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Determination of Residual Solvents in Vitamin Powder by SPME-GC/FID

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Introduction

Manufacturing of drug substance, excipients, and/or drug products uses or produces volatile organic solvents. Since volatile organic solvents do not provide therapeutic benefit, they should be removed to the levels to satisfy product specifications. ICH (International Conference on Harmonization) published a guideline (Q3C) specifying the acceptable levels of volatile organic solvents in drug substances and drug products. The residual solvents are classified into three classes. Class 1 residual solvents are human carcinogens and environmental hazards. Class 2 residual solvents are inherently toxic so that their use should be limited. Class 3 residual solvents are less toxic than class 1 and class 2 solvents, and their use is recommended where practical. The levels of class 3 solvents may be determined by loss on drying <731>, while chromatographic analysis is required for the determination of class 1 and class 2 solvents.

Introduction (contd.)

SPME (solid phase microextraction) is a solventless technique suitable for qualitative and quantitative determination of volatile and semivolatile analytes. The ability to extract analytes from the headspace eliminates non-volatile material from being transferred to the analytical column. Several SPME fiber choices are available, each with an affinity for specific analyte classes. Proper fiber selection leads to increased sensitivity. SPME can be performed manually (SPME sampling stand + hotplate/stirrer) or automated. This research investigated the use of headspace SPME for the determination of residual solvents in vitamin powder and products. And it was demonstrated that SPME coupled with GC/FID could be effectively used to quantify residual solvents in vitamin powder.

Experimental

Chemicals and Materials

SPME fibers, GC inlet liners, vials, OVI-G43 GC column, and residual solvents standards (class 1, class 2 – mixture A, class 2 – mixture B, class 2 – mixture C) were obtained from Supelco.

Preparation of Standard and Sample Solutions

Class 1 Standard Stock Solution – Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100 mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100 mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10 mL volumetric flask, dilute with water to volume, and mix.

Experimental (contd.)

Class 1 Standard Solution – Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions – Transfer 1.0 mL of USP Residual Solvents Class 2 – Mixture A RS to a 100 mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution A.* Transfer 1.0 mL of USP Residual Solvents Class 2 – Mixture B RS to a 100 mL volumetric flask, dilute with water to volume, and mix. This is *Class 2 Standard Stock Solution B.*

Class 2 Mixture A Standard Solution – Transfer 1.0 mL of *Class 2 Standard Stock Solution A* to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Experimental (contd.)

Class 2 Mixture B Standard Solution – Transfer 5.0 mL of *Class 2 Standard Stock Solution B* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution – Transfer about 250 mg of the article under test, accurately weighed, to a 25 mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution – Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution – Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution,* apply the stopper, cap, and mix.

Experimental (contd.)

Headspace SPME Procedure

fiber:	PDMS/DVB/Carboxen®
incubation:	45 min @ 40 ºC
extraction:	30 min @ 40 ºC
desorption:	1 min @ 270 ºC
injection:	Splitless/split open @ 0.1 min with 0.75 mm liner

GC Conditions

column:	OVI-G43, 30 m x 0.53 mm, 3 µm
oven program:	40 ºC (20 min) to 240 ºC @ 10 ºC/min, hold 20 min
injector temp.:	270 ºC
det.:	FID @ 250 ºC
carrier gas:	He, 4 psi constant pressure, 35 cm/sec at 40 ºC

Results and Discussion

System Suitability

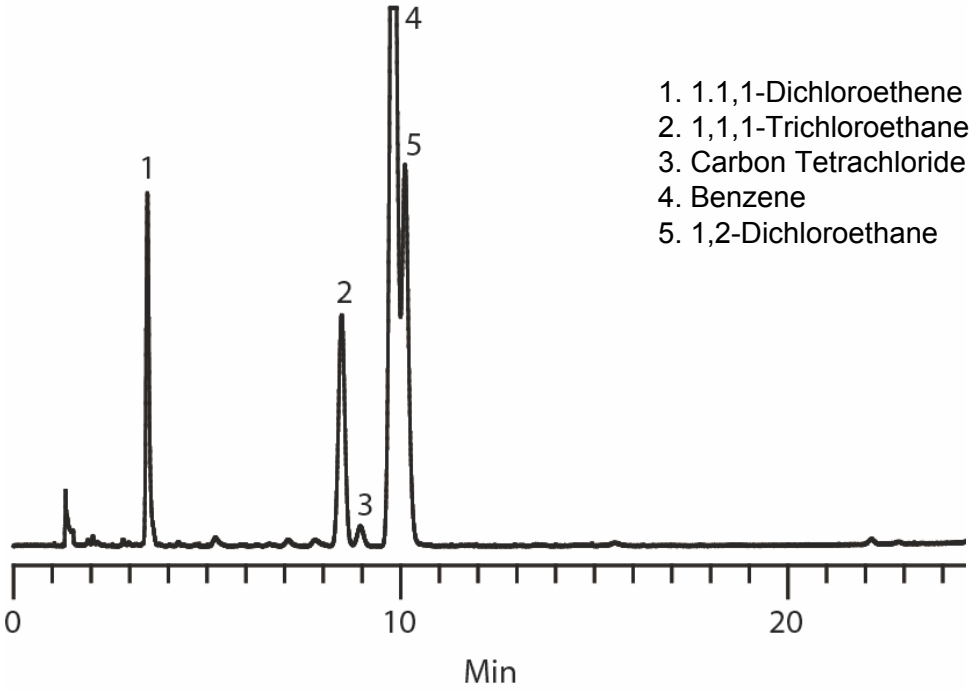
The signal-to-noise ratio of 1,1,1-trichloroethane in the class 1 standard solution is 162, which is larger than the criteria. Pass.

The signal-to-noise ratio of benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichlorethene, and 1,1,1-trichloroethane in the class 1 system suitability solution is 533, 11, 231, 205, and 134, respectively, which is larger than the criteria (3). Pass.

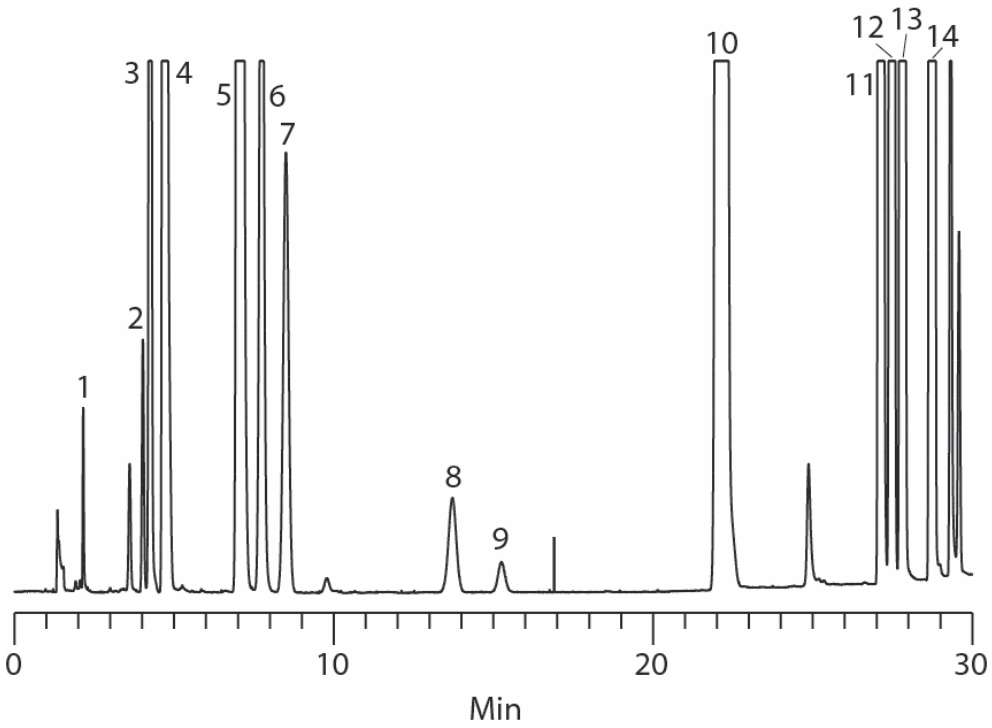
The resolution, R, between acetonitrile and methylene chloride in the class 2 mixture A standard solution is 3.8, which is larger than the criteria (1). Pass.

Results and Discussion (contd.)

Chromatograms obtained with Headspace SPME



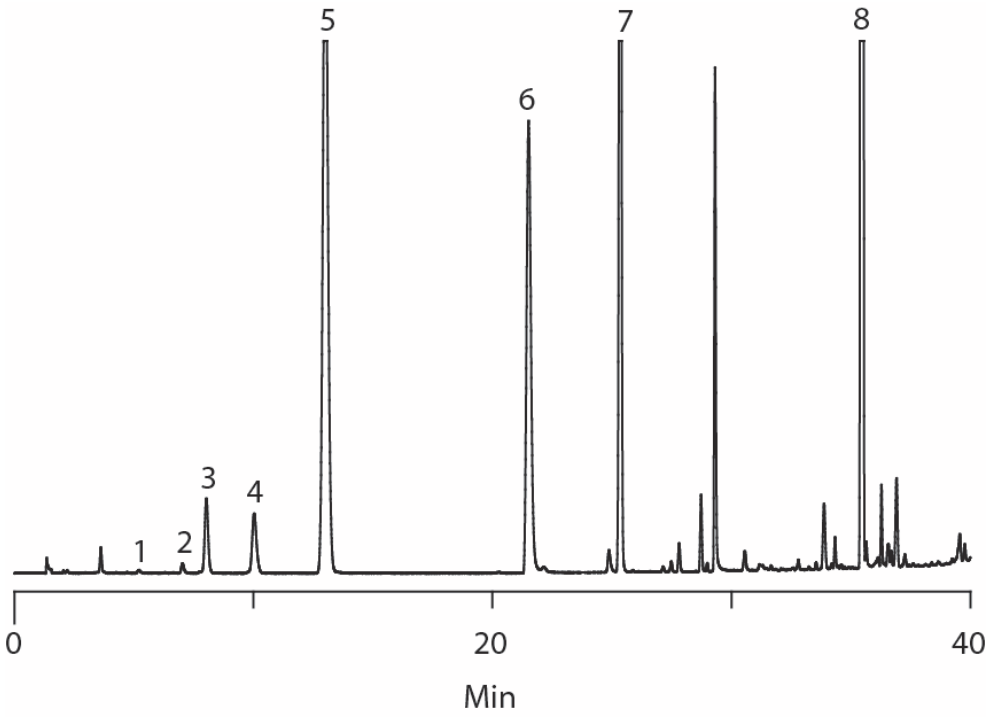
Results and Discussion (contd.)



Standard solution of class 2 – mixture A

1. Methanol
2. Acetonitrile
3. Dichloromethane
4. *trans*-1,2-Dichloroethene
5. *cis*-1,2-Dichloroethene
6. Tetrahydrofuran
7. Cyclohexane
8. Methylcyclohexane
9. 1,4-Dioxane
10. Toluene
11. Chlorobenzene
12. Ethylbenzene
13. m-Xylene/ p-Xylene
14. o-Xylene

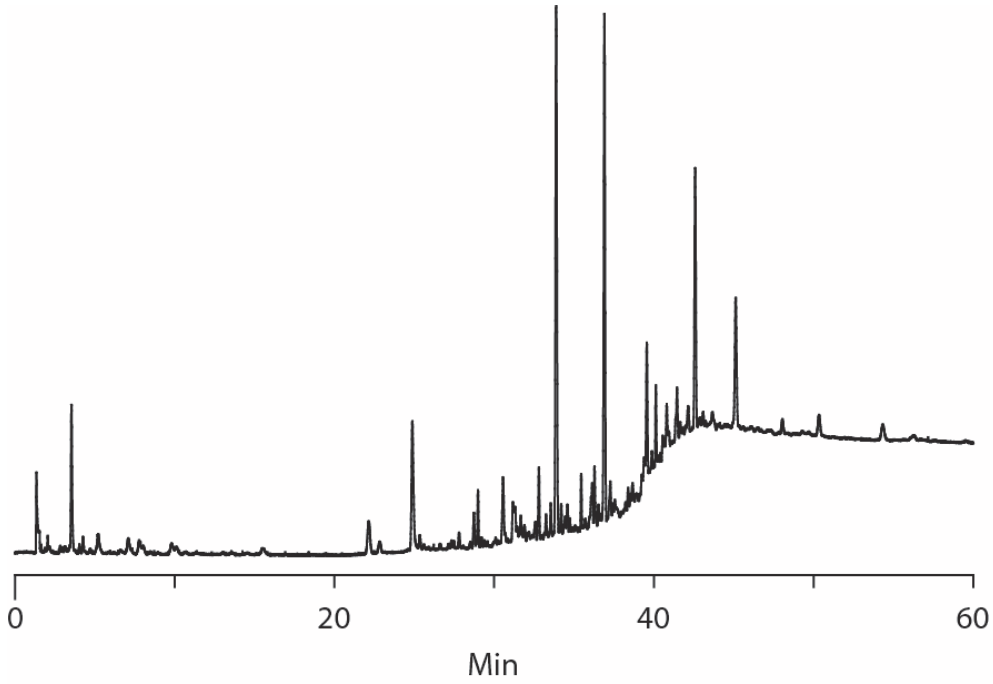
Results and Discussion (contd.)



1. Hexane
2. Nitromethane
3. Chloroform
4. 1,2-Dimethoxyethane
5. Trichloroethylene
6. Pyridine
7. 2-Hexanone
8. Tetralin

Standard solution of class 2 – mixture B

Results and Discussion (contd.)



Vitamin B12 sample

No peak response of any peak in the sample solution is greater than or equal to a corresponding peak in either the class 1 standard solution or either of the two Class 2 mixture standard solutions, so the sample meets the requirement of this test.

Conclusion

Headspace SPME could be used to determine of residual solvents (class 1, class 2 mixture A, and class 2 mixture B) in drug substances and drug products.

References

1. ICH Q3C. Impurities Guideline for Residual Solvents.
2. USP 30 <467> Residual Solvents.
3. Costin C. Camarasu. Headspace SPME method development for the analysis of volatile polar residual solvents by GC-MS. Journal of Pharmaceutical and Biomedical Analysis. 23 (2000) 197-210.
4. Costin C. Camarasu, Mária Mezel-Szüts, Gábor Bertók Varga. Residual solvents determination in pharmaceutical products by GC-HS and GC-MS-SPME. Journal of Pharmaceutical and Biomedical Analysis. 18 (1998) 623-638.