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Analysis of Residual Solvents in Pharmaceutical Products by Headspace-GC-FID with Nitrogen Carrier Gas Following USP<467> - Procedure A

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❑ Introduction

Various organic solvents are used in the manufacturing process in pharmaceuticals. Residues of the organic solvents in drug active ingredients or final products are monitored as a critical quality control procedure [1]. According to USP<467> monograph, usage of Class 1 solvents must be avoided, while usage of Class 2 solvents is to be limited [2]. A headspace (HS) - gas chromatography (GC) method with helium as carrier gas was set up for analysis of residual solvents in pharmaceuticals following USP <467> [3]. Helium is a popular choice of GC carrier gas for its efficiency but its supply is depleting and it has become more expensive. Nitrogen is a less expensive gas, and it is allowed to be used as GC carrier gas in USP<467>. Here, we describe HS-GC method using nitrogen to replace helium as the carrier gas to analyse Class 1 and Class 2 solvents following USP<467> Procedure A criteria.

❑ Experimental

Analytical conditions and sample preparation

HS-20 headspace autosampler paired with Nexis GC-2030 (Shimadzu Corporation, Japan) were used in this work. The analytical conditions following Procedure A under water-soluble article section in USP<467> are shown in Table 1. Certified USP<467> Class 1 and 2 Standard solutions were purchased from Restek. The standards were prepared according to USP<467> Procedure A before analysis.

Table 1: HS-GC analytical conditions for residual solvent analysis following USP <467>

Instruments and Column information	
GC-FID	Nexis GC-2030
Auto Injector	HS-20
Column	SH-Rxi-624Sil MS 30m x 0.32mm ID x 1.8µm df
HS parameter	
Oven Temperature	80°C
Sample Line Temperature	110°C
Transfer Line Temperature	120°C
Injection Time	1 min
Pressurizing Gas Pressure	75 kPa
Equilibrating Time	60 min
Shaking Level	2
GC-FID parameter	
Injection Mode	Split mode Split ratio 5
Carrier Gas	Nitrogen
Gas Flow Condition	Constant linear velocity mode Linear velocity 35cm/s
Oven Temperature Programming	40°C (20min) →10°C/min to 240°C (20min)
Detector Temperature	250°C
Hydrogen Flow	32 mL/min
Synthetic Air Flow	200 mL/min
Make-up Gas Flow	24 mL/min

❑ Results and Discussion

Class 1 Standard

Class 1 Standard (five solvents) was analysed for 7 times to determine the peak area percentage relative standard deviation (%RSD) and signal to noise ratio (S/N). The S/N ratios were calculated using USP method (Table 2). The chromatogram of Class 1 Standard is displayed in Figure 1.

The lowest S/N value for 1,1,1-trichloroethane (peak 2) obtained is 97, which is much greater than the requirement stated in USP<467> (i.e., S/N ratio is not less than 5). Carbon tetrachloride (peak 3), which sensitivity is the lowest among the Class 1 solvents,

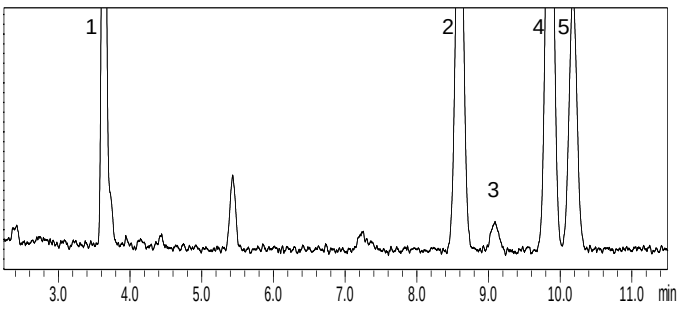

Figure 1: HS-GC-FID chromatogram of Class 1 Standard following Procedure A in USP<467>. Peak labelling refers Table 1.

Table 2: Peak area repeatability (n=7) and signal to noise ratio (S/N) for Class 1 Standard

Peak No.	Solvent	%RSD (n=7) of peak area	S/N ratio data 1	S/N ratio data 2	S/N ratio data 3	S/N ratio data 4	S/N ratio data 5	S/N ratio data 6	S/N ratio data 7
1	1,1-Dichloroethene	7.2	78	86	94	80	117	100	101
2	1,1,1-Trichloroethane	5.5	126	97	106	98	104	121	114
3	Carbon tetrachloride	6.2	10	7	7	8	8	11	10
4	Benzene	4.4	180	138	142	178	134	179	171
5	1,2-Dichloroethane	2.9	65	67	62	63	73	80	75

had S/N ratio values of 7 or greater. The repeatability of peak areas, %RSD (n=7), for the five solvents obtained ranges from 2.9% to 7.2%. These results indicate that Class 1 Standard can be analysed using nitrogen carrier gas to replace He in GC-FID analysis, achieving sensitivity stated in the USP<467> Procedure A.

Class 2 Standard

Class 2 Standard has two groups, Class 2A and Class 2B. The chromatograms are shown in Figures 2 and 3, respectively. The repeatability results of Class 2A and Class 2B are compiled into Table 3. The peak area %RSD (n=7) values obtained for all the solvents are below 4%.

One concern with using nitrogen as carrier gas is possible loss in peak resolution (R_s) when using same linear velocity as helium. As demonstrated in Figure 4, the specific resolution between acetonitrile and methylene chloride obtained with nitrogen carrier gas (R_s = 2.3) is almost the same as that using helium carrier gas (R_s = 2.4). This meets the stated criteria of USP<467> that R_s of these 2 compounds must not be less than 1.

In summary, the results above indicate that the HS-GC analysis method with nitrogen as carrier gas can achieve required sensitivity (S/N) and peak resolution stated in the criteria of USP<467> Procedure A. Moreover, this method has also demonstrated good peak area repeatability.

Table 3: Peak area repeatability (n=7) for Class 2A and 2B Standards

Class 2A standard		
No.	Compound	%RSD (n=7) of peak area
A1	Methanol	1.3
A2	Acetonitrile	2.2
A3	Methylene chloride	2.9
A4	Trans-1,2-Dichlorethene	1.5
A5	Cis-1,2-Dichloroethene	1.8
A6	Tetrahydrofuran	2.4
A7	Cyclohexane	1.6
A8	Methylcyclohexane	3.1
A9	1,4-Dioxane	2.9
A10	Toluene	1.8
A11	Chlorobenzene	1.9
A12	Ethylbenzene	1.7
A13	m-xylene and p-xylene	1.6
A14	o-xylene	1.8
A15	Cumene	1.6
Class 2B standard		
No.	Compound	%RSD (n=7) of peak area
B1	Hexane	2.3
B2	Nitromethane	1.3
B3	Chloroform	1.3
B4	1,2-Dimethoxyethane	3.6
B5	Trichloroethene	1.8
B6	Pyridine	1.8
B7	Methylbutylketone	1.6
B8	Tetralin	1.2

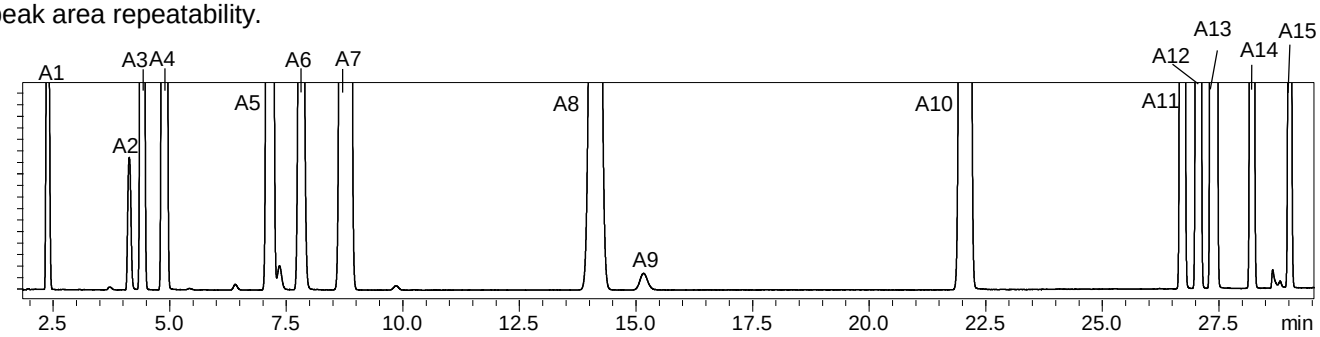

Figure 2: Chromatogram of Class 2A Standard analysed using Procedure A

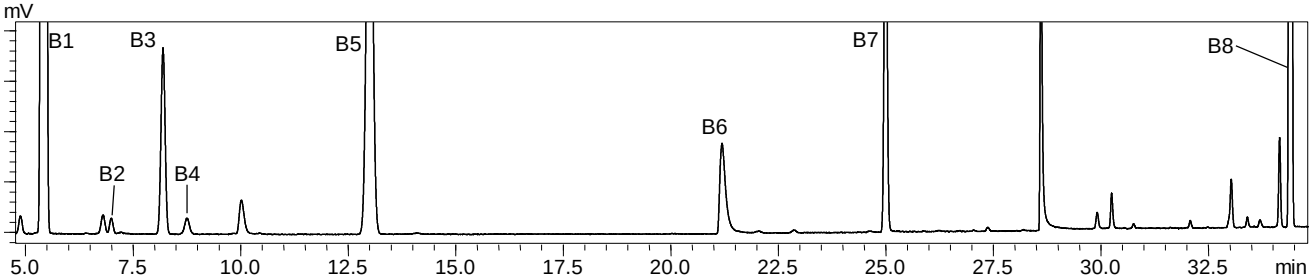

Figure 3: Chromatogram of Class 2B Standard analysed using Procedure A

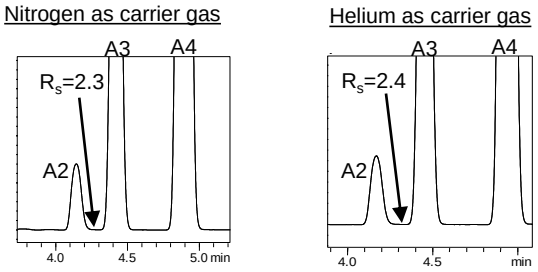

Figure 4: Comparison of resolution between acetonitrile peak (A2) and methylene chloride peak (A3) using nitrogen and helium as carrier gases

❑ Conclusions

This study demonstrates the feasibility of using nitrogen as carrier gas in HS-GC-FID analysis of residual solvents in pharmaceuticals. The results using Class 1 and Class 2 standards fulfil the criteria stated in USP<467> Procedure A from water-soluble article section.

❑ References

1. Grodowska, K., Parczewski, A., *Acta Pol Pharm*. 67(1):3-12(2010)
2. The United States Pharmacopeia, *USP <467> RESIDUAL SOLVENTS.*
3. Shimadzu Application News 290, *Analysis of Residual Solvents in drug products using Nexis GC-2030 combined with HS-20 headspace sampler - USP <467> Residual Solvents Procedure A*

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