Pharmaceutical QA/QC: Residual Solvents by USP <467> and Analyzing Leachable Organics in Formulations

Agilent Science and Technology Symposium

May 2014

Residual Solvents by USP <467>

Method Overview

Residual Solvents
Application Overview

- Organic Volatile Impurities (OVI's) include organic chemicals used to manufacture of active pharmaceutical ingredients (APIs), products or excipients.
- Refer to the amount of organic solvent not removed during purification of the final drug product
- Monitored for safety and/or environmental reasons and for their effect on the final product
  - May effect solubility, stability or bioavailability
- Residual solvent levels are controlled (USP, ICH, EP)

Residual Solvents

Compound Classifications Based on Risk to Human Health

Class 1 Residual Solvents: Solvents to be Avoided

- Known human carcinogens
- Strongly suspected human carcinogens
- Environmental hazards

Class 2 Residual Solvents: Solvents to be Limited

- Non-genotoxic animal carcinogens, or possible causative agents of other irreversible toxicity, such as neurotoxicity
- Solvents suspected of other significant but reversible toxicities.

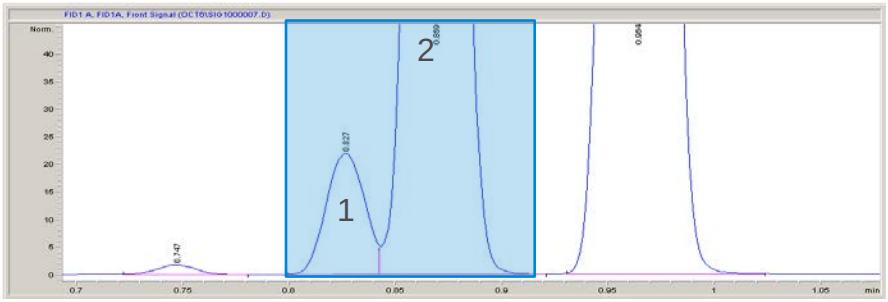
Class 3 Residual Solvents: Solvents with Low Potential Toxicity

- Solvents with low toxic potential to humans; no health-based exposure limit required

Residual Solvents
USP 467, Procedure A

First procedure to run determine residual solvent identified exceeds permitted daily exposure (PDE) limit

- Procedure A uses a 624 phase column
- Requires resolution for Acetonitrile and Methylene chloride ≥ 1
- Class 1 compounds require signal to noise ≥ 3
- 1,1,1 Trichloroethane S/N ≥ 5



USP requirement: *R* =1 or greater

1. Acetonitrile
2. Methylene chloride

Residual Solvents
USP 467, Procedure B

- Require when residual solvent identified above the permitted daily exposure (PDE) limit
- Procedure B uses a Wax phase with a different selectivity
- Requires resolution of acetonitrile and cis-dichloroethene ≥ 1
- Class 1 benzene signal to ≥ 5
- If limit is exceed and confirmed by Procedure B, analyte must be quantified using Procedure C
  - Uses G43 or G16 phase depending on which gives best separation

GPD Analyzers: Residual Solvents by USP <467>

Sensitive, Robust and Reproducible Analysis

Target Analyzers for 2014
Focusing on High Volume Opportunities for G3445B Systems

Pharmaceutical USP <467>

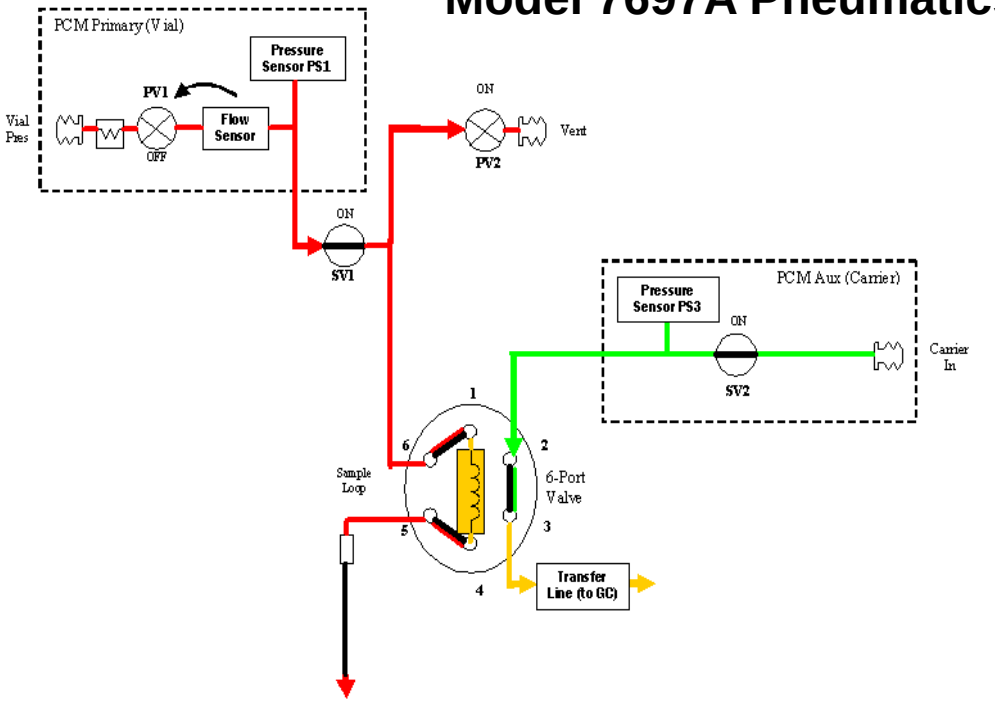
- Residual Solvents GC/FID/MS (481)
- Residual Solvents GC/FID (681)
- Residual Solvents GC/FID/FID (682)

Model 7697A Vial Sampling Pneumatics
Designed to minimize carryover

Model 7697A Features

- Inert Sample pathway with fused silica transfer line
- Advanced EPC controlled vial sampling
- Optimized thermal zones with uniform heating
- 111 Vial capacity with three priority positions
- Integrated bar code reader
- Method optimization tools
- Compatibility with hydrogen
- Automatic vial leak test
- Integrated Headspace Control Software

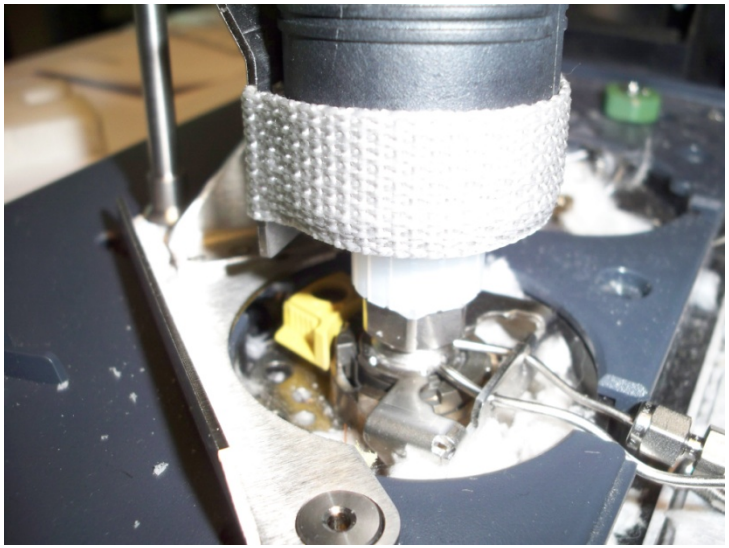
Model 7697A Pneumatics



- PCM Pneumatics allow sampling at pressures above ambient
- Improves sampling efficiency
- Eliminates Carry Over

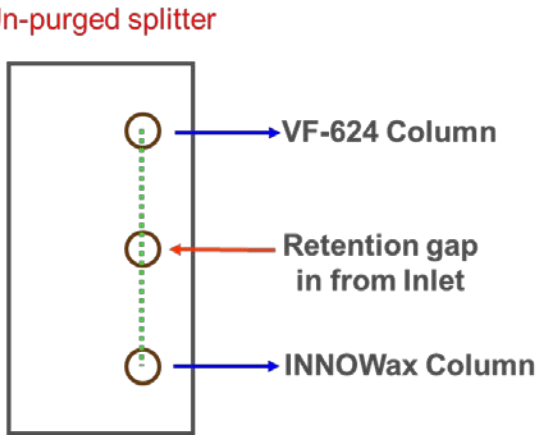
GC/FID/FID Configuration for USP 467

Reproducible transfer from the headspace sampler



Split/Splitless connection to HSP

- Ultra Inert Transfer Line (0.53 mm)
- Deactivated used silica inserted through septum
- Ultra Inert Liner (1 mm)



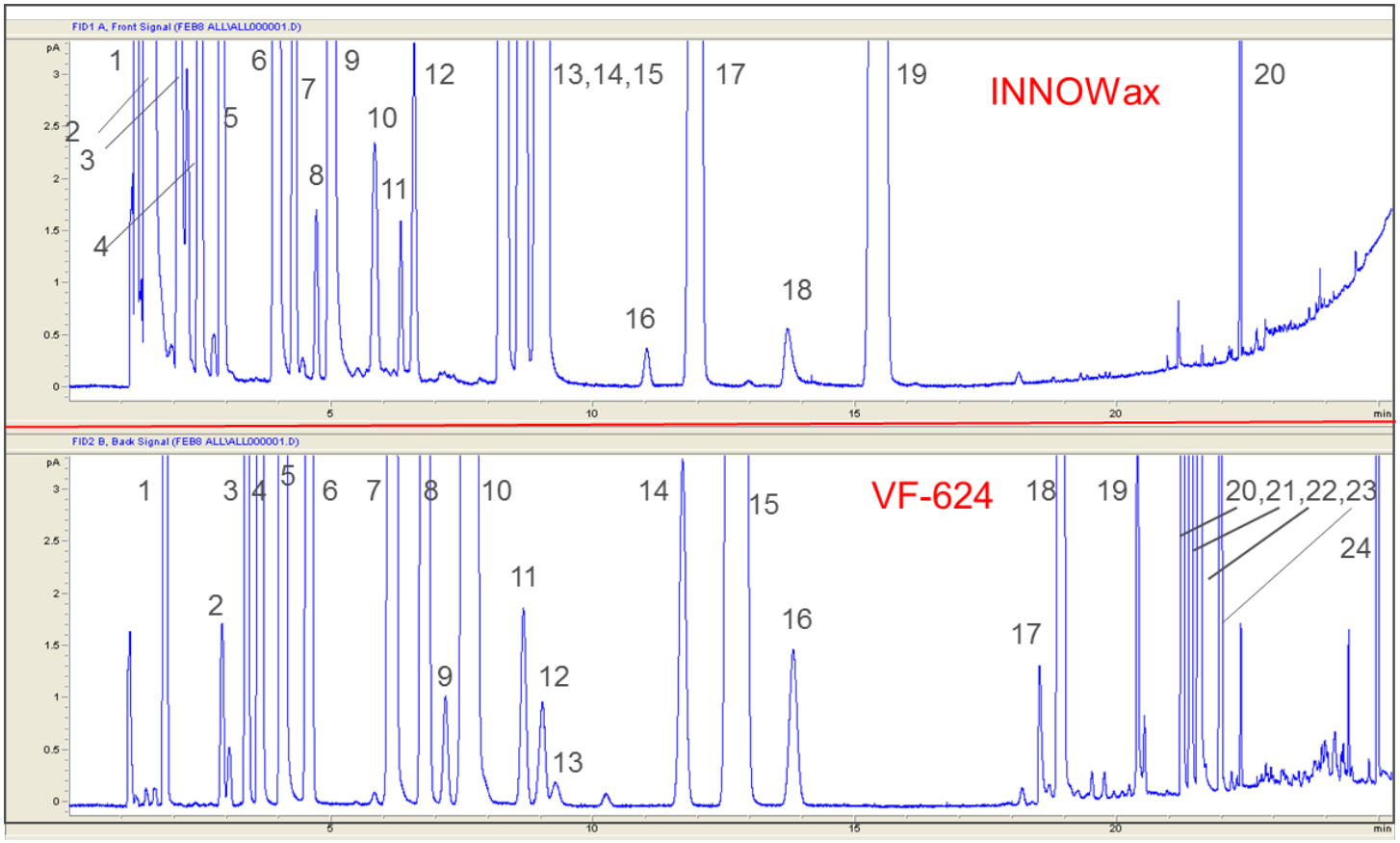
Capillary Flow Technology (CFT) Splitter

- EPC Controlled Flow Split provides reproducible flow to both columns
- Leak free connections
- Improved repeatability and reproducibility

Performance Advantage

UPS <467> Analysis by GC/FID/FID

All Classes, Volatiles Interface, 20ml Vials



INNOWax Column

1. Hexane
2. Cyclohexane, Methycyclohexane, 1,1 dichloroethene
3. Trans 1,2 dichloroethene, THF, 1,1,1 trichloroethane, Carbon tetrachloride
4. Methanol, 1,2 dimethyoxyethane
5. Methylene chloride, Benzene
6. Cis 1,2 dichloroethene, Trichloroethene
7. Acetonitrile
8. Chloroform
9. Toluene
10. 1,4 dioxane
11. 1,2 dichloroethane
12. 2-hexanone
13. Ethylbenzene
14. p-xylene
15. m-xylene,
16. Nitromethane (not seen)
17. o-xylene
18. Pyridine
19. Chlorobenzene
20. Tetralin

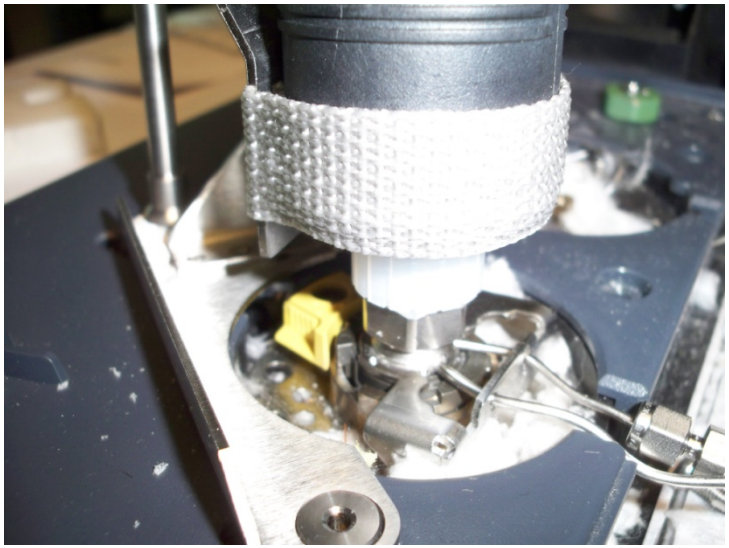
VF-624 Column

1. Methanol
2. 1,1 dichloroethene
3. Acetonitrile
4. Methylene chloride
5. Trans-1,2 dichloroethene
6. Hexane
7. Cis-1,2 dichloroethene, nitromethane
8. Tetrahydrofuran
9. Chloroform
10. Cyclohexane, Carbon tetrachloride, 1,1,1-trichloroethane
11. Benzene
12. 1,2 dichloroethane
13. 1,2 dimethoxyethane
14. Trichloroethene
15. Methycyclohexane
16. 1,4 dioxane
17. Pyridine
18. Toluene
19. 2-hexanone
20. Chlorobenzene
21. Ethylbenzene
22. m, p-xylene
23. o-xylene
24. Tetralin

7890 oven program: 35 C (17 min) to 240 C (5 min) @ 20 C/min

GC/FID/MS Configuration for USP 467

Reproducible transfer from the headspace sampler



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Capillary Flow Technology (CFT) Splitter

- EPC Controlled Flow Split provides reproducible flow from one column to both dectetors
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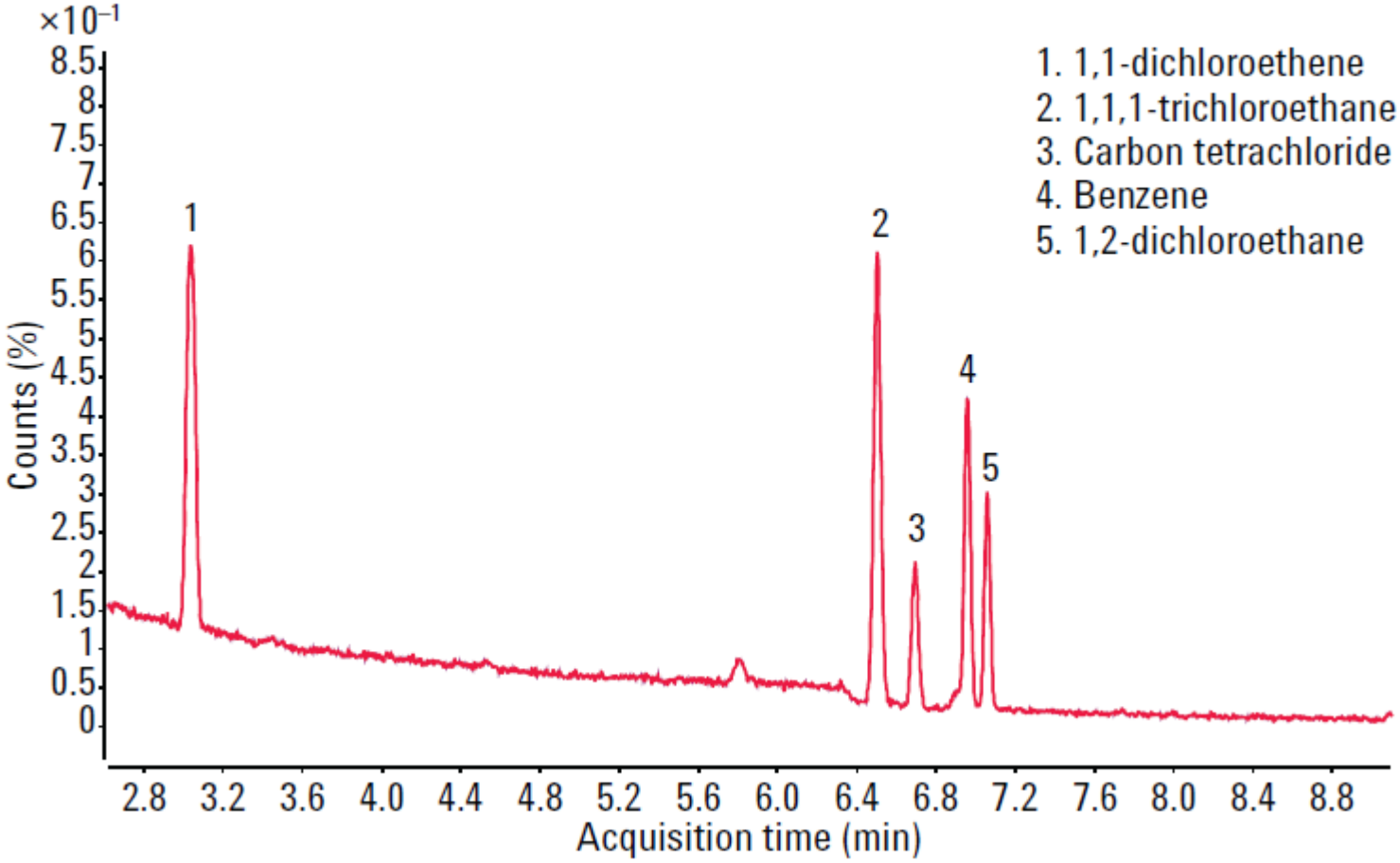
- Improved repeatability and reproducibility

Performance Advantage

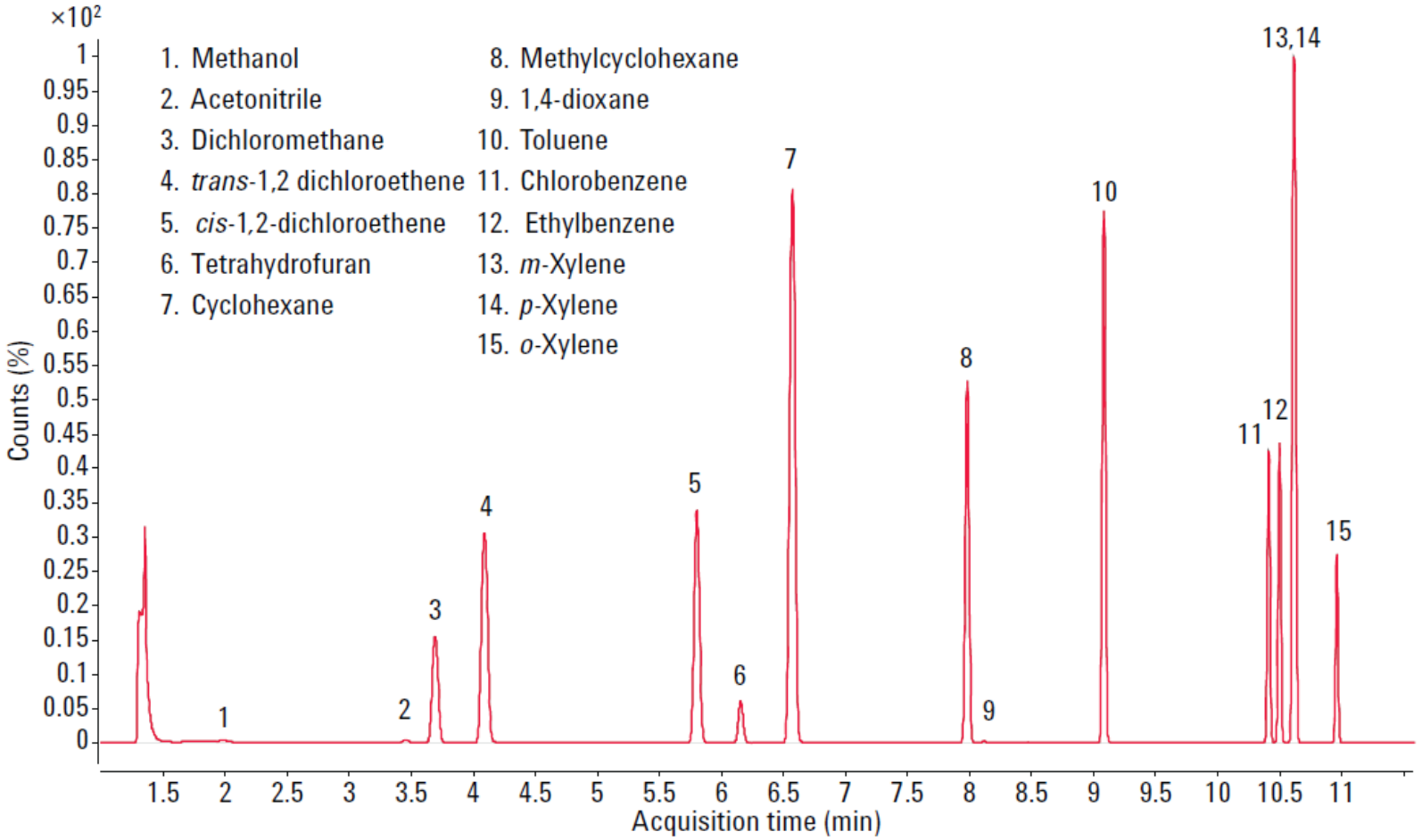
TIC for Class 1 Residuals Solvents

Detected at their limit concentrations

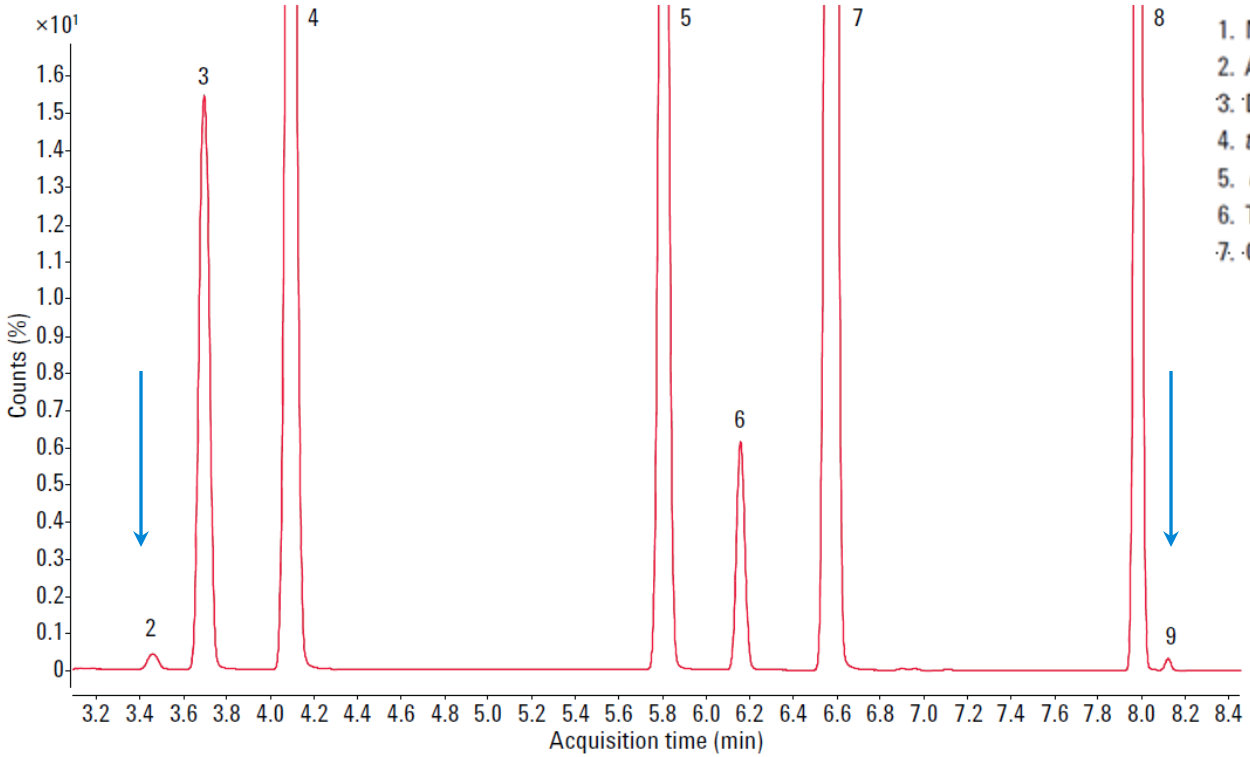


TIC for Class 2A Solvents

Detected at their limit concentrations



TIC for Class 2A Solvents
Zoom for Acetonitrile and 1,4-Dioxane

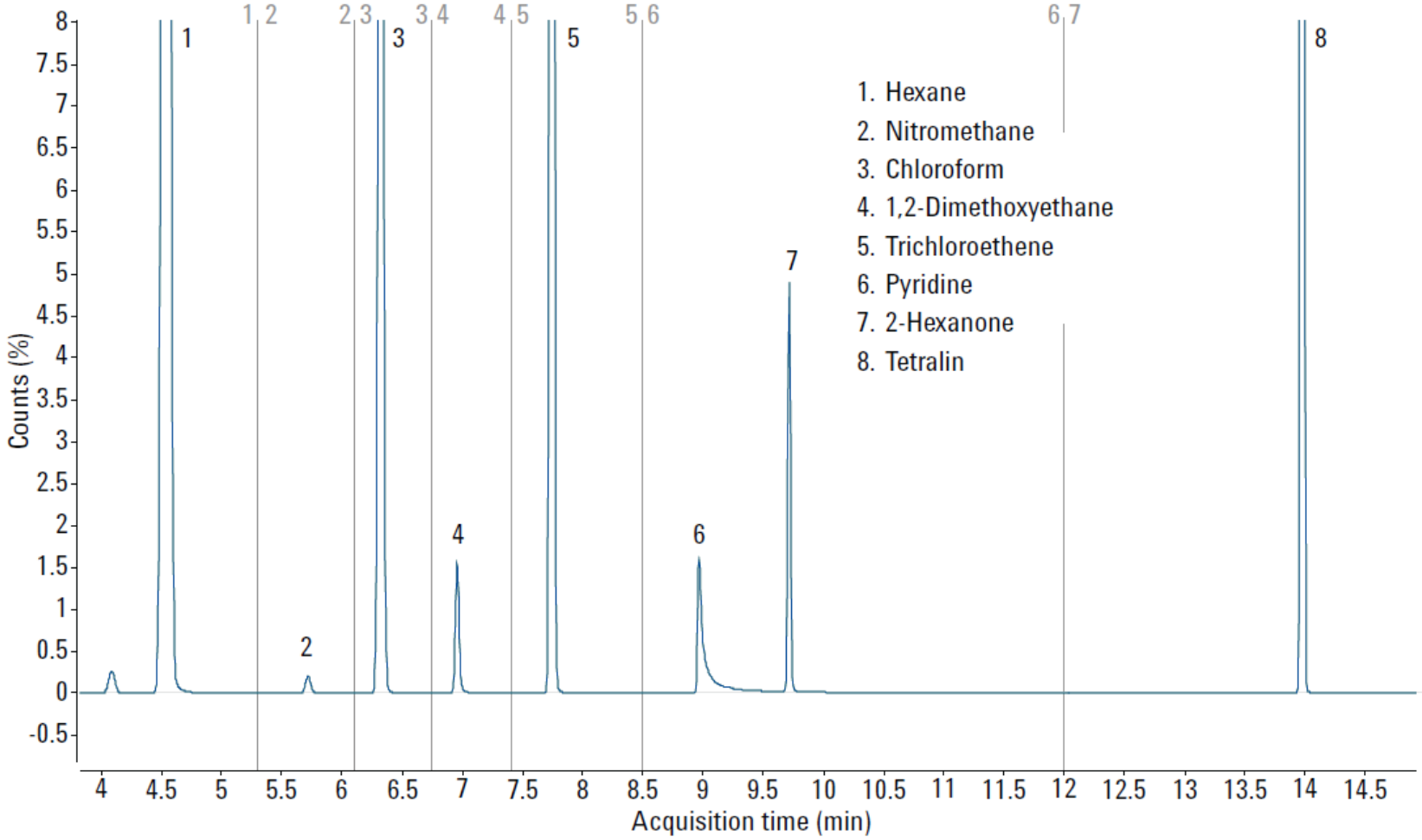


1. Methanol
2. Acetonitrile
3. Dichloromethane
4. *trans*-1,2 dichloroethene
5. *cis*-1,2-dichloroethene
6. Tetrahydrofuran
7. Cyclohexane
8. Methylcyclohexane
9. 1,4-dioxane
10. Toluene
11. Chlorobenzene
12. Ethylbenzene
13. *m*-Xylene
14. *p*-Xylene
15. *o*-Xylene

Figure 4. A zoom in on the chromatogram to illustrate compounds with low response, acetonitrile and 1,4-Dioxane. Refer to Figure 3 for peak numbers.

TIC for Class 2B Solvents

Detected at their limit concentrations



Repeatability for Scan Data
Class 1 Class 2A and Class 2B Solvents

Compounds	UPSP Limit (ppm)	Scan RSD (%)	SIM RSD (%)
Class 1 n=8			
1,1 dichloroethene	8	0.9	
1,1,1 trichloroethane	1,500	1.9	
Carbon tetrachloride	4	1.5	
Benzene	2	0.7	
1,2 dichloroethane	5	0.9	

Compounds	UPSP Limit (ppm)	Scan RSD (%)	SIM RSD (%)
Class 2A n=9			
Hexane	290	3.2	
Nitromethane	50	3.8	
Chloroform	60	2.5	
1,2 dimethoxyethane	100	2.7	
Trichloroethene	80	2.5	
Pyridine	200	3.9	
2-hexanone	50	2.4	
Tetralin	100	2.5	

Compounds	UPSP Limit (ppm)	Scan RSD (%)	SIM RSD (%)
Class 2A n=10			
Methanol	3,000	2.8	2.4
Acetonitrile	410	3.3	2.3
Dichloromethane	600	2.5	2.2
trans-1,2 dichloroethene	1,870	2.4	2.2
cis-1,2 dichloroethene	1,870	2.1	2.1
Tetrahydrofuran	720	3.0	2.2
Cyclohexene	3,880	2.7	1.3
Methycyclohexane	1,180	4.3	1.6
1,4 Dioxane	380	2.6	2.3
Toluene	890	0.7	2.0
Chlorobenze	360	1.9	2.1
Ethylbenzene	2,170	1.9	2.1
m-Xylene, *p*-Xylene	2,170	2.1	1.8
o-Xylene	2,170	2.1	1.8

USP <467> System Suitability

All configurations meet these requirements:

Procedure A

- S/N for 1,1,1-trichlorethane >5
- S/N of all Class 1 solvents >3
- Resolution of Acetonitrile and methylene chloride >1.0

Procedure B

- S/N of Benzene >5
- S/N of all Class 1 solvents >3
- Resolution of Acetonitrile and trichloroethylene>3

Residual Solvent Analysis
Technology for Enhanced Performance

Superior HSS thermal management – Outstanding repeatability

- Thermal zones with set-point stability of better than +/- 0.1 C
- Need/loop consistent thermal setup with vial zone
- EPC equipped with ambient temperature compensation

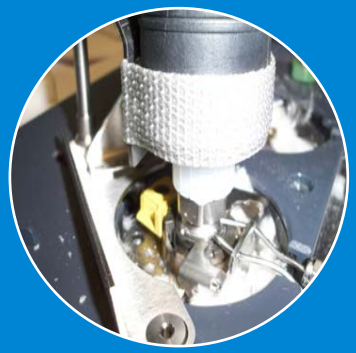
Superior HSS/GC pneumatic control -- Eliminated carryover

- User programmable needle/loop purge are used for effectively system cleaning between runs.
- Vial sampling pressure and backpressure under precise EPC control

CFT splitter for dual channel – Outstanding Performance

- Replaces problematic two hole ferrules or “Y” splitters
- Precise reproducible split of sample between columns

USP <467> Residual Solvent Analyzers
Value Overview

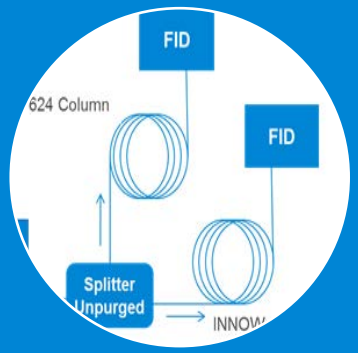


Headspace Sampler Coupled to S/SL Inlet

- Outstanding
- Inert sample path,
- Thermal zones with set-point stability ±0.1 C,
- EPC sampling ctrl.

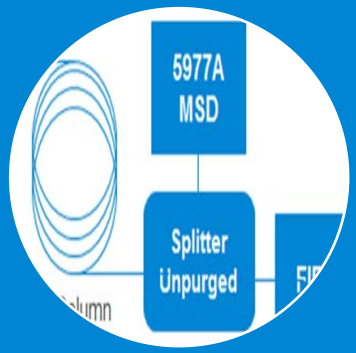
CFT Splitter

- Replaces two hole ferrules or “Y” splitters
- Precise reproducible split between columns or detectors
- Reproducible and repeatable data



Dual Column-Dual FID Configuration

- Provides quantitation and confirmation on with a single injection
- Dissimilar columns provide different retention times



GC/FID/MS Configuration

- Provides quantitation and confirmation with a single injection
- FID Quantitation
- MSD Confirmation

All configurations meet System Suitability Requirements for USP <467>

Determination of Extractable and Leachable Organics in Pharmaceutical Packaging Materials

HSS/GC/MS Analysis

Extractable and Leachable Organics Analysis
Application Overview

Extractable:

- Chemical substances obtained by exposing packaging to a variety of solvents under exaggerated incubation conditions of time and temperature

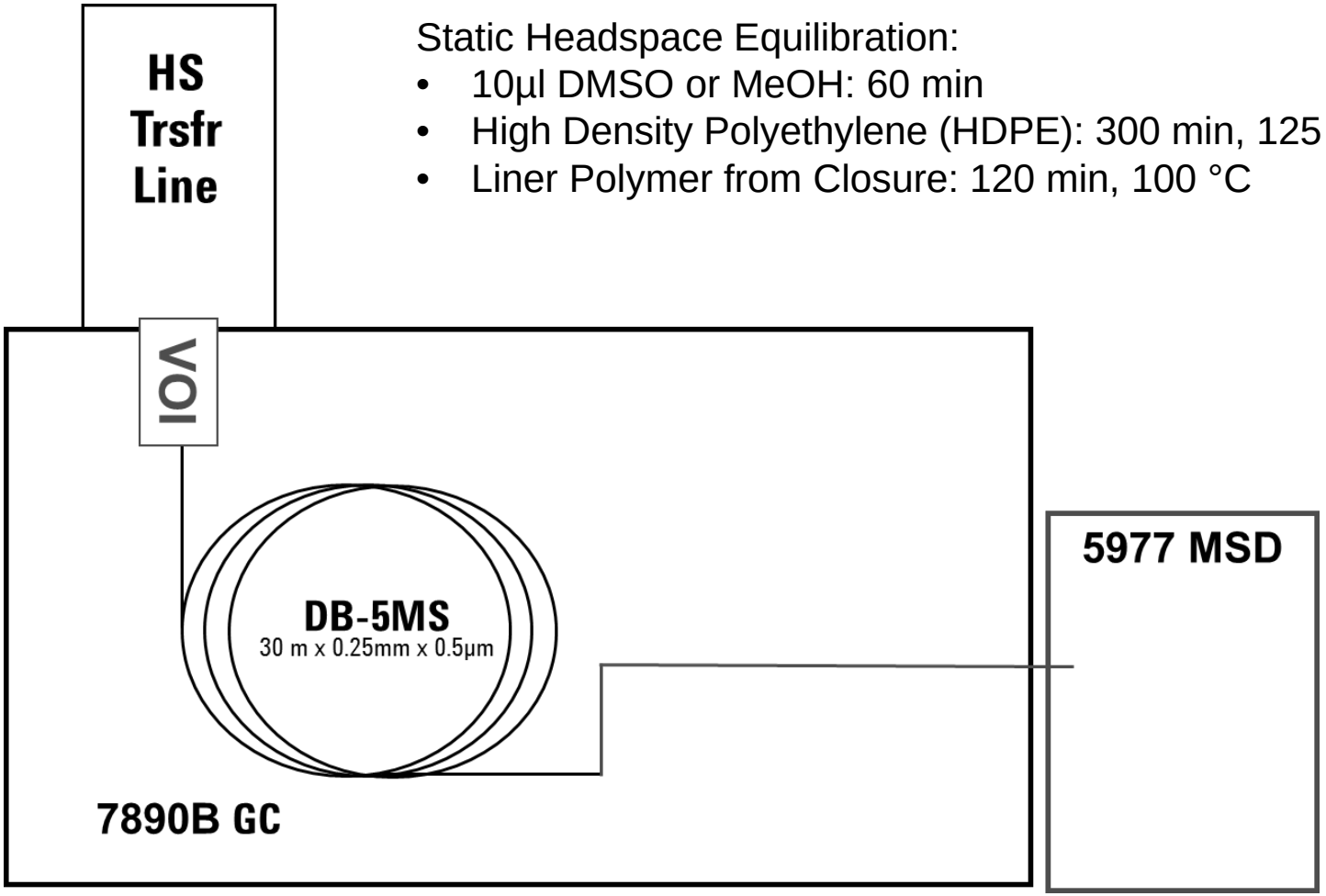
Leachable

- Chemical Substances that migrate under normal condition of use from the CCS into a drug product.

Typical Compounds

- Polymer residual monomers, additives (plasticizers, phenolic oxidants, UV stabilizers, colorants, catalysts), laminate adhesives, inks, epoxides, urethanes acrylates and polyesters

Extractable and Leachable Organics Analysis
Typical System configuration HSS/GC/MS



Static Headspace Equilibration:

- 10µl DMSO or MeOH: 60 min
- High Density Polyethylene (HDPE): 300 min, 125 °C
- Liner Polymer from Closure: 120 min, 100 °C

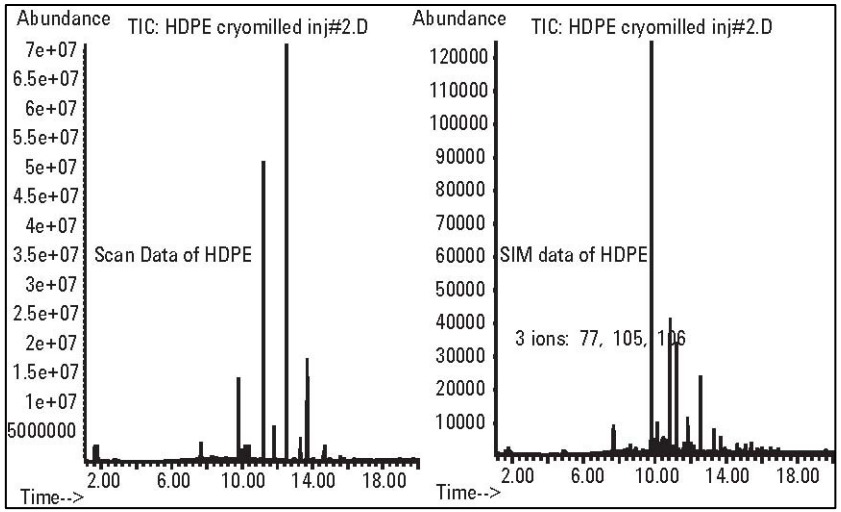
Extractable and Leachable Organics Analysis
Typical System configuration HSS/GC/MS

Static Headspace Equilibration:
- 10µl DMSO or MeOH: 60 min
- High Density Polyethylene (HDPE): 300 min, 125 °C
- Liner Polymer from Closure: 120 min, 100 °C

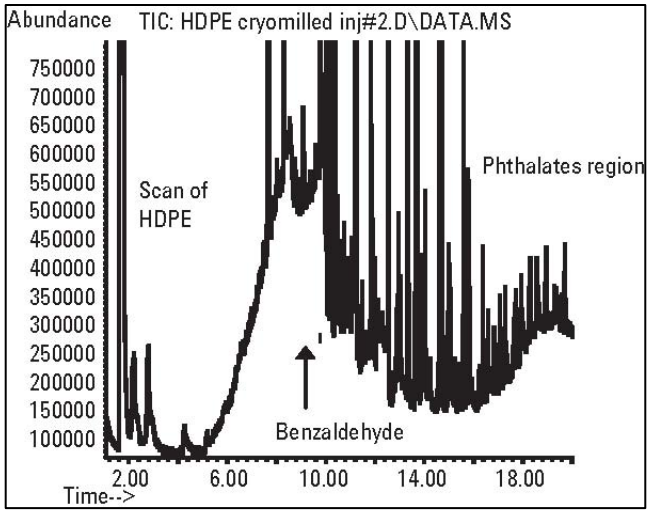
Static Headspace Extraction:
- Partition between condensed and gas phase
- Multiple Headspace Extraction (MHE) technique used
  - Single extraction will not force all analyte into headspace
  - Calculates highest attainable amount of extractable compounds that could be concentrated in the drug

Equilibration temperatures below melting point for materials

Extractable and Leachable Organics Analysis
Experimental Results

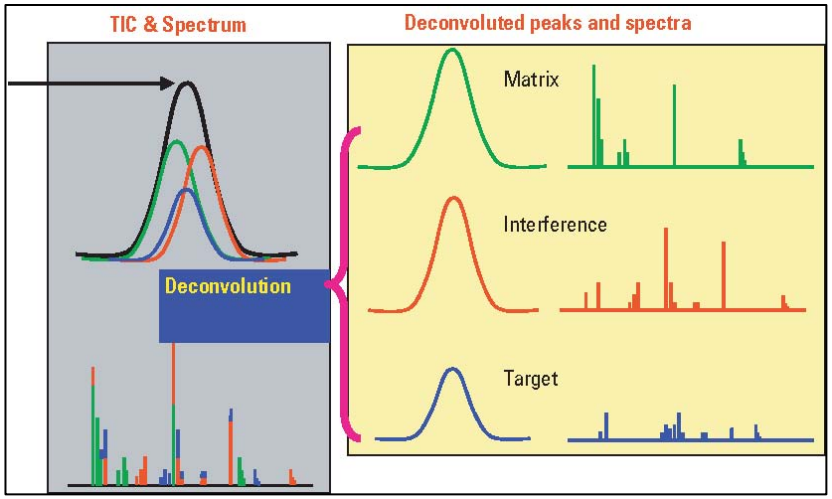


Synchronous Sim/SCAN data: 0.208 g sample of cryo-milled HPDE polymer

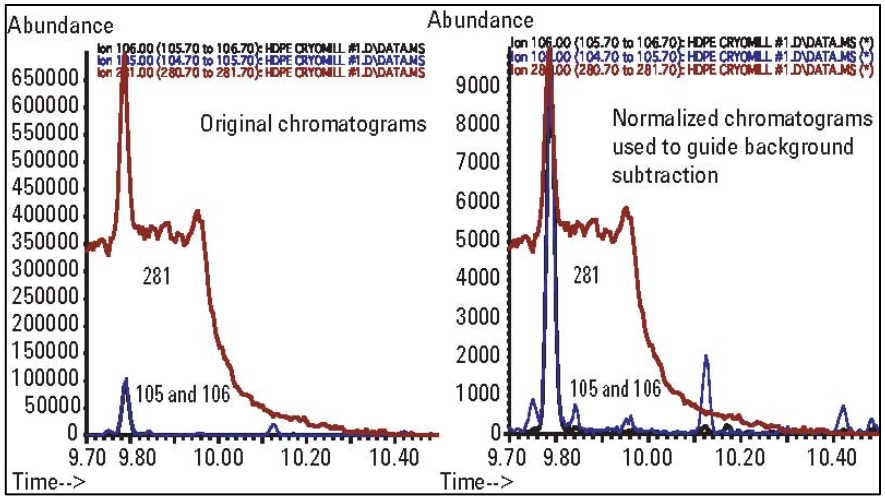


Enlargement of Scan Data from HPDE Sample

Extractable and Leachable Organics Analysis
Experimental Results

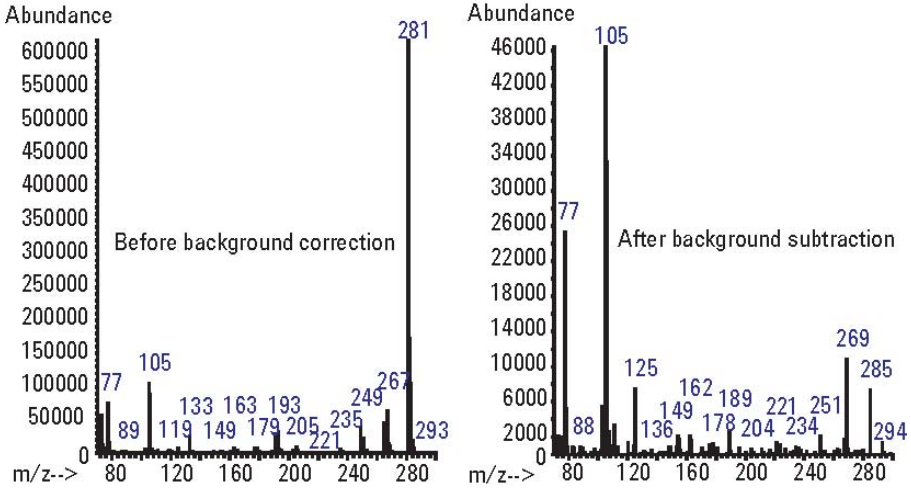


AMDIS Deconvolution pulls out individual components and their spectra

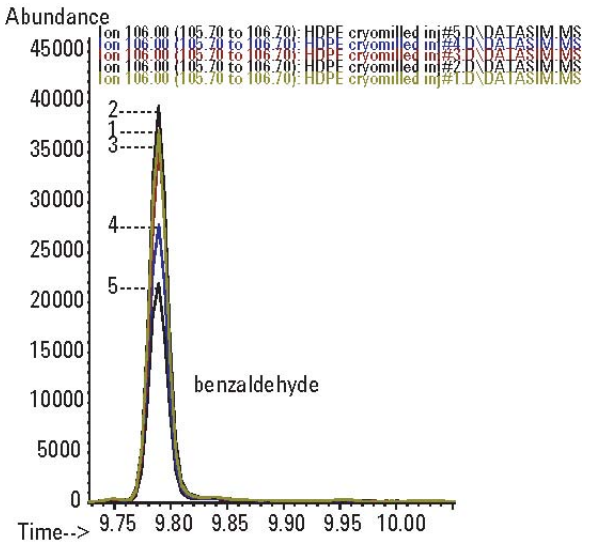


MS Deconvolution attempted for peak at 9.8 min

Extractable and Leachable Organics Analysis
Experimental Results



Spectrum for peak at 9.8 min before and after background subtraction



Multiple headspace extraction data for benzaldehyde peak from HDPE (Number by peak represent extraction number)

Extractable and Leachable Organics Analysis
Experimental Results Benzaldehyde in HDPE

Benzaldehyde in 0.208 grams of HDPE polymer (cryomilled)					
extraction #	**sample**	**standard**		standard	stats
1	126081	90157		0.821008	108302.5
2	129433	72611		0.004898	0.016243
3	118095	58834		0.998153	0.015487
4	98261	49099		1621.638	3
5	84345	40898		0.388965	0.00072
6	68811	32992			
7	56676	27095		sample	stats
8	45872	22746		0.897668	151819.2
				0.023684	0.078551
regression correlation (E4 or E11)	0.873825502	0.998153435		0.873826	0.074896
slope (k) = ln(E2 or E9)	-0.107955422	-0.197222062		20.7766	3
				0.116544	0.016828
total area = (A(1)/(1-e(-k)))	1232073	503694			
analyte in vial (mg)	0.026906838	0.011			
sample amt (mg) in vial	208				
concentration (ppm) in wt/wt	129.36				
concentration (wt-%)=ppm * (10 ^ -4)	0.0856				

MHE Raw Data

Extractable and Leachable Organics Analysis
Experimental Results Benzaldehyde in HDPE

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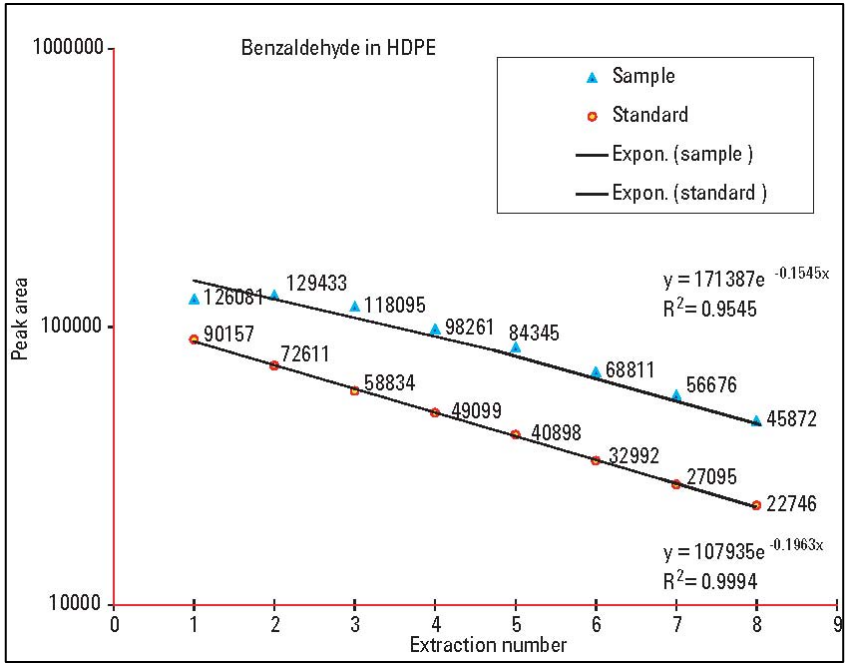
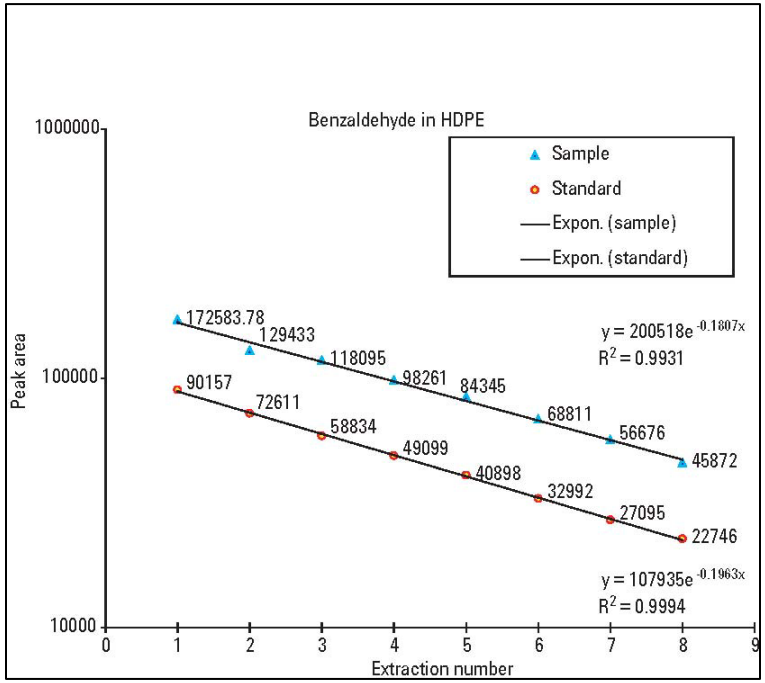
concentration (wt-%)=ppm * (10 ^ -4)	0.0856				

MHE Corrected Data for 1st Extraction

Extractable and Leachable Organics Analysis
Experimental Results Benzaldehyde in HDPE



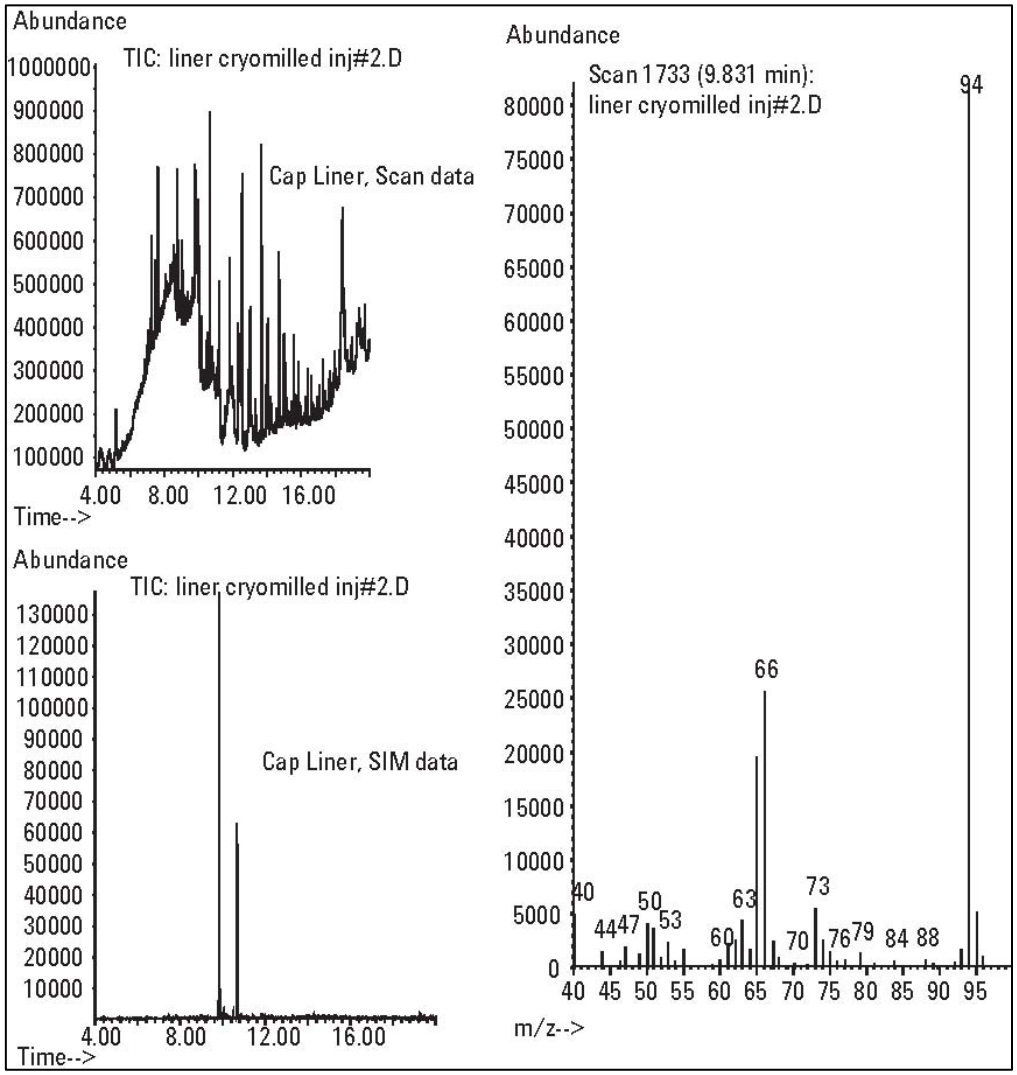
Semi-logarithmic Plot of MHE Raw Data



Semi-logarithmic Plot of MHE Corrected Data

Extractable and Leachable Organics Analysis

Phenol in Liner Polymer Liner



- Synchronous SIM/Scan data for 0.084 g cryo-milled liner polymer
- Background subtracted spectrum at 9.83 min

Extractable and Leachable Organics Analysis
Experimental Results Benzaldehyde in HDPE

phenol in 0.084 grams of liner polymer (cryomilled)					
extraction #	**sample**	**standard**		standard	stats
1	25882.12	33028		0.630118	54417.16
2	19906.73	22052		0.013536	0.044895
3	15631.47	14377		0.99743	0.042806
4	11977	8406		1164.101	3
5	9017	5314		2.133035	0.005497
6	7093	3389			
7	5729	1881		sample	stats
8	4643	1223		0.769746	33794.04
				0.004119	0.013662
regression correlation (E4 or E11)	0.999257247	0.997429527		0.999257	0.013026
slope (k) = ln(E2 or E9)	-0.261695112	-0.461847924		4036.026	3
				0.684843	0.000509
total area = (A(1)/(1-e(-k)))	112407	89293			
analyte in vial (mg)	5.31233E-05	0.0000422			
sample amt (mg) in vial	84				
concentration (ppm) in wt/wt	0.63				
concentration (wt-%)=ppm * (10 ^ -4)	6.32421E-05				

Data for Phenol in Liner Polymer

Extractable and Leachable Organics Analysis
MHE Analysis by HSS/GC/MS

Conclusions:

- Provides excellent sensitivity when using SIM/SCAN mode with MHE
- Allows very low level SIM detection while also searching for in unknowns with scan data
- DRS with Hazardous Chemicals Database provided rapid an accurate identification of targets in complex matrices
- MHE generated quantitative values for target extractable organics for risk evaluation
- Values reported for Benzaldehyde and Phenol determined by MHE compare to Permitted Daily Exposure (PDE) limits

Agilent App. Note: 5989-5494EN

Thank you

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