Ultrapure Methylene Chloride for Interference-Free Analytical Work

Subhra Bhattacharya, Eric Oliver, Mark Jasko, Deva H. Puranam, and Stephen C. Roemer
Thermo Fisher Scientific – Global Chemicals, One Reagent Lane, Fair Lawn, NJ

Abstract

Methylene chloride is widely used as an extraction solvent for trace analysis in pharmaceutical, environmental, food, and chemical industries. With instrumentation advances leading to ever-lower analyte detection limits, we have implemented a quality by design (QBD) approach to produce a grade of methylene chloride that will provide interference-free analysis. Achieving this level of solvent quality has required manufacturing improvements which include an allowable impurity profile for raw material, additional purification processes, stringent quality control measures, and packaging innovations resulting in extremely clean product for trace analytical work. With respect to the environmental industry, use of methylene chloride for extracting slightly water soluble organic constituents is reported in several EPA methods (EPA 500, 600 and 8000 series). To mimic the extraction of trace level analytes using ultrapure solvent, neat samples of methylene chloride were spiked with parts per trillion of lindane and the recovery of lindane was assessed with different concentration processes such as rotary evaporator, Kuderna-Danish (K-D) apparatus, and a combination of both. Gas chromatography hyphenated with various detector systems (GC-MS, GC-ECD, and GC-FID) found that ultrapure methylene chloride produced an interference-free baseline during trace analysis of standards such as lindane. Our QBD approach ensures the consistent production of ultrapure methylene chloride meeting all purity specifications not only "at the time of manufacturing" but when the analyst first opens the container.

Introduction

We implemented a quality by design (QBD) concept to manufacture ultrapure methylene chloride (DCM) for interference-free analytical work. A quality solvent should be free of impurities and show batch to batch consistency.

Steps to Follow to Comply With QBD Approach[1]

- Identify critical impurities in raw materials
- Identify critical process parameters
- Process understanding by a combination of prior experience and new experiment
- Establish a control strategy for the entire process, including raw material controls, process controls and monitors, and product testing at multiple stages of operation
- Continually monitor and update the process to ensure consistent quality

Matrices of QBD Approach

Raw Materials

- Multiple lots of raw material from different suppliers are tested using GC-MS
- Each lot of raw material is tested before processing
- We observed wide variation in quality of raw material not only from supplier to supplier, but also lot to lot from same supplier
- Amount of impurity in raw material is a crucial factor to determine the processing control

Manufacturing Process

- Based on raw material quality, the manufacturing process (Fig. 1) is adjusted to achieve the best quality product (details are proprietary and not disclosed)

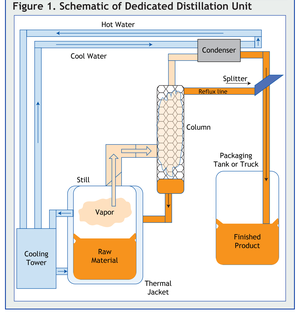
Final Product

- Final products are tested utilizing high end GC-MS, GC-FID, and GC-ECD instrumentation and validated test methods

Product Performance

- Stability study of high purity methylene chloride was performed to check product quality after extended time in amber glass bottle and stainless steel returnable container
- Comparative study of competitors' solvents was conducted to benchmark the quality of Fisher Chemical methylene chloride

Figure 1. Schematic of Dedicated Distillation Unit



Materials and Methods

Standards

GC-ECD Standard

- Ultra Scientific Cat. No. US-102BN (2000 µg/mL). Organochlorine pesticide mixture suitable for EPA 508

GC-MS Standard

- Supelco Supelpreme-HC Internal Standard Mix, Cat. No. 4-8902 (2000 µg/mL). This internal standard mix is recommended for EPA 8270 semi-volatile standards (Table 1).

GC-FID Standard

- Sigma-Aldrich, EPA 525 semi-volatiles calibration mix without pesticides, Cat. No. 506540

Lindane Standard (for spiking)

- Ultra Scientific, Cat. No. EPA-1079

Solvents

- Fisher Chemical, methylene chloride (DCM), D151 Optima grade and D154 GC Resolv grade
- Fisher Chemical, hexane, H306 Optima grade

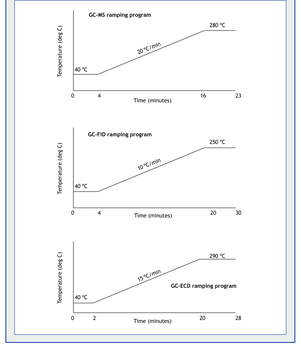
GC Column

- Thermo Scientific TR-1 Gold, 30 m x 0.25 mm x 0.25 µm for GC-MS
- Thermo Scientific TR-5 MS, 30 m x 0.25 mm x 1 µm for GC-ECD and GC-FID

Other Parameters

- Carrier Gas: Helium
- Injector Temp: 220 °C
- Injection Volume: 1 µl
- Injection Mode: Split-less
- Split Flow: 50 mL/min after 1 min
- GC run conditions are provided in Fig. 2

Figure. 2. GC Run Conditions



Results

- Variation in the GC-MS impurity profile was observed from lot to lot in DCM raw material from same supplier (Fig. 3).
- Quality variation in DCM from supplier to supplier was also observed (Fig. 4).
- Table 2 shows the impurity ID from NIST library search for several peaks in raw DCM from three suppliers.
- A method for the analysis of trace pesticide residues in purified DCM was performed by spiking parts per trillion amount of lindane. More than 98% spike recovery was accomplished after 1000 to 1 concentration using a Rotavap/Kurdana-Danish combination method[2] (Table 3).
- Chromatogram of EPA 508 standard in purified DCM revealed no pesticide related impurity peaks present in the solvent (Fig. 5).
- Using QBD approach, processing consistency from lot to lot of DCM was demonstrated by GC-MS (Fig. 6).
- Packaging improvements for high purity DCM (D151 and D154) in amber glass bottle sustained the product quality (Fig. 7).
- Stability of ultrapure DCM was demonstrated after 10 month storage in stainless steel returnable container (Fig. 8).
- Competitors' DCM showed impurities by GC-MS and GC-FID that were absent in the improved Fisher Chemical DCM (Figs. 9 and 10).

Table 1. GC-MS Standard Was Run at 4 ppm Concentration. The Six Compounds in the Standard Were as Follows:

Internal Standard RT (min)	Mass (m/z)	Compound
~8.03 – 8.24	150.07	D4 – 1,4-dichlorobenzene
~9.61 – 9.73	136.2	D8 - Naphthalene
~11.73 – 11.84	164.21	D10 - Acenaphthene
~13.47 – 13.58	188.22	D10 - Phenanthrene
~16.69 – 16.83	240.12	D12 - Chrysene
~19.33 – 19.57	264.26	D12 - Perylene

Figure 3. Lot to Lot Variation of DCM Raw Material From Same Supplier by GC-MS

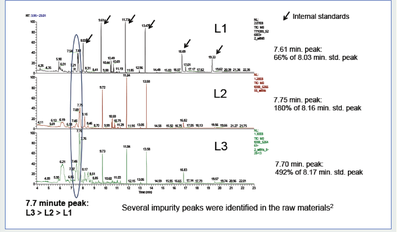


Figure 4. Raw DCM From Three Suppliers Showed Different Impurity Profiles

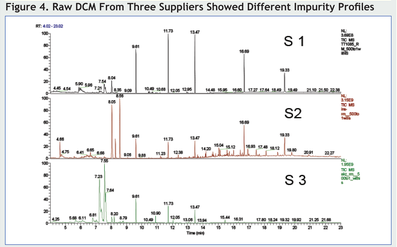


Table 2. Impurity Identification From NIST Library Search

Observed m/z					Observed m/z				
RT (min)	S1	S2	S3	NIST Search Result	RT (min)	S1	S2	S3	NIST Search Result
4.46			132	trichloroethane	7.21	140	140	140	pentamethyl cyclopentate
4.66		91		Toluene	7.33	140		140	2,2,-dimethyl-3-octene
4.75		92		cycloheptatriene	7.54	126	140	140	2,4,4-trimethyl-hexene
5.28		100		3-hexene-1-ol	7.64	140		140	3-ethyl-2,5-dimethyl-3-hexene
5.58		96		Furfural	7.96			137	?
5.7	111		126	3,5,5-trimethyl hexene	8.05		146		1,4-dichlorobenzane
5.94	126			4,4,5-trimethyl-2-hexene	8.28		130		2-ethyl-1hexanol
5.96			166	Tetrachloroethane	8.31			154	?
6.08		126		4-ethyl-3-heptene	8.56		107		0-Toludene
6.22		126		2,3-dimethyl-3-heptene	10.44		210		?
6.41		126		Isomer?	10.49		210		?
6.56		126		Nonene	10.68		280		?
6.65		104		Styrene	10.72		280		?
6.8	112			2-sec-butyl-3-methyl-1-pentene	12.37		189		?
6.96		126		2,3-dimethyl-2-heptene	14.16		268		?
7.02	140			trimethylheptene	14.2		270		?
					15.04		296		?

S1, S2, S3 – three suppliers

Common to all suppliers | S2 only

Table 3. Percent Recovery of Lindane Spike in DCM After Concentration Using Rotavap/KD Hybrid Method[2] as Determined by GC-ECD

	1000 mL to 0.5 mL Concentration		1000 mL to 1 mL Concentration	
Sample	Recovery Amount (ppb)	% Recovery	Recovery Amount (ppb)	% Recovery
1	17.993	89.97	9.89	98.88
2	17.919	89.55	9.98	99.84
3	15.772	78.86	9.88	98.75
Mean		86.13		99.16
SD		6.3		0.6

SD = standard deviation.
In both experiments, 2 x 10 mL hexane exchange was performed.
Rotavap/KD hybrid with a 1000:1 concentration is the preferred sample preparation method.

Figure 5. Ultrapure DCM Concentrated by Hybrid Method (1000 to 1) and Compared With EPA 508 Standard Using GC-ECD

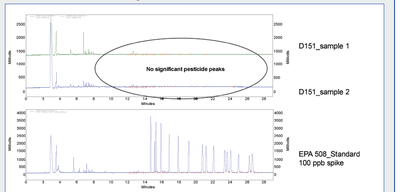


Figure 6. Lot to Lot Consistency in GC-MS for Purified DCM

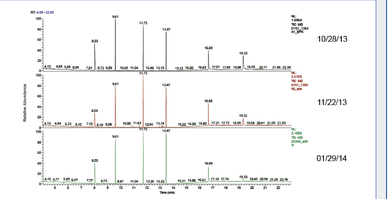


Figure 7. Improved Packaging in Glass Bottle Sustained DCM Quality

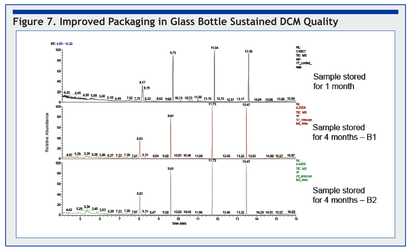


Figure 8. DCM Stability Data in Stainless Steel Returnable Container

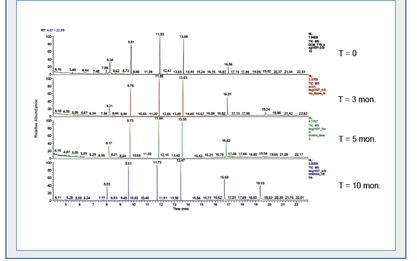


Figure 9. GC-MS Analysis of Competitors' Purified DCM

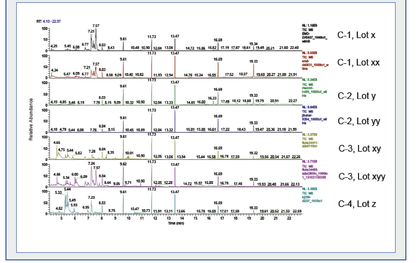
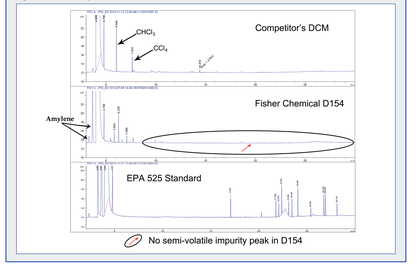


Figure 10. Comparison of GC-FID Data



Discussion

- We observed wide variation of impurity amount in raw material from the same supplier (Fig. 3). The amount of impurity peaks with respect to amount of internal standard was computed as 66% to about 500%.
- Testing each lot of raw DCM is important with respect to adjusting the process parameters. Careful adjustment of those parameters allowed consistent production of high quality finished product (Figs. 5 and 6).
- The raw DCM from different suppliers showed different impurity profiles although the same chemical (amylene) was used to stabilize the raw material (Fig. 4 and Table 2). The middle panel (S2) of Fig. 4 showed a number of aromatic compounds as impurity. One impurity peak at 8.05 minutes was identified as 1,4-dichlorobenzene (co-eluting with an internal standard at 8.03 minutes). The amount of this impurity peak was observed about 25 ppm and this impurity was difficult to remove because of the semi-volatile nature of the compound. This impurity was not found in the DCM from other two suppliers.
- In order to assess the quality of the purified DCM, we concentrated the solvent and then analyzed it using standards (Table 1 and Figs. 5, 6, and 10). To check the integrity of the solvent during evaporation, we added 10 ppt of lindane per liter of DCM and concentrated the spiked solution. A 1000-fold concentration of spiked solvent (1000 ml down to 1 ml) showed a more consistent recovery of >98% by GC-ECD (Table 3).
- No significant impurity peaks were observed by GC-ECD between 10 to 25 minutes where pesticide peaks per EPA 508 are eluted (Fig. 5).
- Purified DCM showed lot to lot consistency and some representative lots are shown in Fig. 6.
- We also improved the packaging of DCM in glass bottle and found that the solvent quality was sustained during shelf-life study (Fig. 7).
- An extended stability study was performed for the storage of DCM in stainless steel returnable container. The quality of DCM was maintained for at least 10 months (Fig. 8).
- DCM from four other competitors was also tested (Figs. 9 and 10). Most showed a number of early eluting impurity peaks in GC-MS under our analysis conditions (Fig. 9). In GC-FID, no semi-volatile impurity peak was detected per EPA 525 standard and the Fisher Chemical D154 was observed superior.

References

1. Quality by Design: Concepts for ANDAs., Lionberger et al., *The AAPS Journal* (2008), 10, 268.
2. GCMS Impurity Profiling of Methylene Chloride — A Solvent Widely Used in Pharmaceutical, Environmental and Chemical Industries, Poster presented in 246th ACS Fall Meeting, Indianapolis, September 8 — 12, 2013.
3. Detecting Trace Amounts of Impurity in Methylene Chloride — Sample Preparation Matters, Poster presented in Eastern Analytical Symposium, Somerset (NJ), November 18 — 20, 2013.