The Utility of Headspace Grade Solvents in the Analysis of Organic Volatile Impurities

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Abstract

The analysis of organic volatile impurities (OVIs) sometimes requires the use of organic solvents for dissolution and/or extraction of samples. Consequently, these solvents must be free from contaminants that could interfere with GC analysis by coeluting with peaks of interest in the sample. This study presents data on dimethylsulfoxide (DMSO), a solvent commonly used for OVI analysis. Headspace grade DMSO is compared to a conventional grade. Solvent cleanliness, as well as compatibility for use in the analysis of the OVIs listed in United States Pharmacopeia (USP) Method <467>, European Pharmacopoeia (EP) Method 2.4.24, and the International Conference on Harmonization (ICH) guidelines are demonstrated.

Introduction

OVIs sometimes remain behind in pharmaceutical preparations as a result of synthetic and manufacturing procedures. For reasons of health and safety, testing is done to ensure that these solvents are not above concentration limits listed by USP and in the ICH guidelines (1,2). Static headspace GC (HS-GC) is a commonly used technique in the analysis of these OVIs. This technique concentrates volatile analytes, and allows for their analysis free from sample matrix. Samples to be analyzed by HS-GC must be dissolved in a suitable solvent; and in addition to being able to dissolve the sample, the solvent chosen must have a low partition coefficient as well. The partition coefficient affects the ability of an analyte to enter into the headspace, and those with lower values will have greater sensitivity in the headspace (3). Alternatively, a dissolution solvent with a high partition coefficient will have low vapor pressure and not affect detection of OVI analytes by “flooding” the headspace.

Introduction (contd.)

Water offers a very low partition coefficient, but cannot be used in all cases. USP <467> and EP 2.4.24 methodologies list procedures for both water soluble and water-insoluble samples. For water-insoluble samples, USP <467> designates the use of DMSO and dimethylformamide (DMF). Other dissolution solvents which have been found to be useful for headspace analysis of water-insoluble samples include dimethylacetamide (DMAC) and 1,3-dimethyl-2-imidazolidinone (DMI), and the later is described for use in EP 2.4.24 (4).

The purity of dissolution solvents used is essential to avoid extraneous peaks in the chromatographic analysis, and prevent interference with the analytes of interest. Many protocols followed by laboratories doing OVI analysis require the analysis of an acceptable blank, and some published methodologies, such as EP Method 2.4.24, require the analysis of a blank to verify the absence of interfering peaks.

Introduction (contd.)

The purity of DMSO solvent samples was evaluated by preparing sample blanks using headspace grade and organic synthesis grade. Both solvent blanks were subjected to HS-GC analysis, and retention times of peaks present in the blanks were compared to an OVI standard prepared in headspace grade solvent. The OVI standard included a variety of common process solvents, representing various classes as described in USP <467> and ICH guidelines.

Additional purity testing was done on both headspace and organic synthesis grades of DMSO, using GC-MS to make tentative identifications of impurities eluting in the primary range of OVIs.

Experimental

Blanks were prepared by pipetting 1 mL of each DMSO sample into a 10 mL headspace vial, and subjecting the sealed vial to HS-GC analysis. A working OVI standard was prepared in the headspace grade DMSO from a stock solution. The stock OVI solution was prepared by using class A pipettes to measure specific volumes of each individual analyte into a volumetric flask, and adding headspace grade DMAC to volume. The weight of each analyte added was calculated using its density. An aliquot of this stock standard was dissolved in the headspace grade DMSO to prepare the working standard. 1 mL of this working standard was then measured into a 10 mL headspace vial for HS-GC analysis. The composition and final concentration of the OVI working standard are summarized in Table 1.

Table 1. OVI Working Standard, Concentrations and Peak IDs

Peak #	Compound	Class	Concentration (µg/mL)
1	Methanol	2	237
2	Ethanol	3	395
3	Acetone	3	235
4	Isopropanol	3	390
5	Acetonitrile	2	39
6	Methylene chloride	2	66
7	tert-Butanol	NC	237
8	Methyl-tert-butyl ether	3	221
9	n-Hexane	2	33
10	n-Propanol	3	240
11	Methyl ethyl ketone	3	240
12	Ethyl acetate	3	271
13	Tetrahydrofuran	2	88
14	Cyclohexane	2	232

NC: Solvent not classified

Table 1. OVI Working Standard, Concentrations and Peak IDs (contd.)

Peak #	Compound	Class	Concentration (µg/mL)
15	Isobutanol	3	241
16	Isopropyl acetate	3	262
17	2-Methyl-tetrahydrofuran	NC	86
18	n-Heptane	3	68
19	1-Methoxy-2-propanol	NC	192
20	1,4-Dioxane	2	52
21	4-Methyl-2-pentanone	3	239
22	Toluene	2	86
23	Diisopropyl ethylamine	NC	94
24	Dimethylformamide	2	74
25	m-Xylene	2	86
26	o-Xylene	2	88
27	Tetramethyl urea	NC	387
28	N-Methylpyrrolidone	2	614

NC: Solvent not classified

Both blanks and the standard were analyzed by HS-GC using the parameters listed in Table 2.

The identification of impurities in DMSO was performed using solid phase microextraction (SPME) to do a headspace extraction. The samples of DMSO were diluted 1:1 with deionized water, and a 2 mL aliquot was extracted by headspace SPME and analyzed by GC-MS using the conditions listed in Table 3.

Table 2. HS-GC Parameters

Headspace Parameters	
Temperatures: Oven	100 °C
Loop	110 °C
Transfer Line	150 °C
Times: Vial Equilibration	10 min.
Pressurization	0.2 min.
Loop Fill	0.2 min.
Loop Equilibration	0.05 min.
Pressures: Vial	15 psi
Transfer Line	25 psi
Loop Volume	1.0 mL
Inject Time	1 min.
GC Parameters	
Column	SPB-624, 30 m x 0.32 mm I.D. x 1.4 µm
Injector and Detector Temps.	225 °C, 270 °C (FID)
Oven Program:	40 °C (4 min.), 8 °C /min. to 60 °C, 5 °C/min. to 85 °C (2 min.), 30 °C /min. to 220 °C(2 min.)
Carrier	Helium, 1.5 mL/min constant flow
Injection:	Headspace, Split 5:1; 2 mm ID liner used

Table 3. Headspace SPME, GC-MS Parameters

SPME, GC-MS Parameters	
Sample	1 mL DMSO + 1 mL deionized water in 4 mL vial
SPME fiber	100 µm PDMS
Extraction	Headspace, 50 °C, 5 min. with stirring
Desorption process	3 min., 250 °C, 0.75 mm ID SPME liner
Column	SPB-624, 30 m x 0.25 mm I.D. x 1.4 µm
Oven	35 °C (3 min.), 8 °C /min. to 220 °C (10 min.)
Detector	MSD, interface at 220 °C
Scan range	m/z = 40 – 450
Carrier gas	Helium, 1 mL/min.

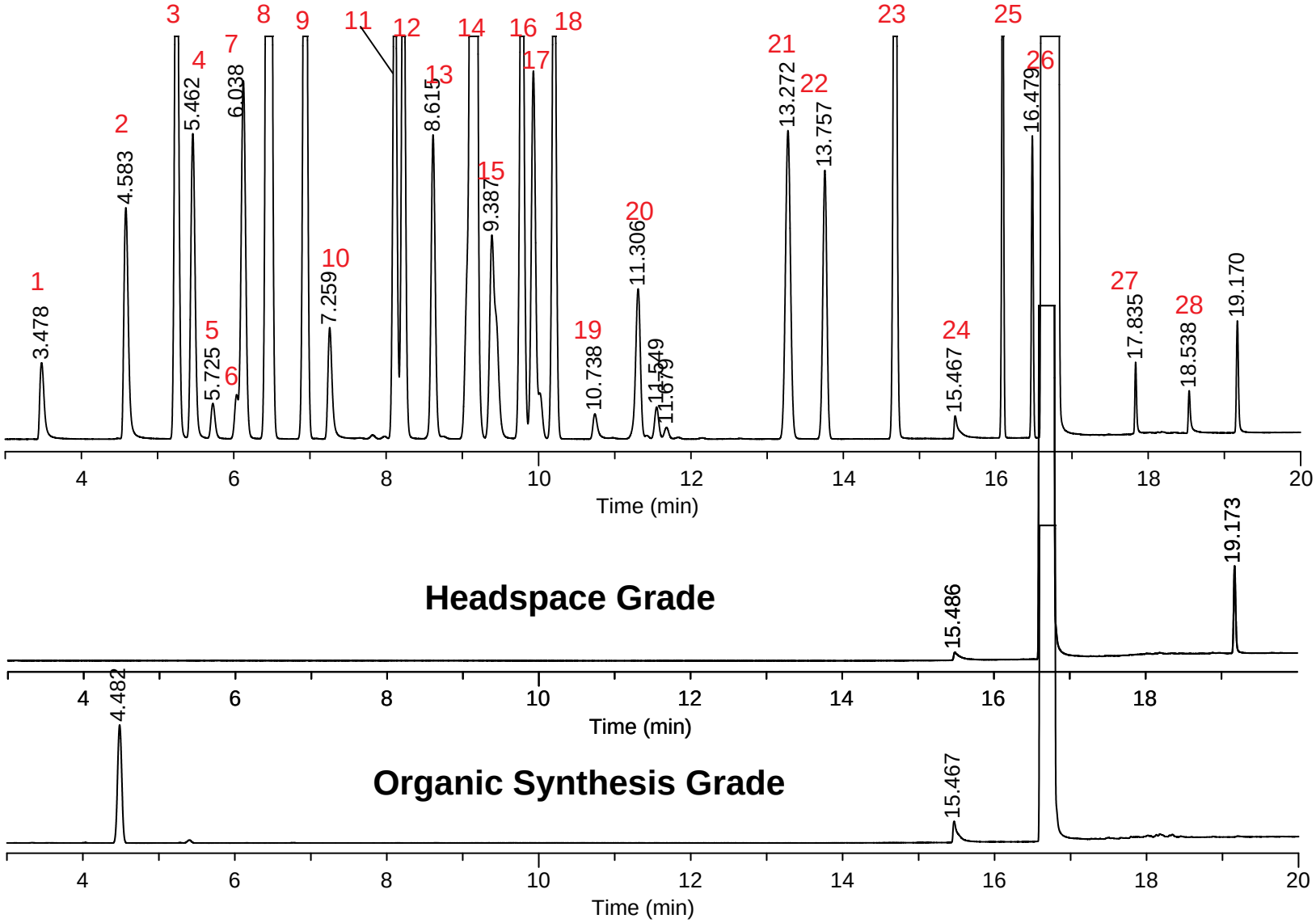
Results

HS-GC Analysis

The results comparing the headspace blanks and OVI standard are presented in Figure 1. The identification of each peak in the OVI standard is listed in Table 1. The resulting chromatograms from the HS-GC analyses indicated:

- Both DMSO blanks contained DMF.
- A peak corresponding to the retention time of DMI was detected in the headspace grade DMSO blank. This same peak was also detected in the OVI working standard, which was prepared in headspace grade DMSO.
- The organic synthesis grade DMSO blank contained a peak eluting close to the retention time of ethanol.
- Overall, the headspace grade DMSO blank had fewer and less significant peaks in the OVI elution range than the organic synthesis grade blank.

Figure 1. HS-GC Analysis Comparison of DMSO Grades



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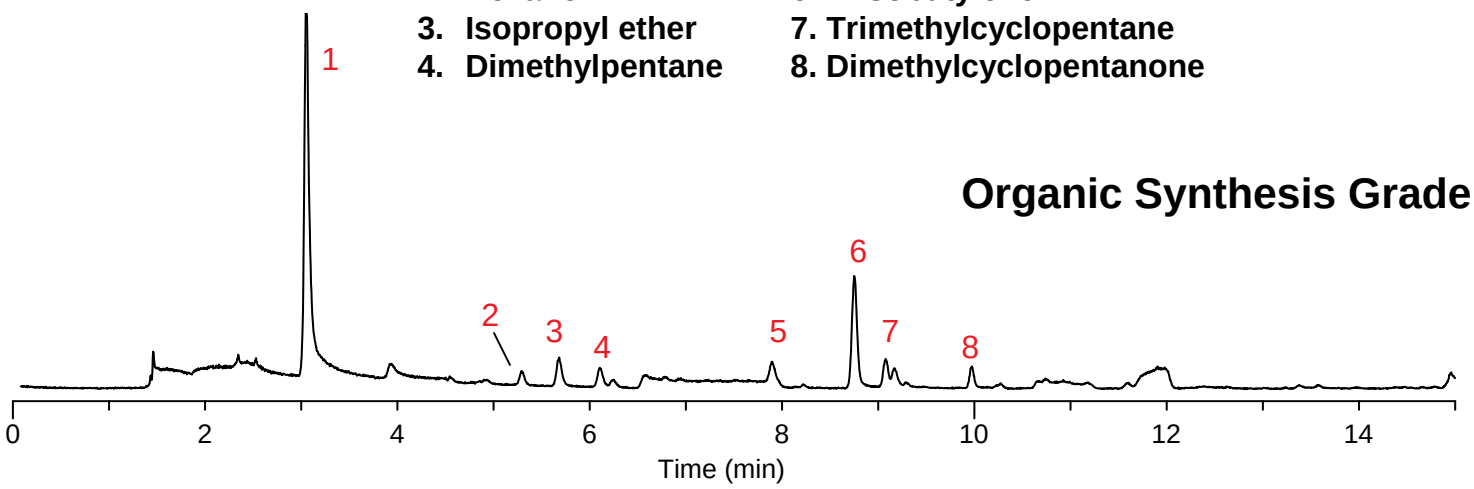
DMSO Impurity Analysis

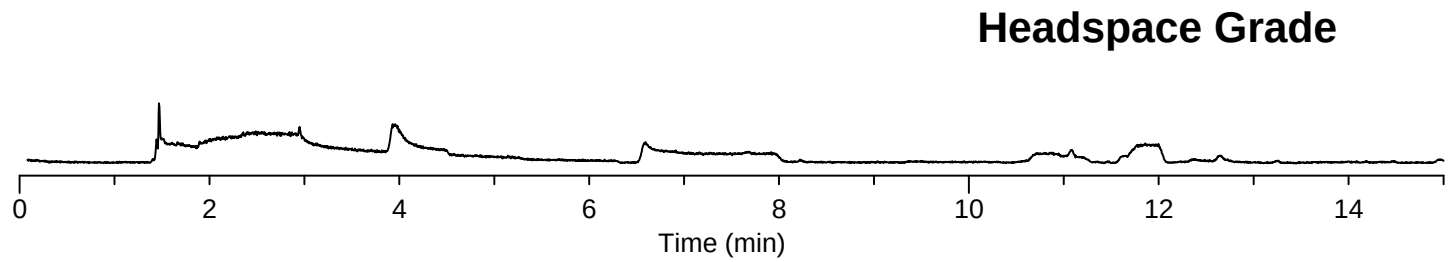
Total ion chromatograms (TICs) from the analysis of headspace and organic synthesis grade DMSO are compared in Figure 2. The scale of both TICs is the same, and the elution range prior to DMSO is shown. These TICs indicate the following:

- Headspace SPME detected the presence of compounds in the organic snythesis grade DMSO that were not present in the headspace grade DMSO.
- The larger peaks were tentatively identified by spectral library match.
- Pentane and hexane, which were detected in the organic synthesis grade DMSO, are class 3 and 2 solvents respectively.
- The baseline disturbances present in both TICs are a result of background artifacts resulting from the headspace SPME.

Figure 2. SPME GC-MS Impurity Analysis of DMSO Grades

1. Pentane
2. Hexane
3. Isopropyl ether
4. Dimethylpentane
5. Isooctane
6. Diisobutylene
7. Trimethylcyclopentane
8. Dimethylcyclopentanone





Headspace grade solvents should be specially tested to ensure that no peaks elute in the same retention time range as the OVIs. The DMSO evaluated in this study was Fluka Brand, and specified for HS-GC use. DMSO, as well as other Fluka Brand solvents designated for HS-GC use require special handling during the manufacturing process, including micro-filtration and packaging under an inert atmosphere. The properties of these solvents are summarized in Table 4 (5). HS-GC data, similar to what is presented here for DMSO, is available for these solvents in a previously presented publication (6).

Table 4. Properties of Solvents Commonly Used for Headspace Analysis, HS-GC vs. Alternate Grade

Name	Acronym	CAS #	Purity HS-GC Grade	Purity Alternate Grade	B.P. (° C)	Vapor Pressure (mm Hg)
Dimethylsulfoxide	DMSO	67-68-5	99.9%	99.8%	189	0.42 (20 ° C)
N,N-Dimethylformamide	DMF	68-12-2	99.9%	99.8%	155	2.70 (20 ° C)
N,N-Dimethylacetamide	DMAC	127-19-5	99.9%	99.9%	165	2.00 (25 ° C) 4.00 (38 ° C)
1,3-Dimethyl-2-imidazolidinone	DMI	80-73-9	99.5%	NA	225	5.00 (83 ° C)

Conclusions

- The headspace grade DMSO was suitable for the analysis of OVIs by HS-GC.
- Headspace grade DMSO produced an HS-GC blank cleaner than that prepared using organic synthesis grade solvent.
- The headspace grade DMSO did not produce any major interference peaks in the elution range of the target analytes.
- Organic synthesis grade DMSO had a large peak eluting in the retention range of the target analytes.
- Headspace SPME and GC-MS detected and tentatively identified compounds in the organic synthesis grade DMSO that were not present in the HS-GC grade. Two of these compounds were solvents listed in the ICH guidelines, USP Method <467>, and EP Method 2.4.24.

Acknowledgement

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References

1. United States Pharmacopoeia (USP), 31st Edition (2008), <467> Residual Solvents.
2. ICH Guidelines for Industry, Q3C Impurities: Residual Solvents, US Dept. of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), ICH December, 1997.
3. Y. Sitaramaraju, A. van Hul, K. Wolfs, A. Van Schepdael, J. Hoogmartens, E. Adams, Static headspace gas chromatography of (semi-)volatile drugs in pharmaceuticals for topical use. *J. of Pharmaceutical and Biomedical Analysis*. **2008**, *47,* 834-840.
4. European Pharmacopoeia (EP) 5.0, Vol.1, (2004), 2.4.24 Identification and Control of Residual Solvents.

References (contd.)

5. L. Dai, A. Quiroga, K. Zhang, H. Runes, D. Yazzie, D. Mistry, N. Chetwyn, M. Dong, *A Generic headspace GC method for residual solvents in pharmaceuticals: benefits, rationale and adaptations for new chemical entities.* Genentech USA (2009).
6. A. Quiroga, M. Dong, K. Stenerson, S. Verma. The Utility of Headspace Grade Solvents in the Analysis of Organic Volatile Impurities. Presented at the Eastern Analytical Symposium, Somerset, N.J., Nov. 2009; Supelco publication T409180.