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)

Performance Advantage

Capillary Flow Technology (CFT) Splitter
- EPC Controlled Flow Split provides reproducible flow to both columns
- Leak free connections
- Improved repeatability and reproducibility
UPS <467> Analysis by GC/FID/FID
All Classes, Volatiles Interface, 20ml Vials

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

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 from one column to both detectors
- Leak free connections
- 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

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

Counts (%)

Acquisition time (min)
TIC for Class 2A Solvents
Zoom for Acetonitrile and 1,4-Dioxane

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

1. Hexane
2. Nitromethane
3. Chloroform
4. 1,2-Dimethoxyethane
5. Trichloroethene
6. Pyridine
7. 2-Hexanone
8. Tetralin
## Repeatability for Scan Data

Class 1 Class 2A and Class 2B Solvents

<table>
<thead>
<tr>
<th>Compounds</th>
<th>UPSP Limit (ppm)</th>
<th>Scan RSD (%)</th>
<th>SIM RSD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class 1</strong> n=8</td>
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<tr>
<td>1,1 dichloroethene</td>
<td>8</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>1,1,1 trichloroethane</td>
<td>1,500</td>
<td>1.9</td>
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<tr>
<td>Carbon tetrachloride</td>
<td>4</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>2</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>1,2 dichloroethane</td>
<td>5</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td><strong>Class 2A</strong> n=9</td>
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<tr>
<td>Hexane</td>
<td>290</td>
<td>3.2</td>
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<tr>
<td>Nitromethane</td>
<td>50</td>
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</tr>
<tr>
<td>Chloroform</td>
<td>60</td>
<td>2.5</td>
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<tr>
<td>1,2 dimethoxyethane</td>
<td>100</td>
<td>2.7</td>
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<tr>
<td>Trichloroethene</td>
<td>80</td>
<td>2.5</td>
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<tr>
<td>Pyridine</td>
<td>200</td>
<td>3.9</td>
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<tr>
<td>2-hexanone</td>
<td>50</td>
<td>2.4</td>
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<tr>
<td>Tetralin</td>
<td>100</td>
<td>2.5</td>
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<td><strong>Class 2A</strong> n=10</td>
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<tr>
<td>Methanol</td>
<td>3,000</td>
<td>2.8</td>
<td>2.4</td>
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<td>Acetonitrile</td>
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<tr>
<td>Dichloromethane</td>
<td>600</td>
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<tr>
<td>trans-1,2 dichloroethene</td>
<td>1,870</td>
<td>2.4</td>
<td>2.2</td>
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<td>cis-1,2 dichloroethene</td>
<td>1,870</td>
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<td>2.1</td>
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<td>Tetrahydrofuran</td>
<td>720</td>
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<td>Cyclohexene</td>
<td>3,880</td>
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<td>Methycyclohexane</td>
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<td>1.6</td>
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<td>1,4 Dioxane</td>
<td>380</td>
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<td>2.3</td>
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<td>Toluene</td>
<td>890</td>
<td>0.7</td>
<td>2.0</td>
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<tr>
<td>Chlorobenze</td>
<td>360</td>
<td>1.9</td>
<td>2.1</td>
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<tr>
<td>Ethylbenzene</td>
<td>2,170</td>
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<td>2.1</td>
</tr>
<tr>
<td><em>m</em>-Xylene, <em>p</em>-Xylene</td>
<td>2,170</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td><em>o</em>-Xylene</td>
<td>2,170</td>
<td>2.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>
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
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

<table>
<thead>
<tr>
<th>extraction #</th>
<th>sample</th>
<th>standard</th>
<th>standard stats</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>126081</td>
<td>90157</td>
<td>0.821008 108302.5</td>
</tr>
<tr>
<td>2</td>
<td>129433</td>
<td>72611</td>
<td>0.004898 0.016243</td>
</tr>
<tr>
<td>3</td>
<td>118095</td>
<td>58834</td>
<td>0.998153 0.015487</td>
</tr>
<tr>
<td>4</td>
<td>98261</td>
<td>49099</td>
<td>1621.638 3</td>
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<td>5</td>
<td>84345</td>
<td>40898</td>
<td>0.388965 0.00072</td>
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<td>27095</td>
<td></td>
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<tr>
<td>8</td>
<td>45872</td>
<td>22746</td>
<td>0.897668 151819.2</td>
</tr>
</tbody>
</table>

Regression correlation (E4 or E11) 0.873825602 0.998153435 0.873826 0.074896

Slope (k) = ln(E2 or E9) -0.107955422 -0.197222062 20.7766 3

Total area = A(1)/(1-e(-k)) 1232073 503694 0.116544 0.016828

Analyte in vial (mg) 0.026906838 0.011

Sample amount (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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<td>49099</td>
<td>1621.638</td>
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<td>40898</td>
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<th></th>
<th>sample</th>
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<tbody>
<tr>
<td>regression correlation (E4 or E11)</td>
<td>0.873825502</td>
<td>0.998153435</td>
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<tr>
<td>slope (k) = ln(E2 or E9)</td>
<td>-0.107955422</td>
<td>-0.197222062</td>
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<tr>
<td>total area = (A(1)/(1-e(-k)))</td>
<td>1232073</td>
<td>503694</td>
</tr>
<tr>
<td>analyte in vial (mg)</td>
<td>0.026906838</td>
<td>0.011</td>
</tr>
<tr>
<td>sample amt (mg) in vial</td>
<td>208</td>
<td></td>
</tr>
<tr>
<td>concentration (ppm) in wt/wt</td>
<td>129.36</td>
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</tr>
<tr>
<td>concentration (wt-%)=ppm * (10^-4)</td>
<td>0.0856</td>
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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

<table>
<thead>
<tr>
<th>extraction #</th>
<th>sample</th>
<th>standard</th>
<th>standard</th>
<th>stats</th>
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</thead>
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<td>1223</td>
<td>0.769746</td>
<td>33794.04</td>
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</table>

regression correlation (E4 or E11) 0.999257247 0.997429527 0.999257 0.013662
slope (k) = ln(E2 or E9) -0.261695112 -0.461847924 4036.026 3

| 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

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