



Headspace Grade Solvents for Trace Analysis of Organic Volatile Chemicals

*Subhra Bhattacharya, Eric Oliver
and Stephen C. Roemer
Thermo Fisher Scientific – Fisher Chemical,
One Reagent Lane, Fair Lawn, NJ*

Thermo
SCIENTIFIC



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.



For a limited time: Buy 1 Case, Get 1 Case on GC HeadSpace solvents!

Please visit: www.fishersci.com/solventsale to redeem today!

- Solvents: All GC headspace grade solvents were from Thermo Fisher Scientific – Fisher Chemical, Fair Lawn, NJ

GC Headspace

Reagent	Fisher Chemical Grade	Pack Size	Packaging	Fisher Scientific Cat. No
Water	GC Headspace	1L	amber glass	W10-1
DMSO, Dimethyl Sulfoxide	GC Headspace	1L	amber glass	D139-1
DMF, Dimethyl Formamide	GC Headspace	1L	amber glass	D133-1
DMAC, Dimethyl Acetamide	GC Headspace	1L	amber glass	D160-1
NMP, N-methyl Pyrrolidone	GC Headspace	1L	amber glass	N140-1

For more information about these products please visit www.fisherchemical.com

- 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

- 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 HSGC 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 HSGC-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 HSGC-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 HSGC-MS spectra of the 8.40 min peak from Aleve sample (run in a different column using a different method).
- An HSGC-FID analysis of a toluene standard at 1 ppm concentration showed the same retention as the unknown peak in Aleve samples. Moreover, GC-MS spectra of the unknown peak and toluene standard are identical, which confirms the presence of toluene in the 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).

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

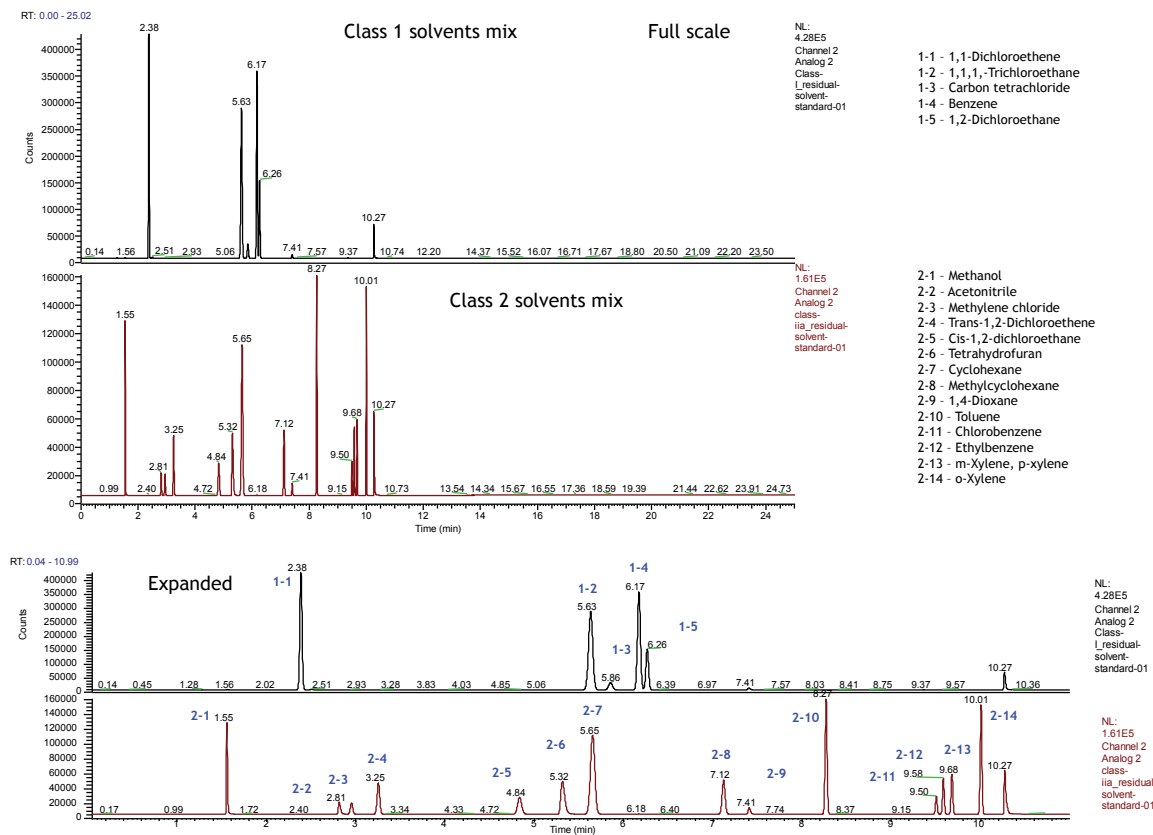


Figure 2. DMSO Neat, Class 1 and Class IIA Standard Mix

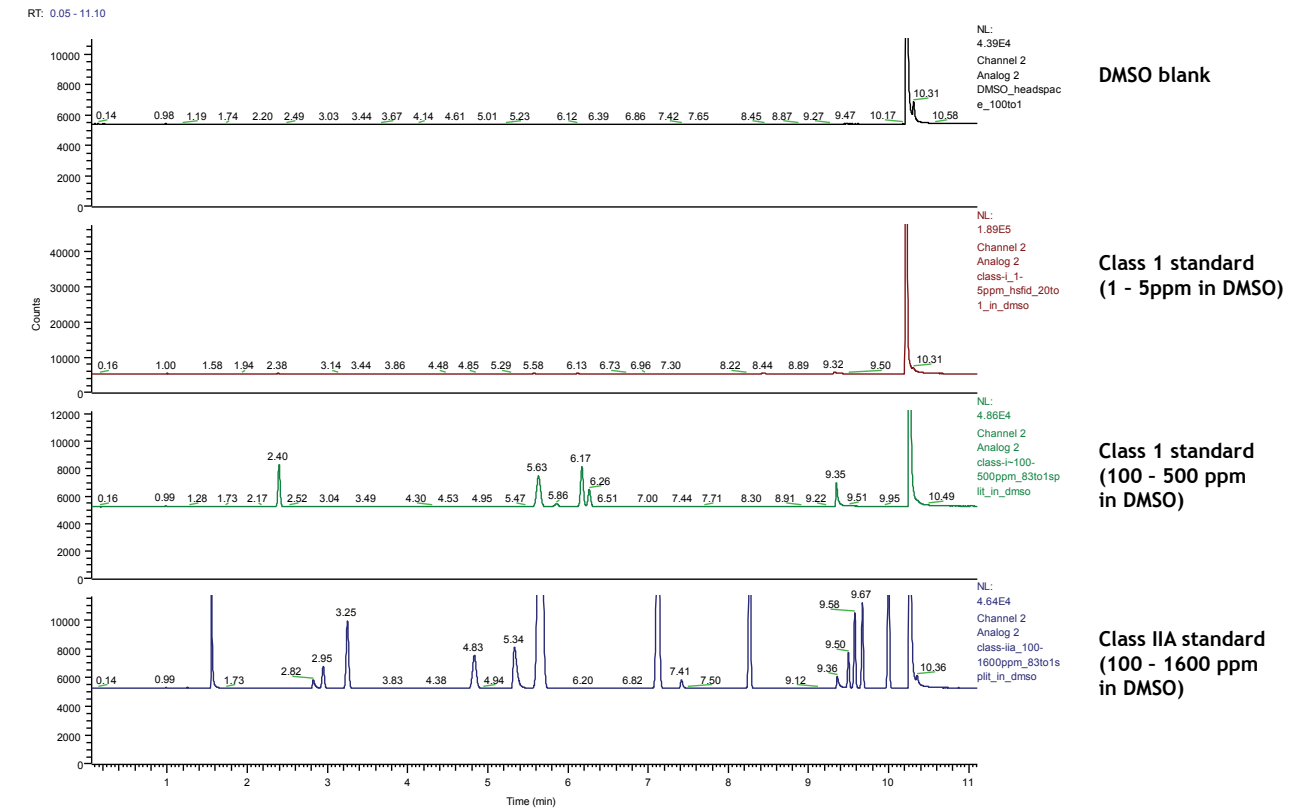


Figure 3. DMSO and Class IIA Standard Mix at Lower Concentration

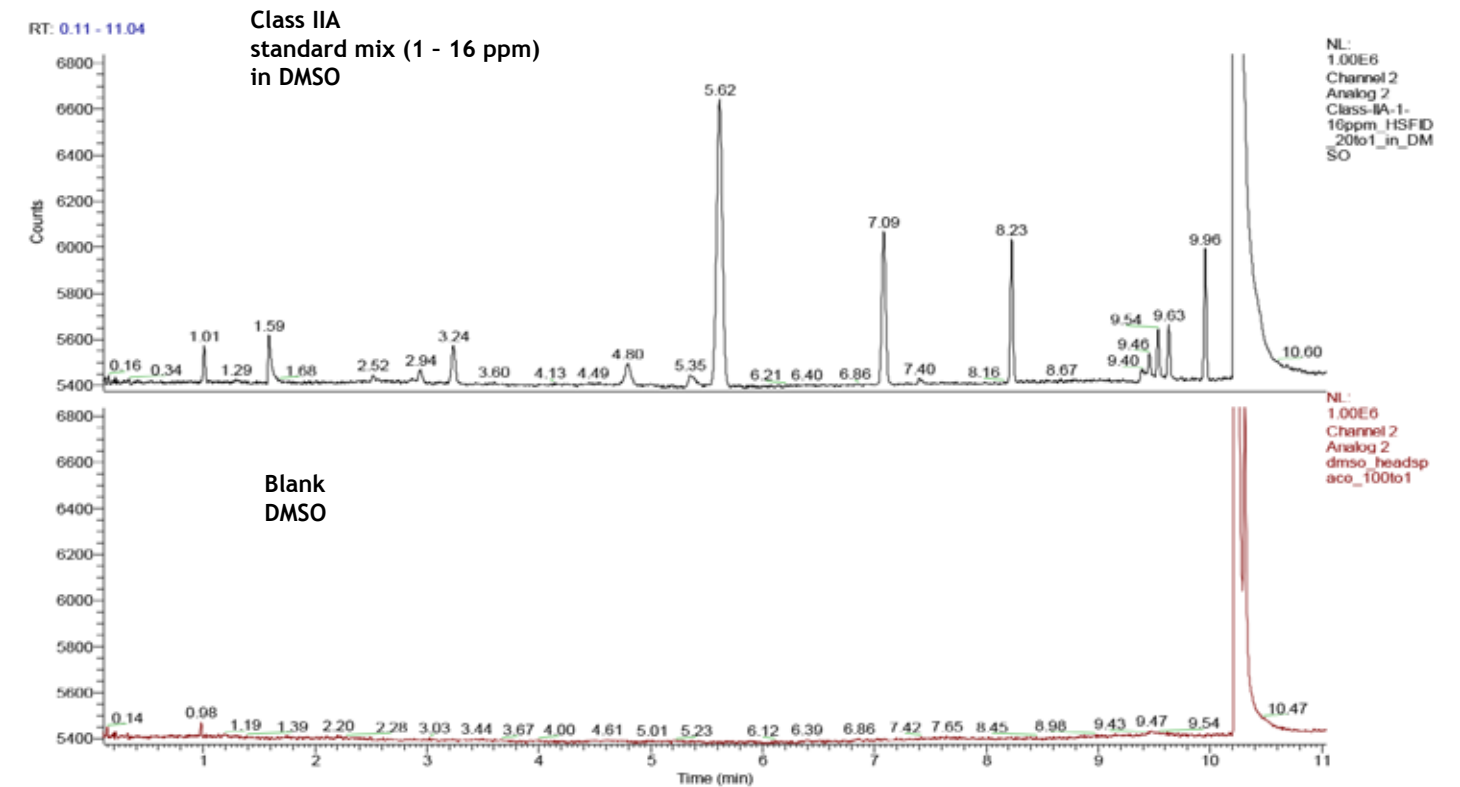


Figure 4. DMAC Neat, Class 1 and Class IIA Standard Mix

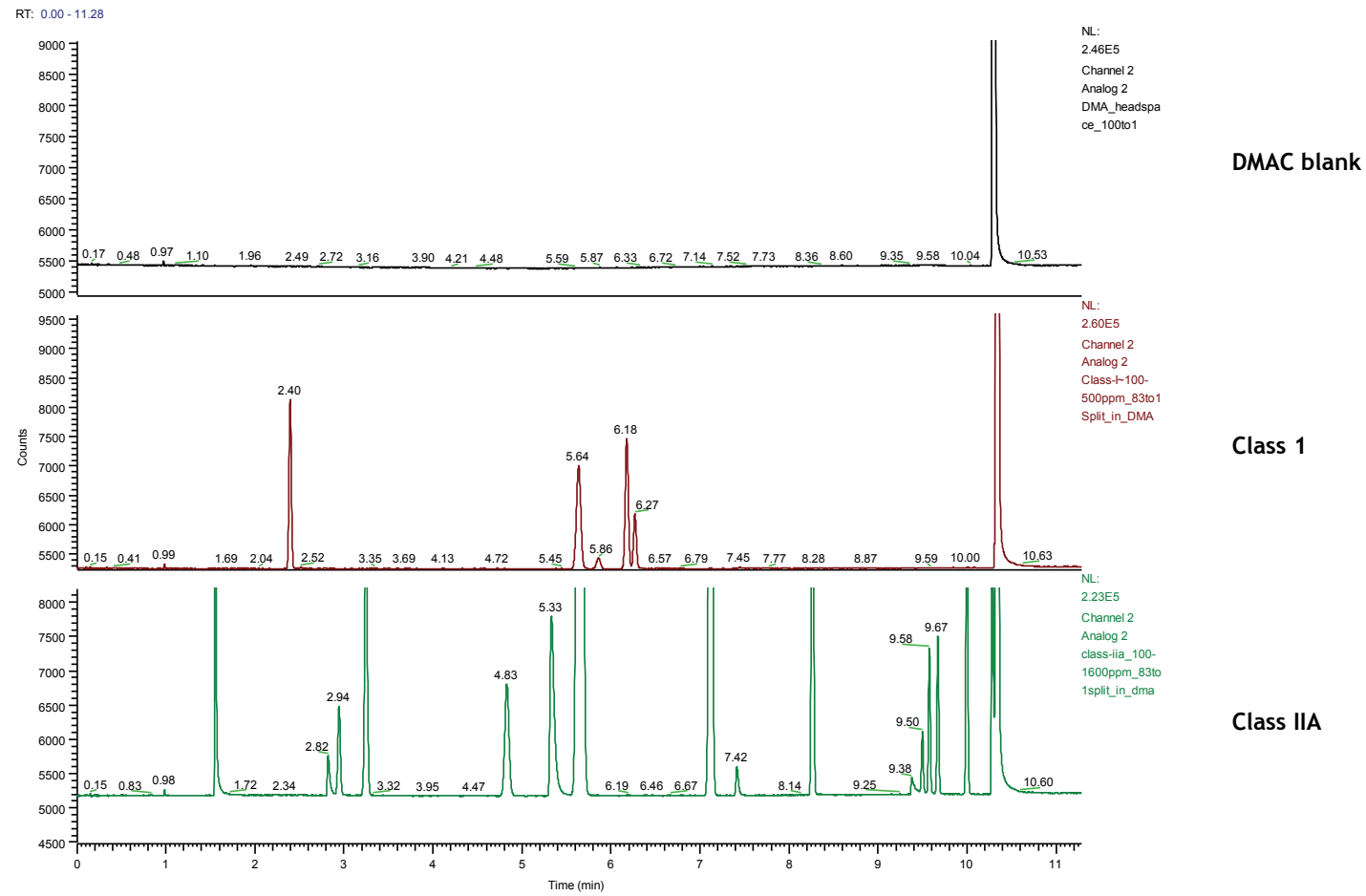


Figure 5. DMF Neat, Class 1 and Class IIA Standard Mix

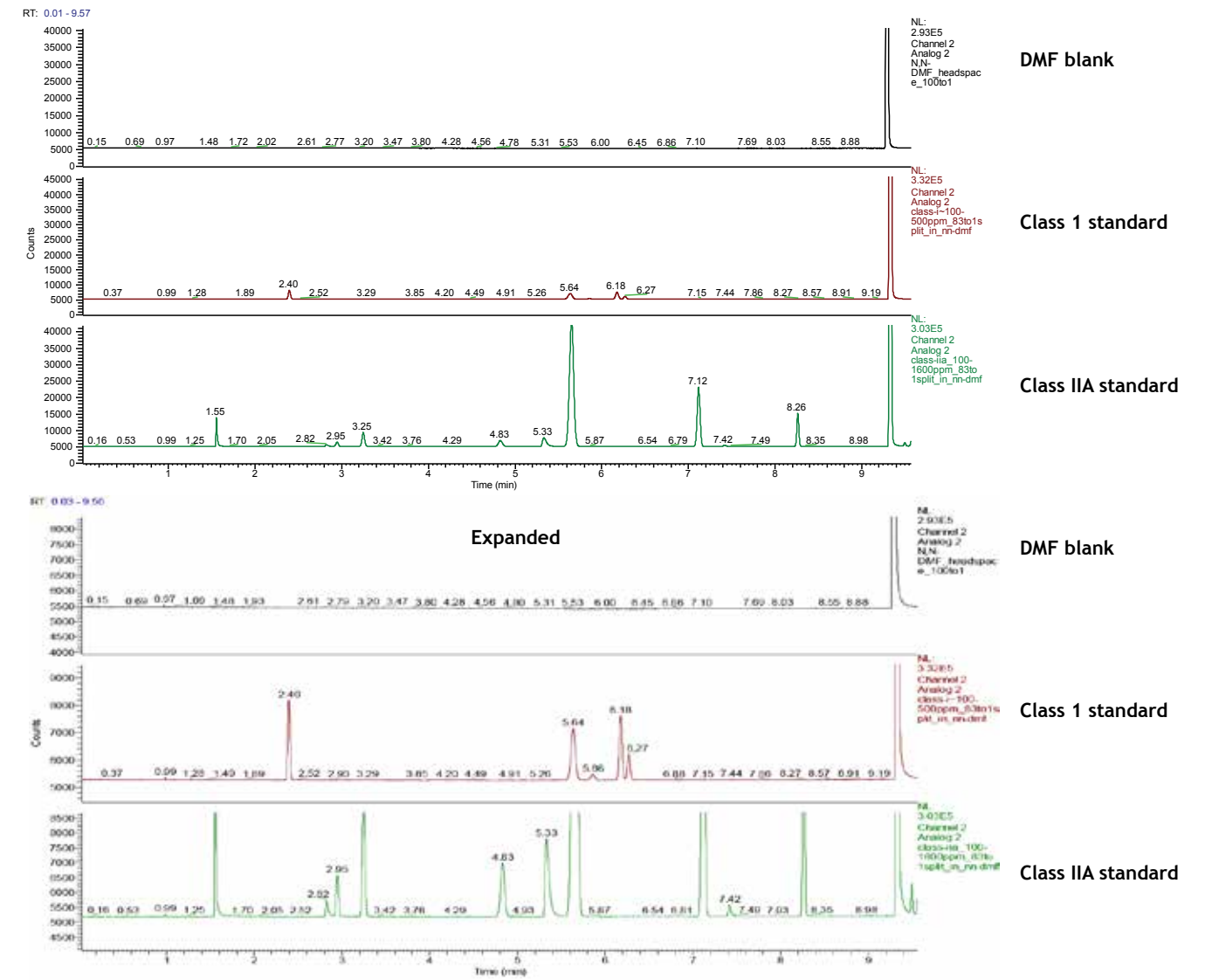


Figure 6. Water Neat, Class 1 and Class IIA Standard Mix

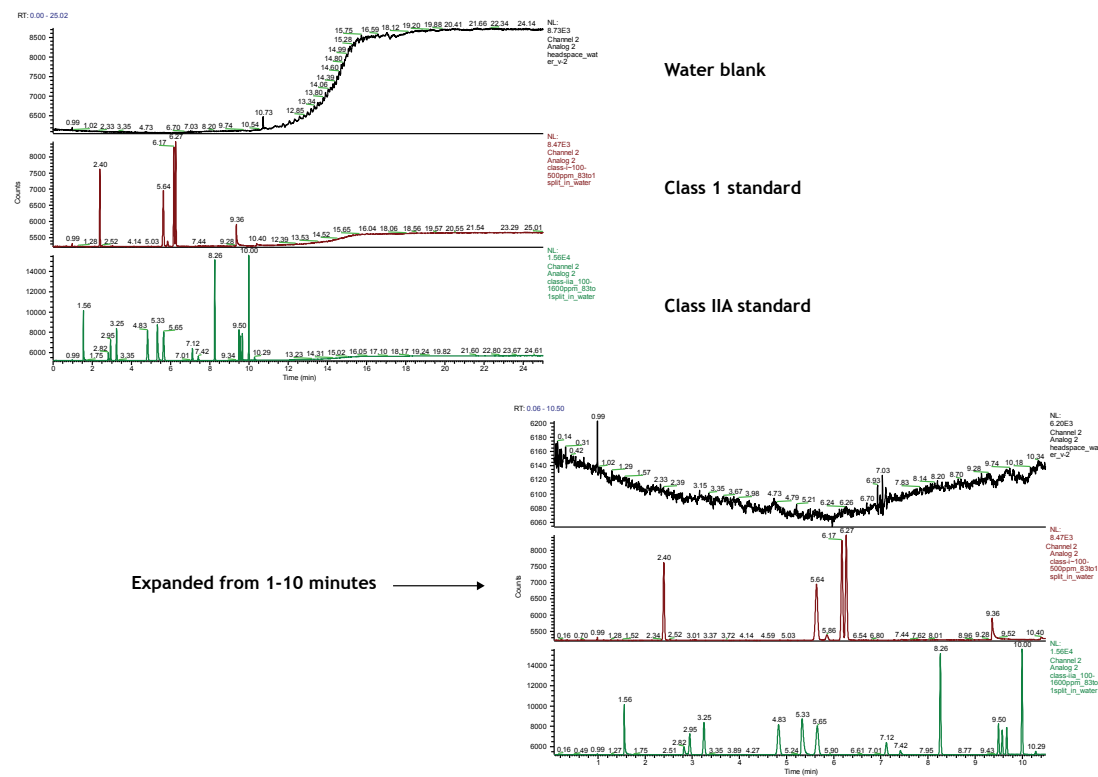


Figure 7. NMP Neat, Class 1 and Class IIA Standard Mix

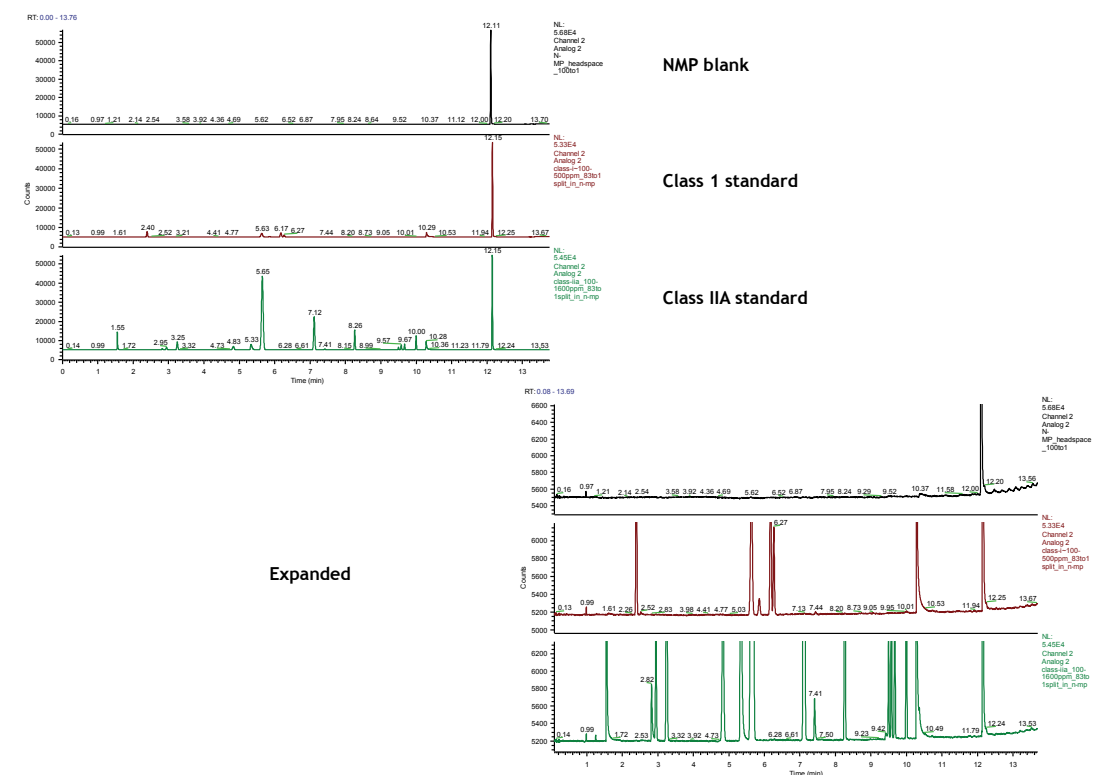
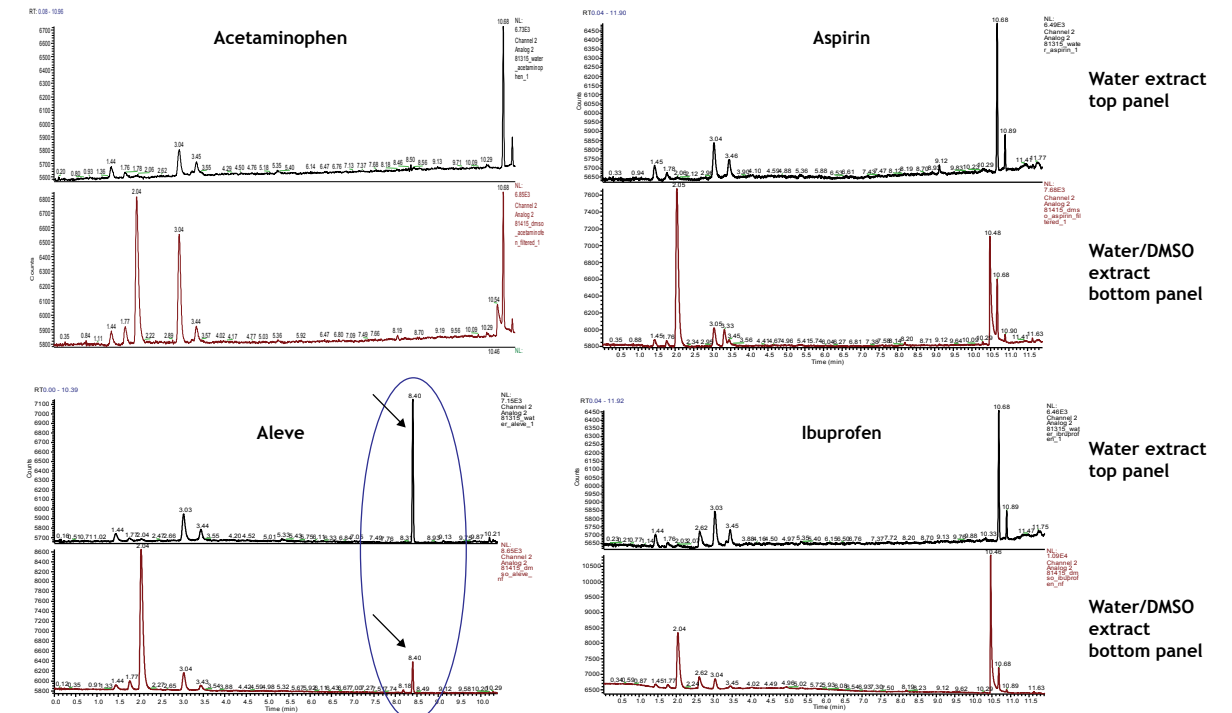
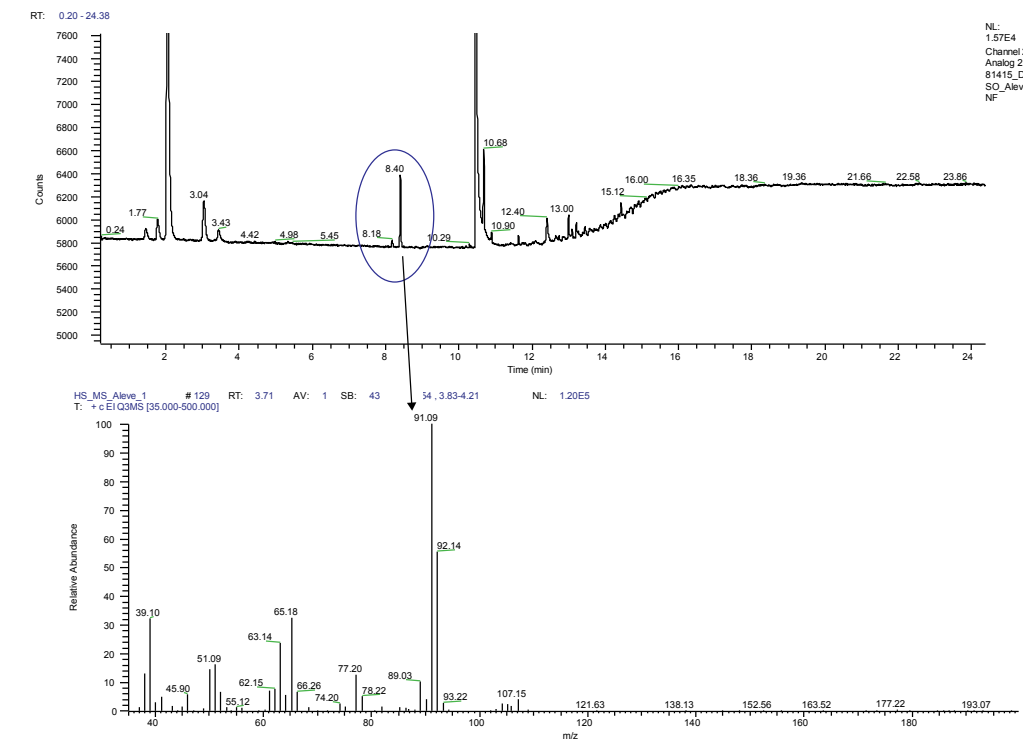


Figure 8. Headspace Analysis of Pain Medications by GC-FID (Expanded)



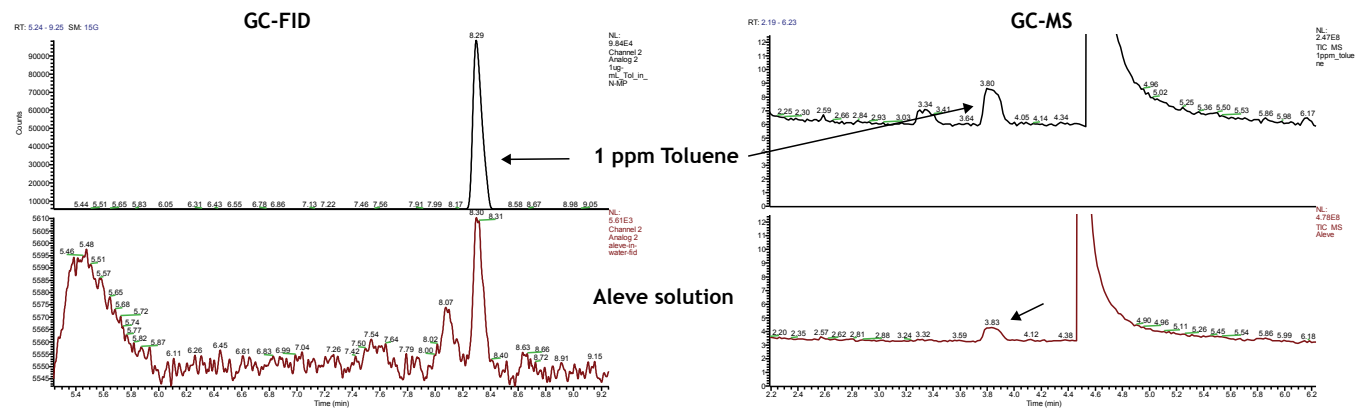
Most of the peaks are common to all the tablets, but the peak at 8.40 minutes was observed for Aleve only.

Figure 9. Impurity Peak in Aleve Medication

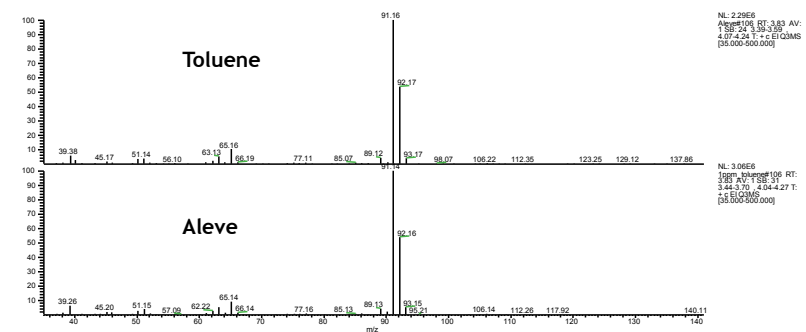


The peak at 8.40 min was only observed in Aleve solution. The sample was run in GC-MS to identify and the library search data showed similarity with toluene.

Figure 10. Aleve Peak Confirmation by Standard



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).



- 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 base line 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



Headspace Grade Solvents for Trace Analysis of Organic Volatile Chemicals

To place an order, contact your local Fisher Scientific office.



©2015 Thermo Fisher Scientific Inc. All rights reserved.
All other trademarks are the property of Thermo Fisher Scientific Inc. and its subsidiaries.

AMERICAS

Canada

Fisher Scientific Canada
www.fishersci.ca
Tel: 800-234-7437
Fax: 800-463-2996

Latin America

Fisher Scientific Global Export,
Latin America
www.fishersci.com
Tel: 770-871-4725
Fax: 770-871-4726

United States

Fisher HealthCare
www.fisherhealthcare.com
Tel: 800-640-0640
Fax: 800-290-0290

Fisher Scientific
www.fishersci.com
Tel: 800-766-7000
Fax: 800-926-1166

EUROPE

Austria

info.austria@thermofisher.com
www.at.fishersci.com
Tel: 0800 20 88 40
Fax: 0800 20 66 90

Belgium

be.fisher@thermofisher.com
www.be.fishersci.com
Tel: 056 260 260
Fax: 056 260 270

Czech Republic

info.cz@thermofisher.com
www.thermofisher.cz
Tel: 466 798 230
Fax: 466 435 008

Denmark

kundeservice@thermofisher.com
www.dk.fishersci.com
Tel: 70 27 99 20
Fax: 70 27 99 29

Finland

fisher.fi@thermofisher.com
www.fi.fishersci.com
Tel: 09-802 76 280
Fax: 09-802 76 235

France

fr.fisher@thermofisher.com
www.fr.fishersci.com
Tel: 03 88 67 14 14
Fax: 03 88 67 11 68

Germany

info.germany@thermofisher.com
www.de.fishersci.com
Tel: 2304 932-5
Fax: 2304 932-950

Ireland

fsie.sales@thermofisher.com
www.ie.fishersci.com
Tel: 01 885 5854
Fax: 01 899 1855

Italy

it.fisher@thermofisher.com
www.it.fishersci.com
Tel: 02 950 59 478
Fax: 02 950 59 479

Lithuania

sales.lt@thermofisher.com
www.lt.fishersci.com
T: +370 5 2444442
F: +370 5 2392756

The Netherlands

nl.info@thermofisher.com
www.nl.fishersci.com
Tel: 020 487 70 00
Fax: 020 487 70 70

Norway

fisher.no@thermofisher.com
www.no.fishersci.com
Tel: 22 95 59 59
Fax: 22 95 59 40

Portugal

pt.fisher@thermofisher.com
www.pt.fishersci.com
Tel: 21 425 33 50
Fax: 21 425 33 51

Spain

es.fisher@thermofisher.com
www.es.fishersci.com
Tel: 902 239 303
Fax: 902 239 404

Sweden

fisher.se@thermofisher.com
www.se.fishersci.com
Tel: 31 352 32 00
Fax: 31 352 32 50

Switzerland

info.ch@thermofisher.com
www.ch.fishersci.com
Tel: 056 618 41 11
Fax: 056 618 41 41

United Kingdom

fsuk.sales@thermofisher.com
www.fisher.co.uk
Tel: 01509 555500
Fax: 01509 555111

ASIA

India

lsi_marketing@thermofisher.com
www.fishersci.in
Tel: +91-22-6680 3000
Fax: +91-22-6680 3001

Korea

sales.fsk@thermofisher.com
www.fishersci.co.kr
Tel: 02-3420-8700
Fax: 02-3420-8710

Malaysia

enquiry.my@thermofisher.com
www.fishersci.com.my
Tel: (603) 51228888
Fax: (603) 5121 8899

Singapore

enquiry.sg@thermofisher.com
www.fishersci.com.sg
Tel: (65) 6873 6006
Fax: (65) 6873 5005

OCEANIA

Australia

AUinfo@thermofisher.com
www.thermofisher.com.au
Tel: 1300-735-292
Fax: 1800-067-639

New Zealand

NZinfo@thermofisher.com
www.thermofisher.co.nz
Tel: 0800-933-966
Fax: +64 9 980 6788