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Application News

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

❑ Introduction

USP <467> monograph describes Procedure A and B for analysing residual solvents in pharmaceutical products by Headspace Gas Chromatography (HS-GC) [1]. Procedure A is the main method, while Procedure B is to be carried out as verification when certain criteria is not met in Procedure A result. In Application News AD-0209, analysis of residual solvents in pharmaceutical products was done following Procedure A which was performed using nitrogen carrier gas, an inexpensive and abundant alternative to helium [2]. Here, we describe HS-GC method using nitrogen as the carrier gas to analyse Class 1 and Class 2 solvents following USP<467> Procedure B criteria.

❑ Experimental

Analytical conditions and sample preparation

HS-20 headspace autosampler and Nexis GC-2030 (Shimadzu Corporation, Japan) were used in this work. The analytical conditions following Procedure B 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 B 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-Stabilwax 30 m x 0.32 mm ID x 0.25 µm 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 10
Carrier Gas	Nitrogen
Gas Flow Condition	Constant linear velocity mode Linear velocity 35 cm/s
Oven Temperature Programming	50 °C (20 min) →6 °C/min to 165 °C (20 min)
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. Carbon tetrachloride was co-eluted with 1,1,1-Trichloroethane when Procedure B was used (Figure 1).

The lowest S/N value for benzene (Peak 4) obtained was 93, which is greater than the requirement stated in USP<467> (i.e., S/N ratio is not less than 5). The S/N ratio for the rest of the Class 1 Standards were greater than 3 which conformed to the requirement stated in USP<467>.

The repeatability of peak areas, %RSD (n=7), for the five solvents (2 solvents co-elute) obtained ranges from 1.8% to 5.1%. These results indicate that when using nitrogen carrier gas as a substitute of helium carrier gas, Procedure B criteria can still be fulfilled for Class 1 Standard.

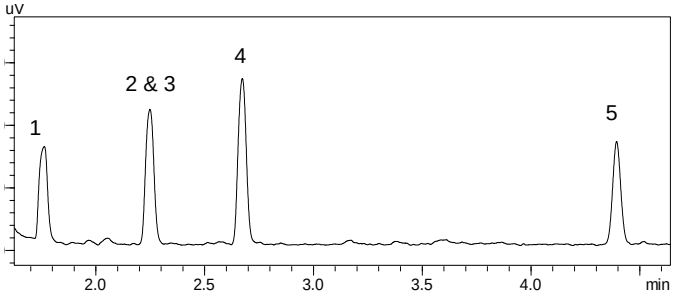

Figure 1: HS-GC-FID chromatogram of Class 1 Standard following Procedure B in USP<467>. Peak labelling refers to Table 2.

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	5.1	23	54	36	37	32	32	79
2 & 3	1,1,1-trichloroethane and Carbon Tetrachloride	2.2	38	86	70	84	56	65	86
4	Benzene	1.8	119	127	108	138	93	107	104
5	1,2-dichloroethane	2.1	40	48	46	60	50	58	40

Class 2 Standard

Class 2 Standard consists of 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 ranges from 0.7% to 9.1%.

The average (n=7) specific resolution between cis-1,2-dichloroethene and acetonitrile obtained with nitrogen carrier gas was 2.9. This meets the requirement of USP<467> that R_s of these 2 compounds must not be less than 1.

In summary, the results for Class 1 Standard and Class 2 Standard indicate that the HS-GC analysis method with nitrogen as carrier gas can achieve required sensitivity (S/N) and peak resolution as stated in the criteria of USP<467> Procedure B.

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	Cyclohexane	5.7
A2	Methylcyclohexane	5.7
A3 & A4	trans-1,2-Dichloroethene and THF	4.7
A5	Methanol	1.3
A6	DCM	5.7
A7	Cis-1,2-Dichloroethene	5.8
A8	Acetonitrile	2.2
A9	Toluene	5.6
A10	1,4-Dioxane	1.6
A11	EthylBenzene	5.5
A12	p-xylene	5.7
A13	m-xylene	5.6
A14	Cumene	5.5
A15	o-xylene	5.4
A16	Chlorobenzene	5.6
Class 2B standard		
No.	Compound	%RSD (n=7) of peak area
B1	Hexane	9.1
B2	1,2-dimethoxyethane	1.1
B3	Trichloroethene	7.1
B4	chloroform	5.1
B5	Methylbutyylketone	0.7
B6	Nitromethane	4.6
B7	Pyridine	1.1
B8	Tetralin	4.2

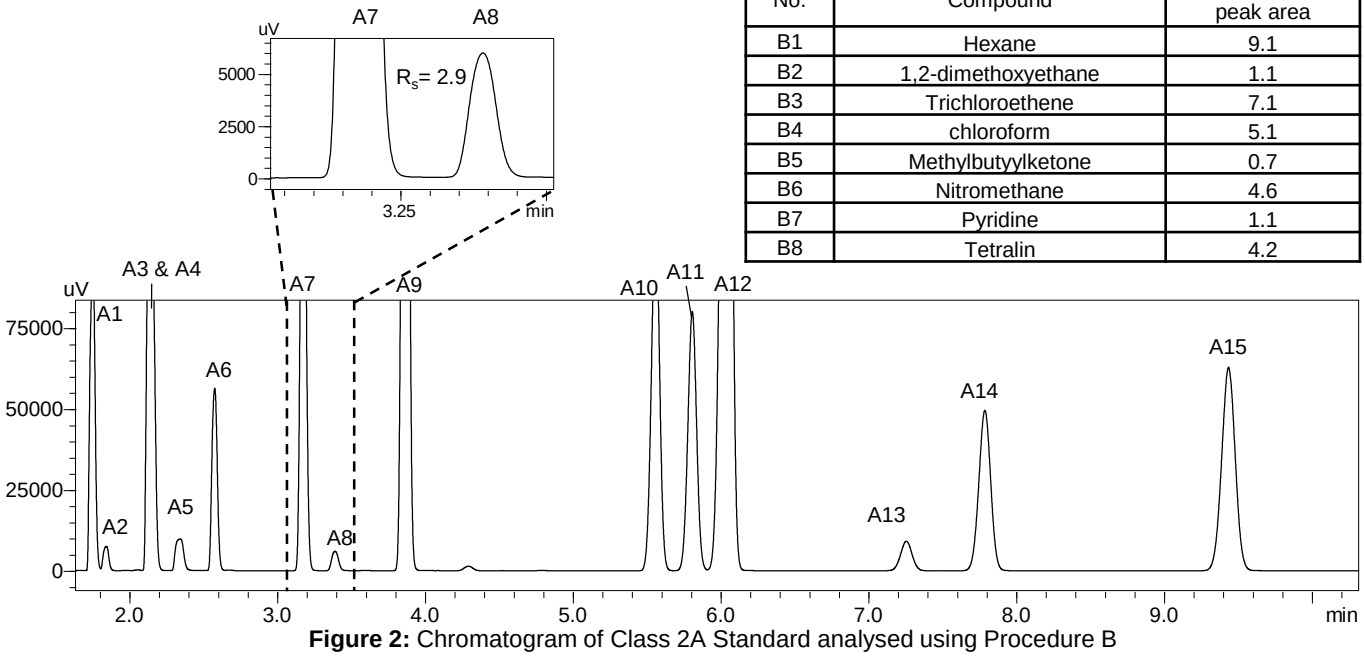

Figure 2: Chromatogram of Class 2A Standard analysed using Procedure B

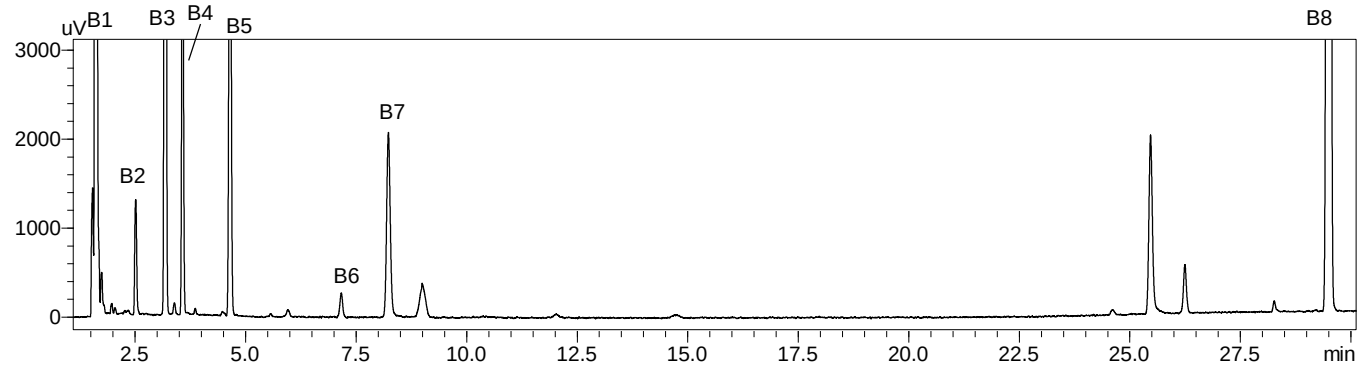

Figure 3: Chromatogram of Class 2B Standard analysed using Procedure B

❑ Conclusions

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

❑ References

1. The United States Pharmacopeia, *USP <467> RESIDUAL SOLVENTS.*
2. Shimadzu Application News AD-0209, Analysis of Residual Solvents in Pharmaceutical Products by Headspace-GC-FID with Nitrogen Carrier Gas Following USP<467> -Procedure A

SHIMADZU (Asia Pacific) Pte. Ltd
79 Science Park Drive, #02-01/08 Cintech IV, Singapore 118264,
www.shimadzu.com.sg; Tel: +65-6778 6280 Fax: +65-6778 2050