APPLICATION NOTE

Gas Chromatography

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Pressure-Balanced Headspace for the Determination of Class I, II and III Residual Solvents in Pharmaceuticals by USP Chapter <467> Methodology

Introduction

Residual solvents are used in the manufacture of active pharmaceutical ingredients (APIs), excipients, or in preparation of drug products and are not removed during the purification processes. Residual solvents are one of the three main impurities in pharmaceutical materials; the other two are organic and inorganic impurities. Solvents have a number of uses in the pharmaceutical manufacturing process, may sometimes be critical in the synthesis and can determine characteristics like crystal form, purity and solubility. Residual solvents do not provide any therapeutic benefit and should be removed to the extent possible, fulfilling quality-based requirements as per International Conference on Harmonization (ICH) guidelines – this is one of the standards to control the quality and the purity of the pharmaceutical substances, excipients, or drug products.

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Both the ICH and the United States Pharmacopoeia (USP) have guidelines for limiting the amounts of solvents used in pharmaceuticals. The ICH lists three classes of solvents based on their toxicity to humans and environmental health. Until 2008, the USP limited and tested for only chloroform, dioxane, methylene chloride and trichloroethylene. In harmonization with the ICH, the USP has changed the general chapter <467>, which became effective July 1st, 2008. The chapter now includes a comprehensive listing of the Class I, II and III solvents and their control limits, with procedures for identification, confirmation and quantification (Procedure A, B and C, respectively). This chapter is applicable to all the articles that use or produce residual solvents and to all the manufacturers who produce official excipients, APIs and drug products.

USP chapter <467> suggests analysis of residual solvents using a gas chromatograph (GC) equipped with a flame ionization detector (FID) and an automated headspace sampler (HS). The new chapter employs three testing procedures which are used to screen and identify (Procedure A), confirm (Procedure B) and quantitatively determine (Procedure C) the residual solvents in the sample. When the user has information about the specific solvents utilized during the manufacturing of the article, only Procedure C needs to be performed. If the solvents used are unknown, all three procedures are needed for identification and quantitation. If only Class III solvents are used in the manufacture of an article, an alternative loss-on-drying method is permitted, however, if Class II and III solvents are also present, it is advisable to analyze by chromatographic techniques.

This paper will demonstrate the analysis of all three classes of residual solvents by pressure-balanced headspace sample introduction and GC-FID analysis. In addition to a discussion of the instrumental technique, the choice of the diluent will also be studied; two diluents will be used throughout.

Experimental

A PerkinElmer Clarus® GC equipped with an FID detector and a PerkinElmer TurboMatrix™ HS-40 Headspace Sampler is the instrumental platform for this application. The TurboMatrix HS is a pressure-balanced headspace sampler; the basis of sample collection in this system is a calculation of sample volume, allowing gas at a known flow rate to enter the analytical column for a specific time.

When compared to other headspace technology, the pressure-balanced sampling of the TurboMatrix HS provides superior precision and inertness as a result of the simple, inert sample path. This technology does not require gas-sampling valves or other moving parts, reducing the sample contact with hot metal loops and the maintenance associated with moving parts. The TurboMatrix HS-40 includes a multi-position vial oven with overlapped vial thermostatting capability. Overlapped thermostatting automatically optimizes the use of the multi-position oven – this allows the next sample to inject as soon as the GC oven becomes ready, providing unparalleled sample throughput. Complete headspace parameters are described in Table 1.

Table 1. Detailed Headspace Analytical Conditions.

Headspace Unit:	PerkinElmer TurboMatrix HS-40
Headspace Mode:	Constant
Needle Temperature:	105 °C
Transfer Line Temperature:	110 °C
Oven Temperature:	80 °C
Thermostat Time:	20 min
Vial Pressurization Time:	2.0 min
Withdraw Time:	0.1 min
Injection Time:	0.12 min
Column Pressure:	48 psig
Injection Pressure:	48 psig
Vial Pressure:	48 psig
Vial Vent:	On
Transfer Line:	Fused Silica (0.53 mm)

Table 2. Detailed Gas Chromatographic Analytical Conditions.

Gas Chromatograph	PerkinElmer Clarus 600 GC with FID					
Analytical Column (G43)	PerkinElmer Elite-624 (30 m x 0.53 mm i.d. x 3.0 µm df)					
Analytical Column (G16)	PerkinElmer Elite-Wax (30 m x 0.32 mm i.d. x 0.5 µm df)					
Injection Port Type	Programmable Split/Splitless					
Injector Temperature (or Program)	200 °C					
Injection Type	HS-Control					
Injector Temperature	140 °C					
Carrier Gas Type	Helium					
Flow Rate (G43)	3.0 mL/min					
Flow Rate (G16)	1.0 mL/min					
Split Ratio	1:5					
FID Temperature	250 °C					
	Class I and III			**Class II**		
Oven Temperature Program (G43)	**Temperature**	**Hold Time**	**Rate**	**Temperature**	**Hold Time**	**Rate**
	40 °C	20 min	10 °C/min	40 °C	17 min	40 °C/min
	240 °C	10 min	End	240 °C	2 min	End
Oven Temperature Program (G16)	40 °C	20 min	6 °C/min	50 °C	19 min	40 °C/min
	165 °C	1 min	25 °C/min	220 °C	1 min	End
	220 °C	2 min	End			

Building upon the throughput of the TurboMatrix HS, the Clarus 600 GC features a best-in-class oven with high-speed cooling, resulting in a shorter period between the end of one run and the beginning of the next. This becomes especially useful in methods when the initial oven temperature is close to ambient. Complete gas chromatographic conditions are presented in Table 2.

Discussion

In this application note, a comprehensive list of solvents is analyzed, with a method optimized for chromatographic resolution and run time. The analysis of each solvent is performed on both the G16 and G43 phases to provide complete resolution of all solvents included in chapter <467>. In addition to separation on multiple phases, two diluents are used in each class of solvents. The diluent choice is an important variable in method development. The material and analyte solubility, boiling point, as well as the solvents used in manufacture, need to be considered. The response for each analyte changes with the diluent used, thus care should be exercised when selecting the diluent so that sensitivity and resolution can be optimized. Some solvents, typically non-polar, show very good response with water as a diluent, while the others, typically polar, in organic diluents.

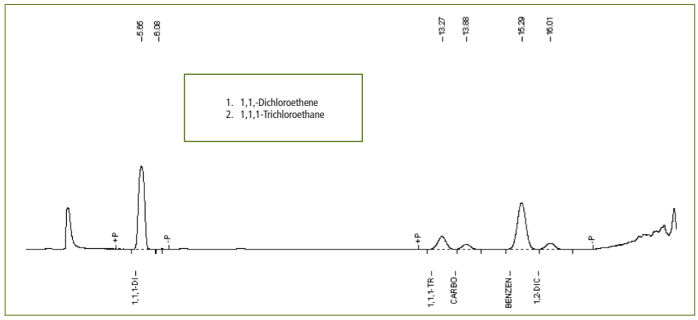

Figure 1. The analysis of Class I solvents in water using a G43 phase.

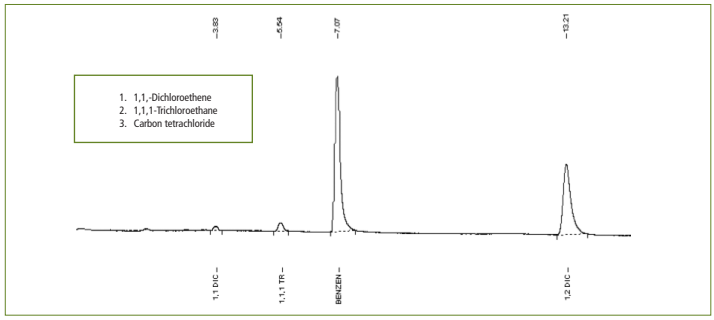

Figure 2. The analysis of Class I solvents in N,N-Dimethylacetamide using a G16 phase.

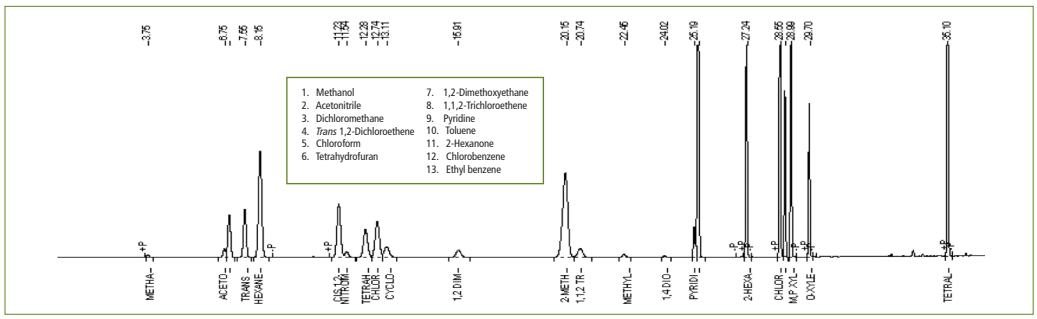

Figure 3. The analysis of Class II in 1,3-Dimethyl-2-Imidazolidinone using a G43 phase.

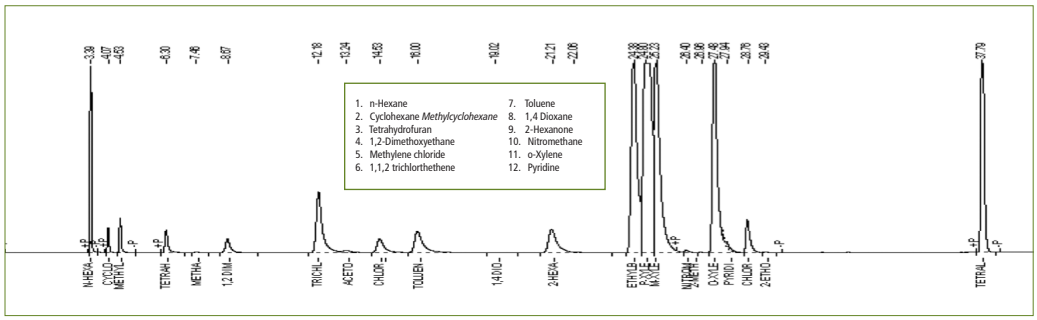

Figure 4. The analysis of Class II in solvents in water using a G16 phase.

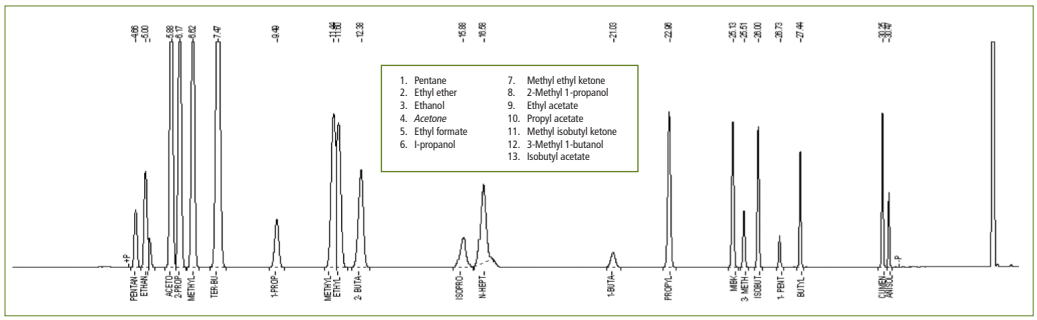

Figure 5. The analysis of Class III solvents in N-Methyl-2-Pyrrolidone using a G43 phase.

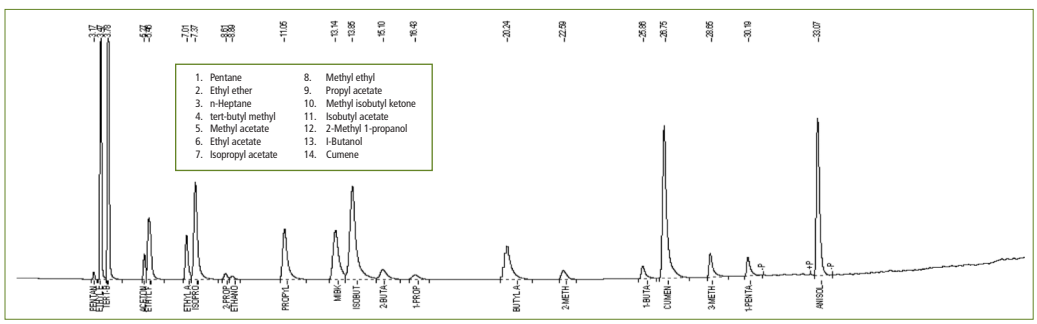

Figure 6. The analysis of Class III solvents in water using a G16 phase.

Procedure A & B – Identification and Confirmation of Materials for Solvents

Procedure A is used to identify the residual solvents in a pharmaceutical sample. In this, all solvents were initially analyzed using the G43 column and associated GC conditions. Multiple diluents are used in Figures 1, 3 and 5.

The residual solvents were confirmed using Procedure B on a G16 column. The elution order is different between the G43 and G16 phases, allowing confirmation of the analyte identification by retention time on 2 orthogonal column phases. In addition, several co-eluting compounds on Procedure A are now resolved, while other compounds now co-elute. Figures 2, 4 and 6 demonstrate the results of the analysis with a G16 phase.

Procedure C – Quantification

After identification and confirmation of residual solvents in pharmaceutical materials by Procedures A and B, the analytes are quantified by the procedure which provides the optimal separation of solvents present in the sample. The exact analytical procedure chosen for quantification is based on the optimal separation conditions for the analytes of interest.

Conclusion

The revised chapter <467> aligns the USP methodology for the analysis of residual solvents with that set by the International Conference on Harmonization. In this paper, we have presented a comprehensive analysis for the identification, confirmation and quantitation of Class I, II, and III solvents. The full suite of analytes is separated while maintaining an efficient analysis.

The overlapping thermostatting of the TurboMatrix HS assured that the system was ready to inject as soon as the GC achieved its starting conditions. Furthermore, the fast-cooling capability of the Clarus 600 GC oven was used to reduce the injection-to-injection time of this application, increasing productivity.

The full list of typically-analyzed solvents was presented with two different diluents, on both the G43 and G16 phases. The choice of diluent is based on both the solubility of the material under test and the boiling point of the least-volatile solvent expected. A combination of column selectivities provided the separation for all of the solvents in Class I, II, and III.

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