WHITE PAPER

Headspace GC Solvents

The pharmaceutical industry uses solvents in the synthesis or recrystallisation of its products which must later be eliminated due to their toxicity and undesirable effects on consumers.

Residual solvents are volatile organic impurities that come from the manufacturing or purification processes of end products. The guide for the control of residual solvents Q3C from the ICH (International Committee on Harmonisation) and the American Pharmacopoeia (USP) and European Pharmacopoeia (Ph Eur) (methods in USP chapter <467> and in Ph Eur chapter 2.4.24), have established the maximum permissible limits for residual solvents.

HeadSpace gas chromatography, is the most appropriate method to analyse and quantify volatile organic solvents in a wide variety of samples. The technique consists of concentrating the volatile compounds of interest in the gas phase of a sample vial and analysing the gas sampled by GC. This allows the detection limits to be reduced to values lower than 1 ppm.

Classification according to toxicity

Residual solvents are divided into four classes according to their toxicity. Solvents in Class 1 are considered very toxic and should be avoided in the manufacture of pharmaceutical products. Class 2 are less toxic, but their levels are limited. Class 3 are a minor risk to human health, but under no circumstance can they be ignored. Class 4 solvents are those that should be analysed, but whose actual toxicity in humans is not known.

Solvents used to analyse these volatile compounds must have a boiling point which is much higher than the compound itself. These solvents will be the matrix through which the sample will be dissolved to analyse the impurities of volatile solvents. In class 3 solvents, when the drying loss is greater than 0.5%, they must be identified and authenticated. If the drying loss is less than 0.5%, it is considered within the accepted levels and it is not necessary to quantify them.

Maximum limits accepted in the ICH guide

Table 1.
Class 1 solvents: must be avoided in pharmaceutical products

Solvent	Caution	Concentration limit (ppm)
Benzene	Cancerogenic	2
Carbon Tetrachloride	Toxic and harmful to the environment	4
1,2-Dichloroethane	Toxic	5
1,1-Dichloroetthane	Toxic	8
1,1,1-Trichloroethane	Harmful for the enviroment	1.500

Table 2.
Class 2 solvents: must be limited in pharmaceutical products

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
Cumene	0.7	70
1,2-Dichloroethane	18.7	1870
Dichloromethane	6	600
1,2-Dimethoxethane	1	100
N,N-Dimethylacetamide	10,9	1,090
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxiethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30	300
2-Methoxiethanol	0.5	50
Methyl butyl ketone	0.5	50
Methylcyclohexane	11.8	1180
Methyl isobutyl ketone	45	4500
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1	100
Toluene	8.9	890
1,1,2-Trichloroethane	0.8	80
Xylene (Add isomers)	21.7	2170

Table 3.
Class 3 solvents: low risk to human health

Solvent	Concentration limit (ppm)
Butyl acetate	50mg per day (5,000ppm)
Ethyl acetate	
Isobutyl acetate	
Isopropyl acetate	
Methyl acetate	
Propyl acetate	
Acetone	
Acetic acid	
Formic acid	
Anisole	
1-Butanol	
2-Butanol	
t-Butyl methyl ether	
Dimethyl sulfoxide	
Ethanol	
Diethyl ether	
Ethyl formate	
Heptane	
Methyl ethyl ketone	
3-Meythl-1-butanol	
2-Meythl-1-propanol	
Pentane	
1-Penthanol	
1-Propanol	
2-Propanol	
Triethylamine	

Analysis of volatile organic compounds via Headspace

Chromatogram 1 shows the most common solvents analysed via the headspace technique, dissolved in DMSO. Analysis conditions are given in Table 1:

Cromatogram 1.

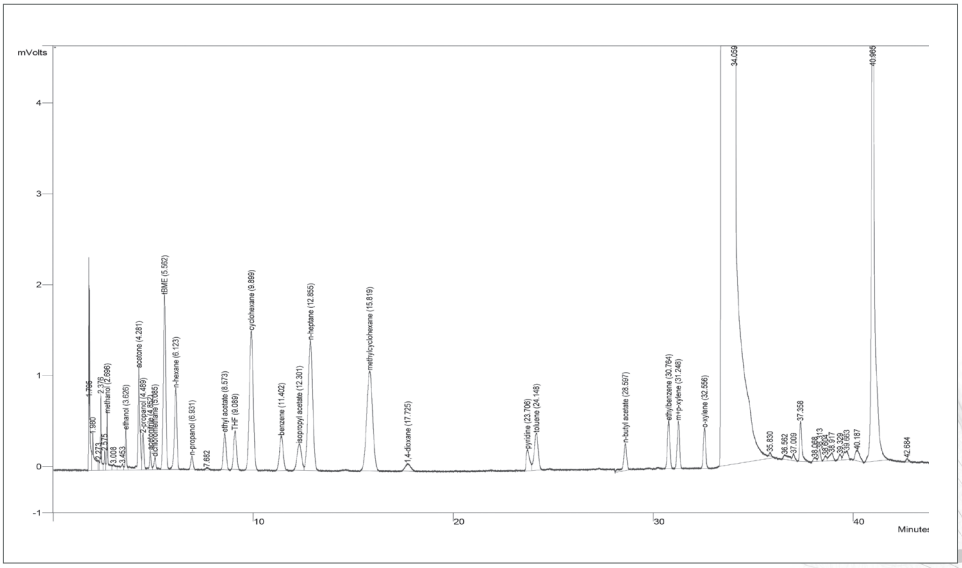


Table 1.

Varian 3900 GC

- Column: 30m x 0,53mm , 3µm Select-624
- Oven program: 40°C (20min), rate 5°C/min to 160°C
- Injection port: 200°C
- Split ratio: 50:1
- Carrier gas: Helium
- Column flow: 4.0mL/min
- Detector: 300°C FID
- H_2O flow: 300 mL/min
- Air flow: 300 mL/min
- Make-up flow: 26 mL/min

OHSS-4.0 headspace sampler

- Loop size: 1 mL
- Equilibration time: 50 min
- Schaker: Yes
- Volume vial: 1 mL
- Volumen vial: 20 mL

DMSO, DMA

- Headspace oven: 120°C
- Loop temperatura: 140°C
- Transfer line temperatura: 140°C

DMSO, DMA

- Headspace oven: 80°C
- Loop temperatura: 90°C
- Transfer line temperatura: 90°C

The procedures described in Ph Eur or USP, show several alternatives for the determination of volatile organic compounds in APIs or end products, distinguishing several methods depending on whether the sample is water soluble or not. In case the sample is not water soluble, DMSO, DMF, DMA, DMI, NMP and benzyl alcohol can be used as alternative solvents.

What do we need to know about the Headspace technique?

Several Headspace techniques have been developed: the dynamic HS or purge and trap HS and static HS.

Dynamic or purge and trap Headspace

In the dynamic or purge and trap HeadSpace, the sample is housed in an open vial, usually 20ml. An extraction is made by passing an inert gas through the vial where the sample is. The analytes are caught in a trap with a solid phase adsorbent, where after a thermal desorption, they are transported by the carrier gas to the gas chromatograph.

In this technique, heating is not necessary as the force of the gas is used, which permits using solvents with a low boiling point. Carrying out a constant purge of the volatile compounds is possible until the residual solvents are completely extracted. This enables a complete extraction and subsequent analysis of the solvents present. By properly combining the nature and the absorbent in the trap, the concentration of analytes at a level of traces with a wide range of volatility is achieved.

Static Headspace

In the static HeadSpace technique, the sample is housed in a hermetically sealed vial with a capsule provided with a septum. The vial can be 6, 10 or 20 ml and is approximately half filled. The vial with the sample is heated in a furnace so that part of the volatile organic compounds changes to a gas phase. The area where the gas is present in the vial is called the Headspace.

Controlling incubation temperature and time in the oven, equilibrium between the liquid phase and gas phase is reached. Once equilibrium is reached, an aliquot of the gas phase is taken and transferred to the chromatograph for analysis.

In any case, for Headspace analysis it is essential that the solvent be free of the compounds of interest to prevent false results, interferences or contaminants.

Scharlab has a complete, specific line of high-boiling point solvents for the analysis of residual solvents via HeadSpace. The main features of the HS-GC grade solvents are:

- Free of residual solvent impurities
- High purity
- Strict, detailed specifications
- Specific quality control via Headspace GC
- Very stable base line with good linearity in the elution range for most residual solvents

Comparison of HeadSpace grade and analytical grade ACS

In this experiment, we evaluated the suitability for the analysis of residual solvents with an HSF grade DMF compared with an analytical grade DMF, both Scharlau brand. The yield of the two DMFs, under the conditions mentioned below, was compared with the chromatogram obtained for a standard mixture of the residual solvents. A 10ml sample was analysed.

The standard mixture comprised a wide variety of residual solvents as established in ICH. The following table shows the composition of the standard mixture.

Varian 3900 GC	Concentration (mg/L)
Dichlorometane	1,06
tBME	2,07
Acetone	2,53
Methanol	2,53
THF	1,42
n-Hexane	0,53
Ethyl acetate	2,16
Ethanol	1,9
Benzene	1,06
Cyclohexane	1,87
Acetonitrile	2,52
2-Propanol	2,18

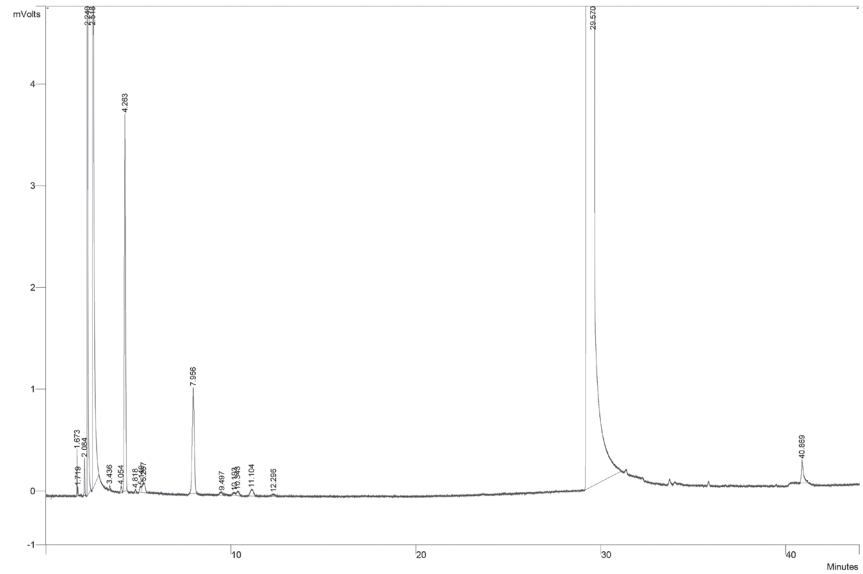
Varian 3900 GC	Concentration (mg/L)
Isopropyl acetate	2,1
n-Propanol	1,92
n-Heptane	1,9
Methylcyclohexane	2,16
1,4-Dioxane	2,47
Toluene	1,74
Pyridine	1,96
Butyl Acetate	2,11
Ethylbenzene	2,09
p-Xilene	2,06
m-xilene	2,06
o-xilene	2,11

The DMF analytical grade chromatogram shows more background noise and the presence of interfering peaks at the area of interest. To avoid incorrect identification and quantification of the volatile impurities present in the sample, the HS product is more suitable.

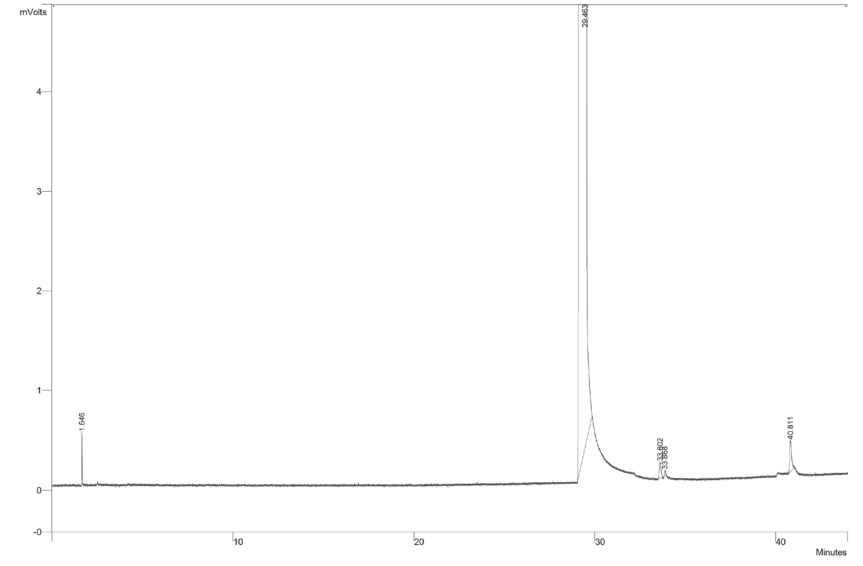
Although some peaks do not directly interfere in the analysis because our sample cannot contain that impurity, the low resolution of the peaks often makes analysis difficult. For example, the retention time of acetone is very similar to that of 2-propanol under the same conditions, which would lead to a possible identification error.

This test analysis is quite demanding, not only for the amount of sample analysed (10.0mL) to lower the detection limit <1 ppm, but also because analysis conditions require thermostating the samples at 80ºC for 50 minutes.

DMF, quality for analysis



DMF, Headspace GC quality



Chromatographic conditions

- Column: 30m x 0,53mm x 3µm, sílice (6% cianopropil-fenil)
- Program temperature: 40°C (20 min), increment of 5°C/min to 160°C
- Injector: 200°C
- Detector: 300°C, FID
- Carrier gas: Helio
- Column flow constant: 4,0ml/min
- Split ratio: 50
- Hydrogen flow: 30ml/min
- Air flow: 300ml/min
- Make up flow: 26ml/min

Headspace conditions

- Oven temp.: 80°C
- Loop temp.: 90°C
- Transfer line temp.: 90°C
- Incubation time with the vial shaken: 50 min
- Injection time: 1 min
- Vial volume: 10,0ml
- Injection volume: 1ml

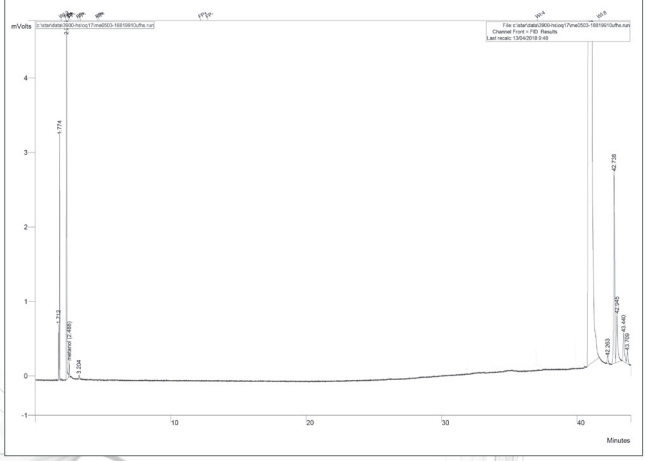
The high quality of the DMF HS, whose chromatogram has no interfering peaks at the range of interest, makes it especially suitable for the analysis of volatile compounds using the Headspace technique.

Comparison of HeadSpace solvents

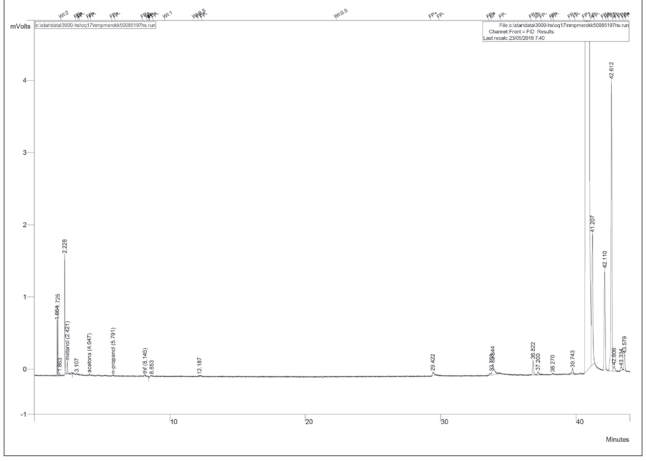
Different HeadSpace-quality 1-Methyl-2-pyrrolidone (NMP) were compared, one being the Scharlau Brand and three other brands on the market.

The Scharlau NMP chromatogram is clean without interfering peaks, while competitor products have peaks at the area of interest which can interfere with the impurities in the sample.

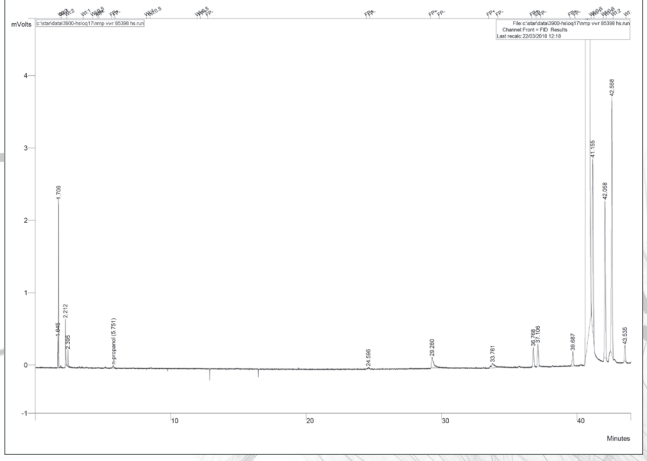
Scharlau NMP



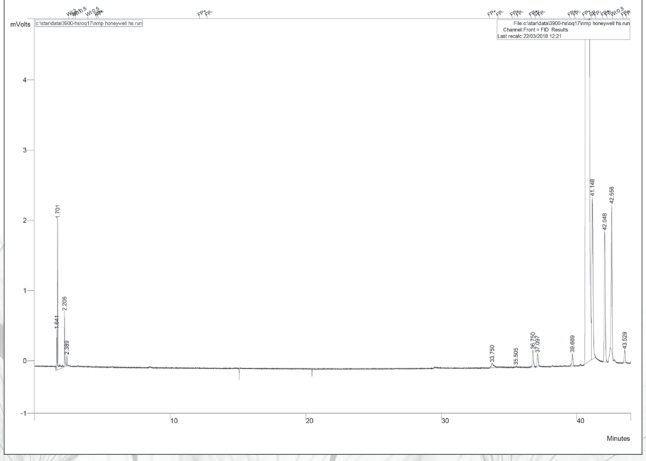
Competitor NMP 1



Competitor NMP 2



Competitor NMP 3



In addition to the optimal results obtained in the comparison, while other competitor brands only ensure residual solvents levels below that established in the ICH Q3C guide, Scharlau Headspace solvents guarantee the lowest levels in these solvents in all batches manufactured.

Scharlau Headspace GC Products

Scharlab manufactures a wide range of Headspace GC solvents. Very strict purification processes are used to eliminate volatile impurities. The bottling process is also critical to prevent the already purified products from being contaminated with traces of residual solvents present in the atmosphere, which is why Scharlab has designed specific bottling processes for these solvents. Each batch is analysed in our Quality Control Laboratory by means of HS-GC to ensure suitability for the analysis of residual solvents and impurity value traces are indicated on the Certificate of Analysis.

Scharlau HS-GC products not only comply with what is established in the ICH Q3C guide, but also established values which are much lower than the recognized limits.

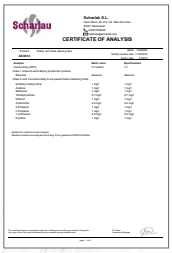
Maximum limits in solvents for Headspace GC are indicated in the following table:

Varian 3900 GC	Scharlau HS-GC Scharlau quality limit (mg/L)
Dichloromethane	0,6
tBME	1
Acetone	1
Methanol	1
THF	0,7
n-Hexane	0,3
Etilene acetate	1
Ethanol	1
Benzene	0
Cyclohexane	1
Acetonitrile	0,4
2-Propanol	1

Varian 3900 GC	Scharlau HS-GC Scharlau quality limit (mg/L)
Isopropyl acetate	1
n-Propanol	1
n-Heptane	1
Methylcyclohexane	1
1,4-Dioxane	0,4
Toluene	0,9
Pyridine	1
Butyl acetate	1
Ethylbenzene	1
p-Xylene	1
m-Xylene	1
o-Xylene	1

New Products

Responding to our users' needs, we have added new HS-quality products to our product range. We appreciate our clients' suggestions to develop new products.



Scharlau also has a line of GC patterns for the identification and quantification of residual solvents contained in the ICH Q3C guide.

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