Headspace Grade Solvents for Trace Analysis of Organic Volatile Chemicals

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Material and Methods

Headspace GC analysis is a common practice in the pharmaceutical industry to detect residual solvents. Per United States Pharmacopoeia (USP), residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of drug substances or excipients. Since residual solvents are difficult to remove completely from drug products, the amount of residual solvent should be evaluated by headspace GC analysis. Based on their toxicity effects, residual solvents are classified as Class 1 (most toxic), Class 2 and Class 3. In headspace GC analysis, the pharmaceutical compound of interest is often dissolved in a high boiling solvent to isolate trace amounts of volatile components. Although water is the most common solvent for this purpose, other solvents can be used when solubility of the pharmaceutical compound is an issue.

We have evaluated five different solvents for headspace analysis. The solvents are water, dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and 1-methyl-2-pyrrolidone (NMP). The purpose of our study is to qualify these high purity solvents for residual solvent analysis in pharmaceuticals. Four different pain medications were purchased from Walgreens and residual solvent analysis performed using DMSO and water. Our results showed that all five headspace solvents are free of trace level impurities and qualified to detect volatile organic components at trace level from pharmaceutical compounds.

Abstract

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GC Headspace

<table>
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<th>Reagent</th>
<th>Fisher Chemical Grade</th>
<th>Pack Size</th>
<th>Packaging</th>
<th>Fisher Scientific Cat. No</th>
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<tr>
<td>Water</td>
<td>GC Headspace</td>
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<td>amber glass</td>
<td>W10-1</td>
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<td>DMSO, Dimethyl Sulfoxide</td>
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<td>NMP, N-methyl Pyrrolidone</td>
<td>GC Headspace</td>
<td>1L</td>
<td>amber glass</td>
<td>N140-1</td>
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</tbody>
</table>

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- Standards: Class 1 (catalog # PHR1063) and Class IIA (catalog # PHR1064) residual solvent standard mix from Sigma-Aldrich, St. Louis, MO
- Samples: pain medication from Walgreens
  1. Ibuprofen
  2. Acetaminophen
  3. Aleve
  4. Aspirin

- Sample preparation:
  1. Ten tablets were dissolved in 10 mL of water and the mix centrifuged. Supernatant (2 mL) was transferred to a 20 mL headspace GC (HSGC) vial.
  2. Ten tablets were dissolved in a mixture of water and DMSO (50:50). The mixture was centrifuged and the supernatant transferred to a 20 mL HSGC vial.

Headspace GC-FID run conditions

- Instrument: Thermo Scientific Trace GC Ultra equipped with headspace RSH auto sampler
  - Column: ZB-624, 30 m x 0.25 mm x 1.4 micron
  - Detector: flame ionization detector (FID)
  - Detector temperature: 250° C
  - Injector temperature: 200° C
  - Syringe volume: 2.5 mL
  - Injection volume: 1.0 mL
  - Split ratio: 20
  - Agitator temperature: 90° C
  - Incubation time: 5 min
  - Hydrogen: 35, Air: 350, Nitrogen: 40
  - Oven temperature:
    - Initial 40° C & hold 5 min
    - Ramp 10° C per min
    - Final 240° C & hold 10 min

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Headspace GC-FID run of Class 1 and Class IIA residual standards (without any dilution) in DMSO is shown in Fig. 1. All five peaks of the Class 1 residual solvent mixture were detected using the method; the 14 peaks from the Class IIA residual solvent mixture were also detected in the same method. The residual solvent peaks are eluted before the DMSO peak (at 10.27 minutes).

Fig. 2 shows an overlay of the expanded chromatograms of DMSO solvent with Class 1 residual solvent standard mix, namely 1 – 5 ppm concentration, 100 – 500 ppm concentration, and the Class IIA standard mix at 100 – 1600 ppm concentration. This data clearly shows that there are no trace amounts of extraneous peaks present in the HS-GC solvent.

Class IIA residual solvent standard mix was diluted further, and the final concentration of components were within the 1 – 16 ppm range. A comparison of this lower concentration standard mix relative to the DMSO blank shows a clean solvent baseline without interference from extraneous peaks (Fig. 3).

Figs. 4 – 7 show the blank HS-GC-FID run of each solvent and the Class 1 and Class IIA standards in the same solvent. No extraneous peaks were observed in any of the solvents.

An HS-GC-FID analysis of all four pain medications is provided in Fig. 8. Some common peaks were observed in all samples; only in the Aleve solution a peak at 8.40 minutes was found different than the other samples.

Fig. 9 provides the HS-GC-MS spectra of the 8.40 min peak from Aleve sample (run in a different method).

An HS-GC-FID analysis of a toluene standard at 1 ppm concentration showed the same retention as the unknown peak in Aleve material. However, the amount of toluene in Aleve is less than 1 ppb, which is much lower than the recommended level of USP (Fig. 10).
Results and Discussion

Figure 4. DMAC Neat, Class 1 and Class IIA Standard Mix

Figure 5. DMF Neat, Class 1 and Class IIA Standard Mix
Figure 6. Water Neat, Class 1 and Class IIA Standard Mix

Figure 7. NMP Neat, Class 1 and Class IIA Standard Mix

Figure 8. Headspace Analysis of Pain Medications by GC-FID (Expanded)

Figure 9. Impurity Peak in Aleve Medication

The sample was run in GC-MS to identify and the library search data showed similarity with toluene. Most of the peaks are common to all the tablets, but the peak at 8.40 minutes was observed for Aleve only.

The peak at 8.40 min was only observed in Aleve solution. The sample was run in GC-MS to identify and the library search data showed similarity with toluene.
The new Fisher Chemical headspace grade solvents included in our study are all highly purified. No extraneous peaks are observed when the blank solvents were analyzed by GC-FID-HS. All five solvents provided an interference free baseline and are suitable for trace analyte detection. HSGC analysis of pain medications demonstrated clearly that detection of parts per billion level impurity peak could be accomplished using these headspace solvents.

Toluene standard peak and the unknown peak in Aleve showed same retention time in GC-FID and GC-MS. GC-MS spectra from both peaks are observed identical. This confirmed the presence of toluene. The amount of toluene in Aleve medication is less than 1 ppb, which is much lower than the USP concentration limit (890 ppm).

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