge due to instrumentation advances leading to ever-lower analyte detection raw materials and the corresponding purified solvents by GCMS generates relevant information regarding the nature of the impurities and help to explore new strategies for producing Iltrapure methylene chloride
- k, GCMS was used to evaluate the impurity profile of raw methylene chloride from different sources as well as the finished product in order to track the movement and accumulation of impurities in the solvent through the distillation and packaging processes. Rotary evaporation was used to concentrate the solvent, 1000-fold for raw material and 4000-fold for distilled product. GCMS data were collected using Thermo Scientific Trace GC Ultra-MSQ instrument. Mass spectra of some of the impurity peaks were investigated further by collecting the fragment specific mass from their extracted ion chromatograms. The impurity peaks were identified by NIST library search.
- Solvents designated "GCMS grade" should provide low mass noise level and have minimal organic contamination to fulfill the high purity requirement of advanced GCMS instruments. The means to achieve this solvent designation has required manufacturing improvements for methylene chloride including additional purification processes, quality control measures, and packaging innovations resulting in extremely clean product for the highest end GC applications.

NTRODUCTION

Synthesis of Methylene Chloride

- The predominant method of manufacturing methylene chloride involves the reaction of hydrogen chloride and methanol to give methyl chloride as the first step.
- Excess methyl chloride is then subjected to thermal chlorination to generate methylene chloride. The thermal chlorination is usually carried out in gas phase. However, at lower temperature and high pressure the liquid phase process is capable of making high selectivity for methylene chloride (Rossberg et al. 1986 and Holbrook 1993).

Gas phase hydrochlorination $CH_{3}OH + HCl \longrightarrow CH_{3}Cl + H_{2}O$ Thermal chlorination

 $CH_{2}Cl + Cl_{2} \longrightarrow CH_{2}Cl_{2} + HCl$ www.dow.com www.ineoschlorvinyls.com

Common Impurities

- All of the chloromethanes are produced in this process. Common reported impurities in commercial products are hydrogen chloride, alcohols, small amounts of water and some decomposition products such as formaldehyde (Kadish and Anderson 1987)
- An older method of methylene chloride production involves direct reaction of excess methane with chlorine at high temperature (400 - 500°C), or at somewhat lower temperatures either catalytically or photo-catalytically. Several longer chain chlorocarbon compounds may remain in the product due to impurities in methane reactant (Kadish and Anderson 1987).
- In methylene chloride trace amounts of degradation compounds are well documented (Hine 1950 and Middleditch 1989). Addition of small amounts of stabilizer helps to prevent degradation of methylene chloride. Common stabilizers used are double bonded compounds such as amylene and cyclohexene which quench the free radicals formed during long term storage.
- The free radical formation leads to photochemical reaction of methylene chloride itself even under the influence of long-wave UV light (Mikheev et al. 1976).

Solvent Applications

- Methvlene chloride is used in many extraction methods where isolation and concentration of organic constituents is necessary. In several EPA methods (e.g. EPA507, 508, 608, 1699, 8270, 8290), methylene chloride is the solvent of choice for extraction of slightly • • • The GC-MS standard was run at 4 ppm concentration. The six peaks were as follows: water soluble organic molecules before analysis using GC, GC-MS, or HPLC-MS.
- In order to meet the requirements of high sensitivity instruments and to detect trace level of analytes in various environmental, pharmaceutical, cosmetic, and food samples, ultrapure methylene chloride is required in order to attain an interference-free base line for GC-MS.
- Several QC check points are utilized in order to identify and monitor the impurity profile during the course of processing and packaging this ultrapure solvent.

MATERIALS AND METHODS

Purification Process

- Methylene chloride raw material from two suppliers was delivered by dedicated tank truck to the processing plant in Fair Lawn, NJ.
- Distillation was carried out in a dedicated still (Figure 1) and the distillate stored in a dedicated receiver before packaging. Finished product (D151 Optima Methylene Chloride) was delivered by dedicated line to amber glass bottle or stainless steel FisherPak

Sample Preparation

- Raw material: 1000 mL of methylene chloride raw material was concentrated to about 1 mL using a rotary evaporator, and the material transferred to a GC vial using a glass transfer pipette.
- Pure product: 4000 mL of purified methylene chloride solvent was concentrated to about 1 mL using a rotary evaporator and transferred to a GC vial using a glass transfer pipette.
- Identification of the impurity peaks were performed using GC-MS technique (Figure 2).

GC-MS Standards

• GC-MS standard mix - Supelco Supelpreme-HC Internal Standard Mix Cat. No. 4-8902 (2000 μg/mL). The internal standard mix is recommended for EPA8270 semi-volatile internal standard mix.





Results

0 4

Internal Standard RT (min)	Mass (m/z)	Compound
~ 8.17	150.07	D4 - 1,4-dichlorobenzene
~ 9.73	136.20	D8 - Naphthalene
~ 11.84	164.21	D10 - Acenaphthene
~ 13.58	188.22	D10 - Phenanthrene
~ 16.81	240.12	D12 - Chrysene
~ 19.56	264.26	D12 - Perylene

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The impurity profile of methylene chloride	e raw materials differs between suppliers	, also from lot to lot for the same supplier.

- NIST library search showed similarity with long chain hydrocarbons for these impurity peaks. Other impurity peaks are provided in

- (Figure 7)
- identifications are shown in Figures 9-11.



Thermo Scientific Trace GC-Ultra-ISQ system equipped with RSH auto sampler and a temperature programmable 1310 Trace GC oven. • • 30 m x 0.25 mm x 0.25 micron TR1-GC gold column (Thermo Scientific) at a flow rate of 1 mL/min



• Figure 3 shows the raw material from supplier # 1 containing impurity peaks primarily in the 5 to 11 minutes region. Two of the impurity peaks in TIC are observed at 5.9 and 7.5 minutes as m/z 126 and m/z 140, respectively. Extracted ion chromatogram (EIC) of m/z 126 also showed the peak at 5.9 minutes. EIC of m/z 140 showed a cluster of peaks at 7.5 minutes and 10.4 - 10.6 minutes region.

• Table 2 provides impurity data for a different lot of raw material from supplier #2 and the impurity profile found was very different. Most of the impurity peaks were in the 12.5 to 14 minutes region.

• In Figure 4, a recent lot of raw material from supplier #1 and the corresponding purified product is shown.

• • Figures 5 and 6 show the raw materials and corresponding purified product from supplier # 2 for two different lots. At a 4000-fold concentration, no impurity peaks were observed in the purified solvent (Figure 5).

• The impurity peaks found between 11.8 and 13.6 minutes are artifacts, and were observed to disappear with column baking

• Figure 8 and Table 3 summarize the impurity profile for three different lots of raw material from supplier #2. The EIC and peak



Table '	1. Impurity P	rofile - Supp	olier #1 Raw	Material Febru

RT	m/z	Probable compound from NIST library
	(observed)	
5.7	111.34	3,5,5,-trimethylhexene (MW 126
5.88	126.3	2,5,5-trimethylhexene
5.95	126.39	2,3-Dimethyl-3-heptene
6.24	144.2	1,2,3,-tricloro-propene
6.46	140.24	2-secbutyl-cyclopntanone
6.8	140.42	2-secbutyl-cyclopntanone – isome
7.23	140.19	Pentamethyl-cyclopentane
7.56	140.37	2,4,4-trimethyl-hexene
7.62	140.25	3,7-Dimethyl-2-Octene
8.19	152.32	2,4,4-trimethyl-hexene
8.38	154.38	Isovaleric anhydride
10.43	140.11	Trimethyl-dodecane
10.48	140.25	Trimethyl-dodecane
10.68	140.12	2,2,-Dimethyl-3-octene
10.71	140.12	2,2,-Dimethyl-3-octene
11.01	140.34	2,2,-Dimethyl-3-octene
12.27	177.04	Diethylphthalate (MW222)
12.53	226.22	Hexadecane

RT (min)	observe m/z	Probable compound from NIST Library s
5.94	126.4	trimethyl hexene
7.34	140.38	?
7.63	140.56	3-methyl-6-methylene-octane
7.96	152.43	?
10.43	140.43	Trimethyl-dodecane
10.48	140.5	Isomer?
10.68	140.34	Isomer?
10.72	140.38	2, 2-dimethyl-3-octene
12.28	222.4	Diethylphthalate
12.5	218.39	1-methyl-nonyl-benzene
12.7	232.39	1-butyl-heptyl-benzene
12.77	232.46	1-propyl-octyl-benzene
12.9	232.46	1-ethyl-nonyl-benzene
13.1	232.52	1-methyl-decyl-benzene
13.23	246.49	1-pentyl-heptyl-benzene
13.26	246.55	1-propyl-nonyl-benzene
13.33	246.55	1-propyl-nonyl-benzene
13.46	246.56	1-ethyl-decyl-benzene
13.66	246.5	Isomers?
13.77	260.5	1-pentyl-Octyl-benzene
13.8	260.41	1-butyl-nonyl-benzene
14	260.54	Isomers?
14.19	260.41	Isomers?









9.04 0.31 134.20 *O-Cymene*

9.12 0.20 134.12 *m*-Cymene

9.35 0.14 134.20 Tetramethyl-benzene

(min) 6.61 9.34 104.24 Styrene 12.30 104.10

6.64 12.30 104.10 Cyclooctatetraene/styren

 8.27
 64.91
 112.16
 2-ethyl-1-hexanol

 8.42
 13.45
 108.09
 2-methyl-Phenol



CONCLUSIONS

- Lot to lot variation of impurity peaks is observed for methylene chloride raw material.
- The impurity profile differs widely between the two suppliers of raw material.
- Identification of impurity peaks from each lot helps to adjust the strategy for producing an ultrapure grade of methylene chloride.
- Even with a wide variation in the type of impurities coupled with high amounts of impurity in the raw solvent, our purification process produced an interference-free base line in GC-MS for D151 Optima Methylene Chloride.
- This is the first report of commercially available methylene chloride tested using a 4000-fold concentration to identify trace impurity peaks. Our results show that D151 Methylene Chloride meets the ultra high purity criteria needed for trace analysis using today's advanced GC-MS instrumentation
- Validation of Fisher D151 Optima Methylene Chloride according to NIOSH* protocol was performed by SKC Inc. (Fiore et al. 2013). *NIOSH: National Institute for Occupational Safety and Health

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