

BIOSOLVE HEADSPACE

Solvents for Analysis of OVI



Headspace Grade Solvents For Analysis Of Organic Volatile Impurities

Organic Volatile Impurities (OVI) in pharmaceuticals, commonly referred as residual solvents, are trace organic volatile chemicals used or produced in the manufacturing of active substances, excipients, or in the preparation of medicinal products.

Appropriate selection of the solvent for the synthesis of medicinal substance is usually a critical parameter in the synthetic process, as it may enhance the yield, or determine characteristics, such as purity, crystal form, dissolution and solubility. Unfortunately, many of the solvents are not completely removed by practical manufacturing techniques; therefore, their content should be evaluated and justified.

The International Conference on Harmonization (ICH) method Q3C¹, United States Pharmacopoeia (USP) method 467², and the European Pharmacopoeia (EP) method 2.4.24³, have set guidelines to identify residual solvents in pharmaceuticals and ensure that these solvents are not above the concentration limits according to the risk they pose for human health.

Revised procedures for the identification and quantification of OVI consist of a static Headspace extraction coupled with a Gas Chromatographic (GC) separation. Static Headspace technique is a precise and well-accepted method for the analysis of residual solvents. This technique is used for concentrating residual solvents from the sample preparation into the gas phase, resulting with the improvement of their detection limits in the GC analysis. Samples analyzed by this technique may need a suitable solvent for dissolution, and procedures for Water-soluble and Water-insoluble samples are describe^{1,2,3}. For Water-insoluble samples, the use of Biosolve Headspace grade solvents: Dimethylacetamide (DMA), Dimethylformamide (DMF), Dimethylimidazolidinone (DMI) and Dimethylsulfoxide (DMSO) is described hereunder, but other high boiling solvents, such as N-Methyl-2-pyrrolidone (NMP) have also been found suitable for the Headspace analysis.

Since 2006, Biosolve optimized its Headspace grade solvents for accurate analysis of residual solvents in medicinal products. The purity of the solvents specifically evaluated by analysis of the Headspace grade solvent against OVI standard solution to ensure the absence of interfering peaks in the GC chromatogram.

The following section demonstrates the compatibility of Biosolve Headspace grade solvents as well as their cleanliness for the analysis of OVI in the Headspace-GC technique. To do just that we chose a variety of common process solvents, representing a wide range of elution by the GC analyses.

Blanks of each Headspace solvent and OVI standard solutions were prepared by pipetting 1 mL of the liquid into 20 mL Headspace vial. Final content of OVI in the standard solutions was calculated for use with 100mg of tested medicinal sample. The composition and concentration of OVI used as standards are summarized in Table 1.



Table 1: Headspace solvents tested and OVI Standard solutions.

	Headspace solvent (Blank)	DMSO	DMA	DMF	DMI
	CAS No.	67-68-5	127-19- 5	68-12-2	80-73-9
	Density:	1.10	0.94	0.95	1.04
	B.Point (°C)	189	165	155	225
#	OVI	Final Concentration µg/g			
1	Methanol	273.6	321.2	289.5	278.4
2	Ethanol	229.5	245.0	259.2	249.2
3	Acetone	230.1	245.6	259.9	249.9
4	2-Propanol	228.4	243.7	257.9	248.0
5	Acetonitrile	37.0	39.5	41.8	40.2
6	Methylene Chloride	60.2	64.3	68.0	65.4
7	Methyl tert-Butyl Ether	53.8	57.4	60.8	58.4
8	n-Hexane	28.8	30.7	32.5	31.3
9	1-Propanol	233.9	249.6	264.1	254.0
10	Methyl Ethyl Ketone	234.2	249.9	264.5	254.3
11	Ethyl Acetate	229.3	244.8	259.0	249.0
12	Tetrahydrofuran	64.5	68.8	72.9	70.1
13	Cyclohexane	34.0	36.3	38.4	36.9
14	Isobutanol	218.5	233.1	246.7	237.2
15	n-Heptane	49.7	53.1	56.2	54.0
16	n-Butanol	220.9	235.8	249.5	239.9
17	1,4-Dioxane	37.6	40.1	42.4	40.8
18	Methyl Isobutyl Ketone	233.0	248.7	263.2	253.0
19	Toluene	78.8	84.1	89.0	85.6
20	Isobutyl Acetate	221.5	236.3	250.1	240.5
21	Butyl Acetate	224.3	239.3	253.3	243.5
22	Dimethylformamide	68.9	73.6	77.9	74.9
23	m-Xylene	126.3	134.8	142.7	137.2
24	o-Xylene	32.0	34.2	36.1	34.7

The comparison of Biosolve Headspace grade solvents to the OVI standard solutions is presented in Figures 1-8. The identification of each peak in the OVI standard solution is listed in Table 1.

The following analysis chromatograms show that:

- ◆ The system peaks in the chromatograms of DMA, DMI & DMSO Headspace solvents are out of the analysis range of OVI.
- ◆ DMF Headspace grade solvent shows a slight degradation peak of Dimethylamine, which created in the presence of moisture while heating the Headspace vial. Despite this, its retention time does not interfere with the analysis of the OVI standard solution.

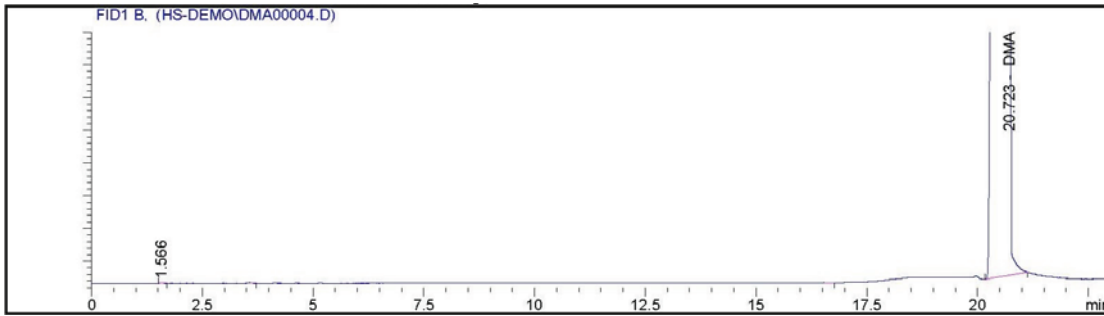
Conclusions

- ◆ Biosolve Headspace grade solvents, DMA, DMF, DMI & DMSO are compatible for detection of OVI with the Headspace-GC technique.
- ◆ Biosolve Headspace grade solvents are highly pure and show no major interfering peaks in a wide range of common residual solvents analysis by GC.
- ◆ Biosolve Headspace grade solvents are suitable dissolution solvents for the analysis of OVI as described by the ICH, USP & EP methods.

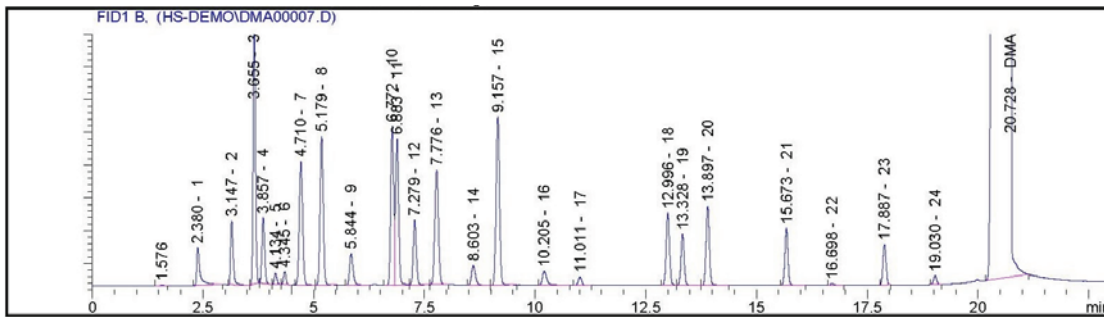
References

1. International Conference on Harmonization (ICH), Harmonised tripartite guideline impurities: guideline for residual solvents Q3C(R5), 2011.
2. United States Pharmacopoeia (USP), 33rd ed. Method <467> Residual Solvents, 2010.
3. European Pharmacopoeia 2.4.24, Residual Solvents (British Pharmacopoeia volume IV, Appendix VIII L., & supplementary chapter IV SC IV D.), 2010.

DMA

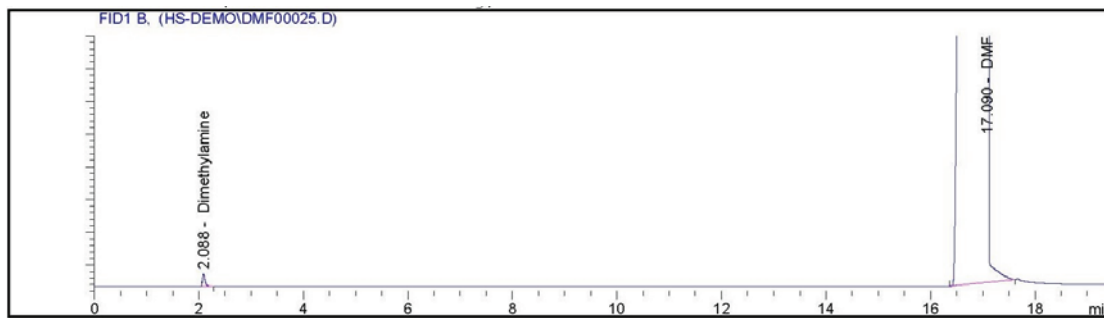


Figures 1: HS-GC Chromatogram of Biosolve DMA Headspace grade solvent

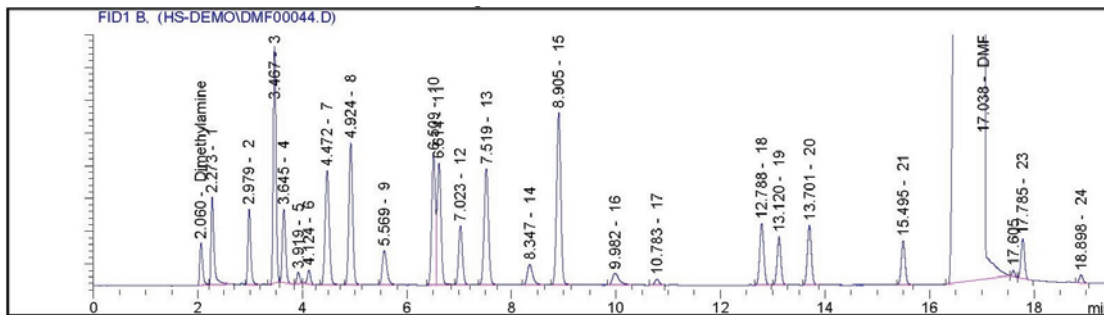


Figures 2: HS-GC Chromatogram of standard OVI's solution in DMA Headspace grade

DMF



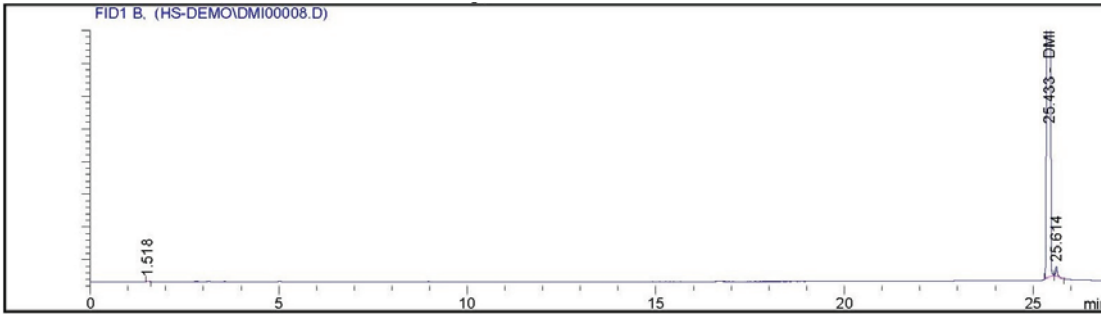
Figures 3: HS-GC Chromatogram of Biosolve DMF Headspace grade



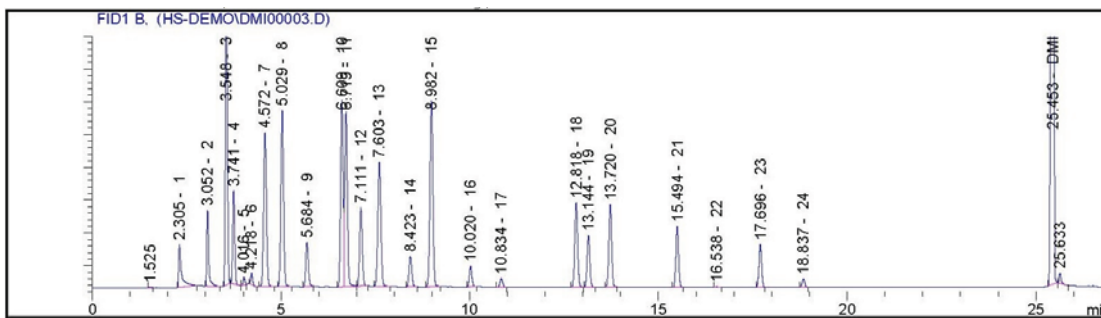
Figures 4: HS-GC Chromatogram of standard OVI's solution in DMF Headspace grade



DMI

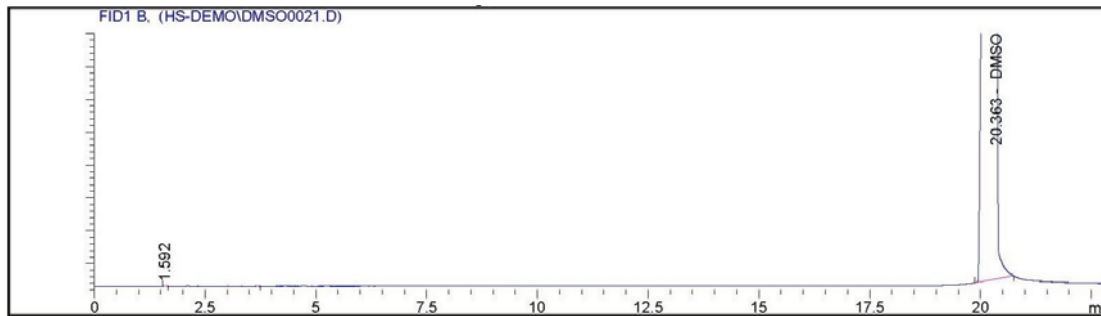


Figures 5: HS-GC Chromatogram of Biosolve DMI Headspace grade solvent

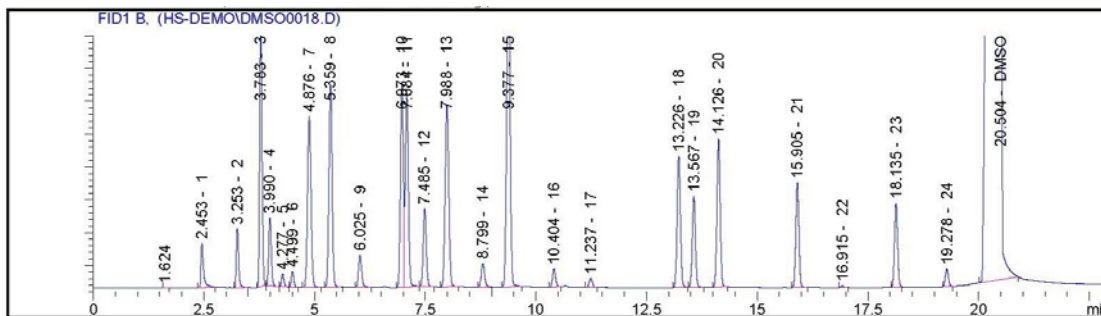


Figures 6: HS-GC Chromatogram of standard OVI's solution in DMI Headspace grade

DMSO



Figures 7: HS-GC Chromatogram of Biosolve DMSO Headspace grade solvent



Figures 8: HS-GC Chromatogram of standard OVI's solution in DMSO Headspace grade

Experimental conditions:

GC - Column: G43 (Cyanopropylphenyl 6%/Dimethylpolysiloxane 94%), 30m x 0.32mm I.D. x 1.8µm; Injector Temp.: 230°C, Detector Temp.: 280°C; Column flow: 9 psi pressure at constant pressure mode; Oven Program: 40 °C 5 min., 5°C /min. to 120°C, 40°C /min. to 200°C 7 min; Injection: split 1:10. Headspace - Oven: 80°C; Loop: 90°C; Transfer Line: 100°C; Vial Equilibration time: 20 min; Loop volume: 1.0 mL.

Specifications

N,N-Dimethylacetamide

C₄H₉NO

EC 204-826-4

CAS [127-19-5]

Danger H:312-332-360D P:261-280-281-322

Cat. No:

042075

Assay (GC, on anhydrous basis)

min. 99.99%

Water (KF)

max. 0.03%

Headspace test for O.V.I.

Passes test

UV cutoff wavelength

190-268nm

T268nm

min. 10%

T275nm

min. 55%

T300nm

min. 85%

T350nm

min. 98%

T400nm

min. 99%

Refractive index (20°C)

1.436-1.438

Standard pack:

04207501

1 L

6X1L G. Bottle 45

042075G5

500 ML

6X0.5L G. Bottle 45



N,N-Dimethylformamide

C₃H₇NO

EC 200-679-5

UN 2265,3,III,F1

CAS [68-12-2]

Danger H:312-319-332-360 P:261-280-281-305+351+338

Cat. No:

041975

Assay (GC, on anhydrous basis)

min. 99.99%

Water (KF)

max. 0.03%

Headspace test for O.V.I.

Passes test

UV cutoff wavelength

190-269nm

T270nm

min. 20%

T275nm

min. 55%

T300nm

min. 85%

T320nm

min. 95%

Refractive index (20°C)

1.429-1.431

Standard pack:

04197501

1 L

6X1L G. Bottle 45

041975G5

500 ML

6X0.5L G. Bottle 45



1,3-Dimethyl-2-Imidazolidinone

C₅H₁₀N₂O

EC 201-304-8

UN 2810,6.1,III,T1

CAS [80-73-9]

Warning H:302-312-315-319 P:280-305+351+338-321-322-362

Cat. No:

090775

Assay (GC, on anhydrous basis)

min. 99.5%

Water (KF)

max. 0.04%





Headspace test for O.V.I.
 UV cutoff wavelength
 T275nm
 T300nm
 T325nm
 T>350nm
 Refractive index (20°C)
 Standard pack:
 09077501
 090775G5

Passes test
 190-270nm
 min. 30%
 min. 60%
 min. 80%
 min. 90%
 1.470-1.473

1 L 6X1L G. Bottle 45
 500 ML 6X0.5L G. Bottle 45

Dimethylsulfoxide

C₂H₆OS
 EC 200-664-3
 CAS [67-68-5]
 Warning H:319 P:305+351+338

Cat. No:

Assay (GC, on anhydrous basis)
 Water (KF)

Headspace test for O.V.I.
 UV cutoff wavelength

T268nm
 T275nm
 T300nm
 T350nm
 T400nm

Refractive index (20°C)

Standard pack:

04477501
 044775G5
 04477532

044775

min. 99.99%
 max. 0.04%
 Passes test
 190-265nm
 min. 30%
 min. 60%
 min. 85%
 min. 95%
 min. 98%
 1.477-1.480

1 L 6X1L G. Bottle 45
 500 ML 6X0.5L G. Bottle 45
 250 ML 6X250ML G. Bottle 45



N-Methyl-2-Pyrrolidone

C₅H₉NO
 EC 212-828-1
 CAS [872-50-4]
 Danger H:315-319-335-360D P:261-280-305+351+338-321

Cat. No:

Assay (GC, on anhydrous basis)
 Water (KF)

Headspace test for O.V.I.
 UV cutoff wavelength

T285nm
 T300nm
 T320nm
 T>350nm

Refractive index (20°C)

Standard pack:

13567501
 135675G5

135675

min. 99.9%
 max. 0.1%
 Passes test
 190-269nm
 min. 30%
 min. 55%
 min. 78%
 min. 97%
 1.469-1.471

1 L 6X1L G. Bottle 45
 500 ML 6X0.5L G. Bottle 45





HEADSPACE



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