

Headspace Grade Solvents for Trace Level Analyte Detection

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ABSTRACT

Headspace gas chromatography is the most suited technique for the analysis of highly volatile organics that are partitioned efficiently into the gas phase from the solid or liquid matrices. Detection of residual solvents in pharmaceuticals is performed by headspace GC analysis. The residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of drug substances or excipients, or in the preparation of drug products per United States Pharmacopoeia (USP) and International Conference on Harmonization (ICH). The residual solvents are difficult to remove completely from the drug products and therefore the amount of residual solvents should be evaluated by headspace GC analysis. USP and ICH guidelines recommend the acceptable amounts of residual solvents in pharmaceuticals for the safety of the patient. Residual solvents are categorized as Class 1 (most toxic), Class 2 and Class 3 according to the toxicity effects. In headspace GC analysis, the pharmaceutical compound of interest is often dissolved in a high boiling solvent to assess the amount of volatile components. Although water is the most common solvent for this type of analysis, other solvents are frequently used when the pharmaceutical compounds are not soluble in water.

We have evaluated five different solvents for headspace GC analysis. The solvents are water, dimethyl sulfoxide (DMSO), N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAC) and 1-methyl-2-pyrrolidinone (NMP). Allergy medications such as Allegra, Alavert, Flonase, Zyrtec, Claritin and Wal-Dryl were purchased from Walgreens. Residual solvent analysis of these over-the-counter allergy medications was performed using different headspace solvents. Our results showed that all five solvents are suitable for detection of trace level volatile organic components from the pharmaceutical compounds.

MATERIAL AND METHODS

- Solvents: All GC headspace grade solvents were from Fisher Scientific including water (Cat. # W10-1), DMSO (Cat. # D139-1), DMAC (Cat. # D160-1), DMF (Cat. # D133-1), and NMP (Cat. # N140-1)
- Standards: Class 1 (Cat. # PHR1063) and Class 2A (Cat. # PHR1064) residual solvent standard mixes were obtained from Sigma-Aldrich, St. Louis, MO
- Samples: Allergy and pain medications were purchased from Walgreens (Table 1)

Sample preparation:

- Two to 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.
- Two to 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.

Table 1. Allergy and Pain Medications Analyzed

| Tablets | Active Ingredients |
|--|--|
| Advil | Chlorpheniramine maleate 4 mg |
| Allegra | Fexofenadine HCl 180 mg |
| Alavert | Loratadine 10 mg |
| Alka-Seltzer plus (liquid filled capsules) | Acetaminophen 325 mg, Doxylamine succinate (6.25 mg) |
| Claritin | Loratadine 10 mg |
| Flonase | Fexofenadine HCl 180 mg |
| Mucinex | Phenylephrine HCl 5 mg |
| Wal-Dryl | Diphenhydramine HCl 25 mg |
| Wal-Phed | Chlorpheniramine maleate 4 mg |

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
 - Flow: 1 mL/min
 - 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 (mL/min)
 - Oven temperature:
 - Initial 40° C & hold 5 min
 - Ramp 10° C per min
 - Final 240° C & hold 10 min

Figure 1. Class 1 and Class 2 Solvent Standards by GC-FID Headspace

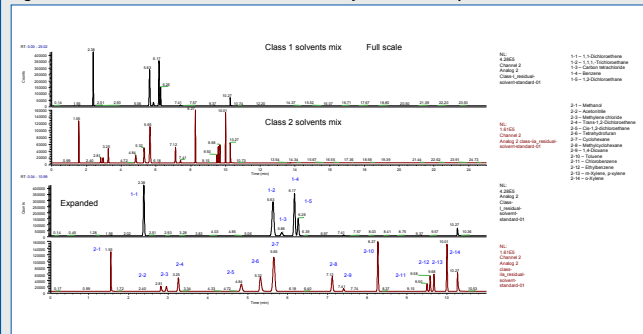
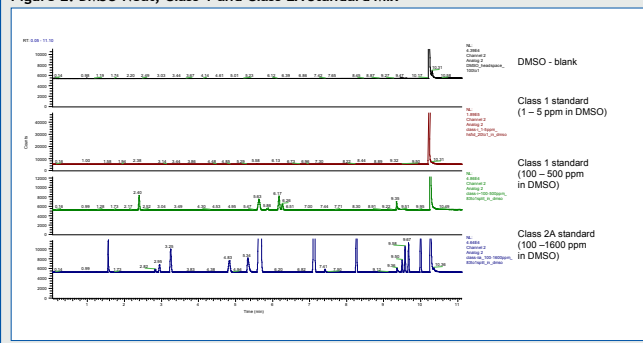
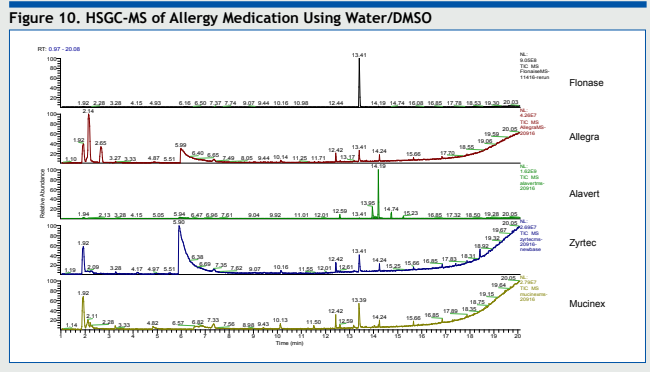
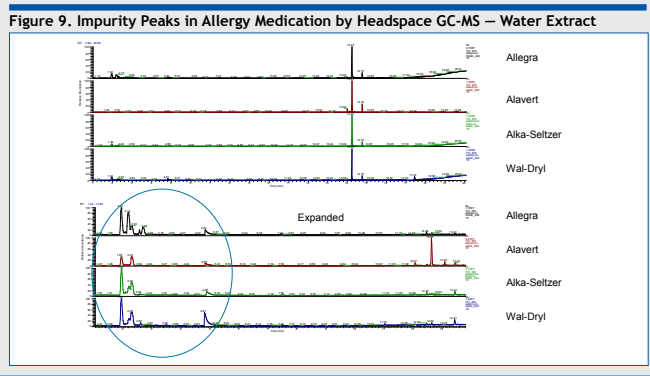
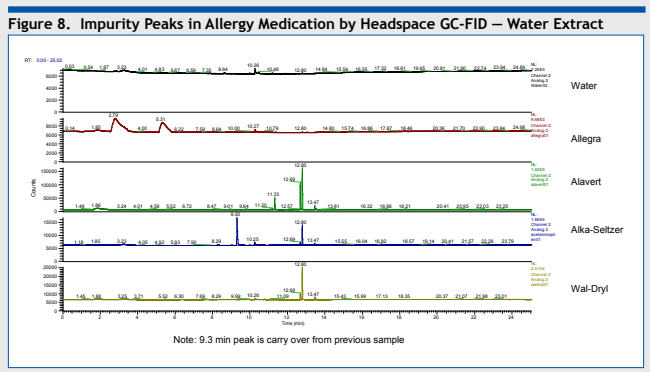
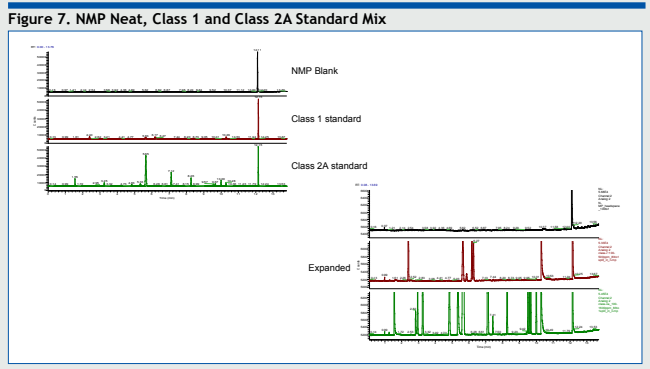
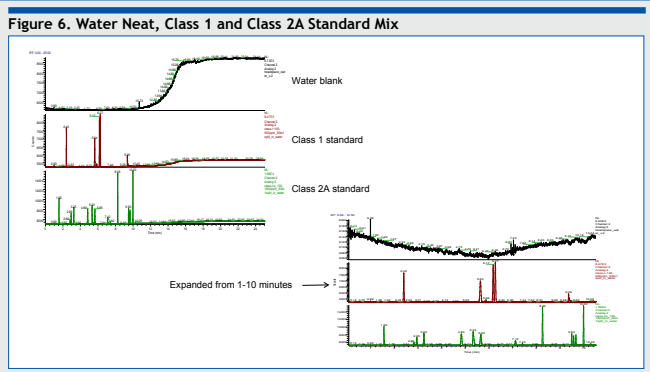
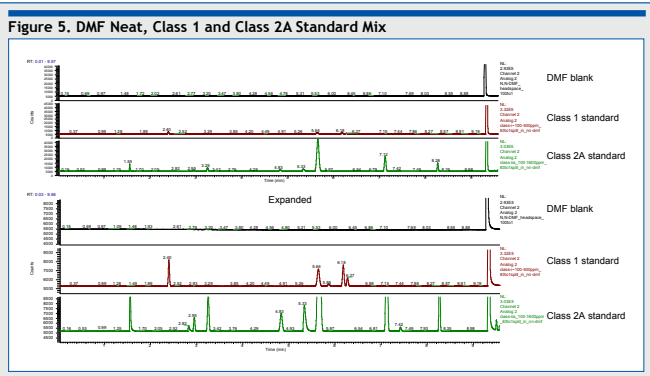
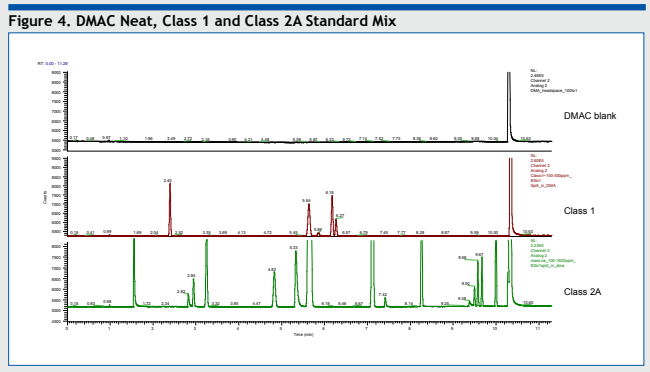
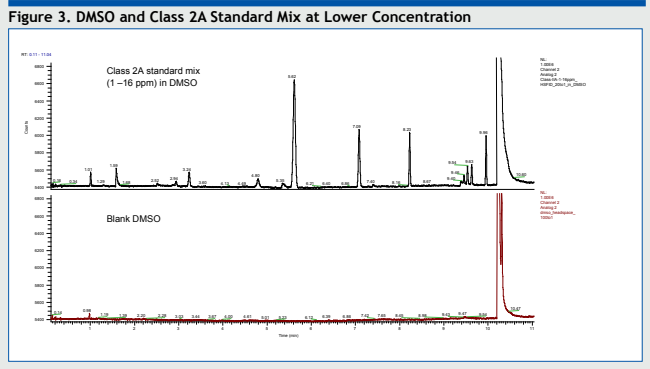


Figure 2. DMSO Neat, Class 1 and Class 2A Standard Mix





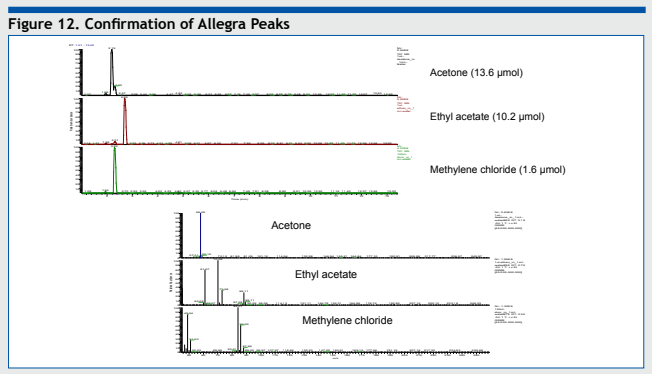
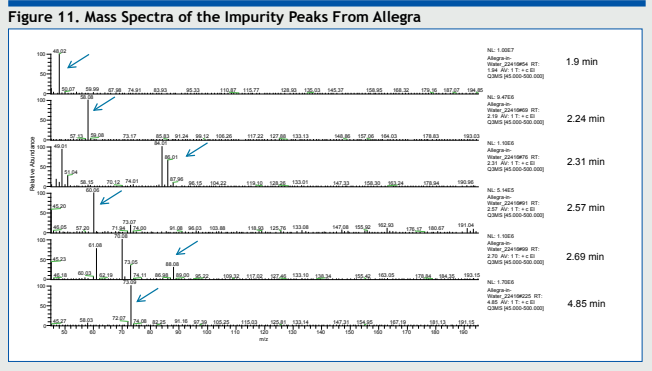


Table 2. Residual Solvent Peaks Information

Retention time, m/z, identity and amount of residual solvents in the allergy medication tested

| Retention Time | m/z | Identity | Quantification |
|----------------|-----|--------------------|------------------------|
| 1.94 | 48 | Unknown | ** |
| 2.19 | 58 | Acetone | 406.93 nmol in Allegra |
| 2.30 | 84 | Methylene chloride | 7.98 nmol in Allegra |
| 2.57 | 60 | Acetic acid | ** |
| 2.69 | 88 | Ethyl acetate | 55.78 nmol in Allegra |
| 4.83 | 73 | DMF | ** |

**Not quantified

RESULTS AND DISCUSSION

- Headspace GC-FID run of Class 1 and Class 2A 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 2A residual solvent mixture were also detected in the same method. The residual solvent peaks are eluted before the DMSO peak (at 10.27 min).
- Fig. 2 shows an overlay of the expanded chromatograms of DMSO solvent with Class 1 residual solvent standard mix, namely 1 - 5 ppm concentration, and the Class 2A standard mix at 100 - 1600 ppm concentration. These data clearly show that trace amounts of extraneous peaks are not present in the HSGC solvent.
- Class 2A 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 HSGC-FID run of each solvent and the Class 1 and Class 2A standards in the same solvent. No extraneous peaks were observed in any of the solvents.
- Fig. 8 shows the overlay of HSGC-FID chromatograms of Allegra, Alavert, Alka-Seltzer and Wal-Dryl tablets extracted in water. For Alka-Seltzer, a carryover peak of DMF at 9.30 min was observed. In Allegra, two peaks were observed at 2.79 min and 5.31 min; those peaks were not found in Alavert, Alka-Seltzer and Wal-Dryl.
- No significant peaks were observed in Claritin, Advil and Wal-Phed (data not shown).
- Fig. 9 provides an overlay of HSGC-MS chromatograms of Allegra, Alavert, Alka-Seltzer and Wal-Dryl tablets extracted in water. The early eluting residual solvent peaks in full scale are shown in the upper panel. The lower panel provides the expanded chromatograms. Allegra medication shows peaks at 1.94, 2.19, 2.30, 2.69, and 4.83 min. In Alavert, the peaks at 1.96, 2.30, and 4.85 min were also observed. Similar peaks were found in Wal-Dryl and Alka-Seltzer medications.
- Fig. 10 shows HSGC-MS of Flonase, Allegra, Alavert, Zyrtec, and Mucinex in water/DMSO solution. The broad peak at 5.9 min is DMSO. Allegra, Zyrtec and Mucinex each showed a peak at 1.92 min. This peak was identified as m/z 48; however, positive identity has not yet been attained (Table 2).
- Both water and water/DMSO extracts clearly indicated the presence of peaks at 1.9, 2.2 and 2.6 min (Figs. 9,10). In addition, water-extracted samples also showed peaks at 2.3 and 4.8 min. Mass spectra of these peaks are provided in Fig. 11, and were identified by NIST library search (Table 2).
- Trace samples of acetone, ethyl acetate and methylene chloride were run to confirm the presence of those peaks in the allergy medication. The presence of all three solvents was confirmed by exact match of the retention time and mass spectra profile. Acetone and ethyl acetate are Class 3 solvents and both methylene chloride and DMF are Class 2 solvents per USP and ICH guideline with a limit of 600 ppm and 880 ppm, respectively. The amounts of residual solvents detected were well below the limits. We quantified acetone, ethyl acetate and methylene chloride from Allegra medication (Table 2); DMF and other solvents were not quantified.

CONCLUSIONS

- The new GC headspace grade solvents from Fisher Scientific are all highly purified and suitable for analyzing residual solvents in pharmaceuticals.
- No extraneous peaks were found when blank solvents were analyzed by GC-FID-HS.
- All five solvents provided an interference free base line and are suitable for trace analyte detection.
- HSGC analysis of allergy medications demonstrated clearly that detection of trace level impurity peaks could be accomplished using these headspace grade solvents.

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