

Routine-grade quantitative performance of TriPlus 500 Headspace Autosampler coupled to TRACE 1310 GC-FID

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Keywords

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Introduction

Testing pharmaceutical products for their potential residual solvents that are used or produced in the manufacture or purification of drug substances is important to ensure patient safety. According to the International Conference on Harmonization (ICH) guidelines,¹ the United States Pharmacopeia (USP) method <467>² describes the assay procedure, classifying and setting solvent concentration limits according to their toxicity and health hazard.

Gas chromatography (GC) coupled to headspace (HS) sampling technique and flame ionization detection (FID) or mass spectrometry (MS) detectors are the analytical methods of choice for this application as most of the target compounds are organic solvents with relatively low boiling points and good thermal stability.

HS generates the partitioning of semi-volatile and volatile compounds from complex liquid and solid matrices and allows for the injection of the volatile fraction in a fast and simple way without the need for time-consuming, and often expensive, sample preparation.

The workflow described by USP <467> provides procedures for screening (procedure A), confirmation (procedure B) and quantitation (procedure C) of residual solvents. According to procedure C, solvent residuals that are above the acceptable limits must be quantified using the formula reported by the regulation.

In this technical note, a Thermo Scientific™ TriPlus™ 500 Headspace Autosampler was coupled to a Thermo Scientific™ TRACE™ 1310 Gas Chromatograph equipped with a Thermo Scientific™ Instant Connect Split/Splitless (SSL) Injector and a Thermo Scientific™ Instant Connect FID to assess the linearity for Class 1, Class 2A and Class 2B residual solvents.

Experimental

Sample and standard preparation

USP <467> Class 1, Class 2A and Class 2B residual solvent solutions in dimethylsulfoxide (DMSO) were sourced from Restek (P/N 36279, 36012, 36280 respectively). Stock solutions were diluted in DMSO as reported in the USP method <467>, procedure C, water-insoluble articles. HPLC-MS grade water (Fisher Scientific P/N W-0112-17) and GC headspace grade DMSO (Fisher Scientific 15572393, purity $\geq 99.9\%$) were used as diluents. The standard solutions were diluted in water to prepare four calibration levels at 12.5%, 25%, 50%, and 200% of the concentration limits reported in the USP <467> method.²

Prior to analysis, 1 mL of each calibration solution was added into a 20 mL crimped capped vial (P/N 20-CV) containing 5 mL water corresponding to 50 mg pharmaceutical product. Each calibration level was prepared and analyzed in triplicate applying the HS-GC method conditions described in USP <467>.

HS-GC-FID Analysis

In the experiments described here, a TriPlus 500 HS autosampler was coupled to a TRACE 1310 Gas Chromatograph equipped with an Instant Connect SSL Injector and an Instant Connect FID.

Chromatographic separation was achieved on a Thermo Scientific™ TraceGOLD™ TG-624 column, 30 m \times 0.32 mm \times 1.8 μ m (P/N 26085-3390).

Details regarding HS-GC conditions are given in Table 1 of a supporting Thermo Scientific residual solvent application note.³

Data processing

Data was acquired and processed using the Federal Drug Administration Title 21 Code of Federal Regulations Part 11 (Title 21 CFR Part 11) compliant Thermo Scientific™ Chromeleon™ Chromatography Data System (CDS) software, version 7.2. Chromeleon CDS is also supplied with several ready-made templates and eWorkflows for the assessment of ICH method validation procedures.

Results and discussion

The experiments conducted aimed to assess the TriPlus 500 Headspace autosampler linearity and method sensitivity for Class 1, Class 2A and Class 2B residual solvents quantification.

All residual solvents showed excellent linear responses over the calibration range with an average coefficient of determination $R^2 \geq 0.999$. Moreover, the residual values (measured as % RSD of average response factors) were <12%, confirming a good linear response (Table 1).

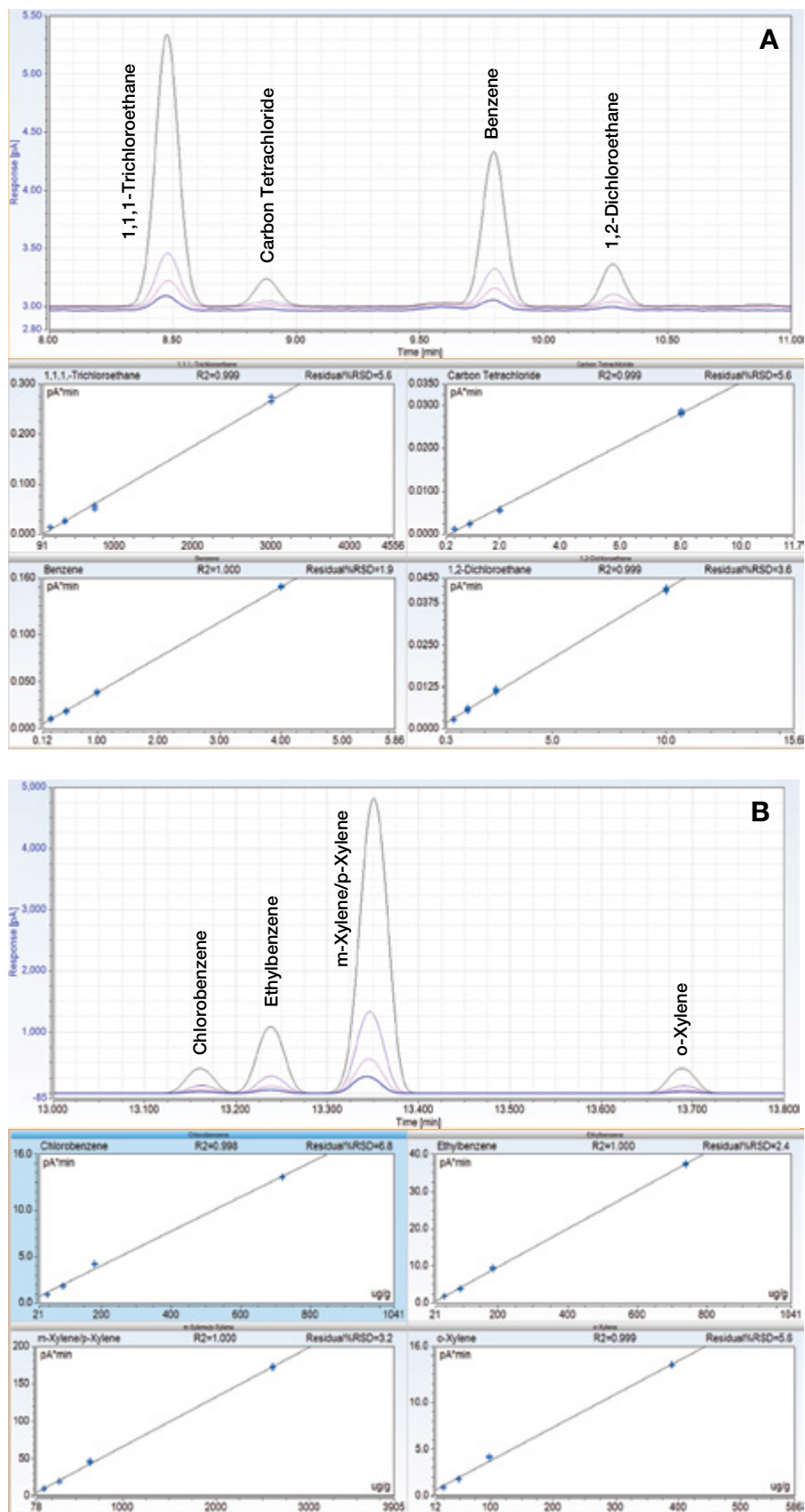
Examples of such calibration responses for Class 1 (1,1,1-trichloroethane, carbon tetrachloride, benzene, 1,2-dichloroethane), Class 2A (chlorobenzene, ethylbenzene, m,p,o-Xylene) and Class 2B (trichloroethene) are reported in Figure 1.

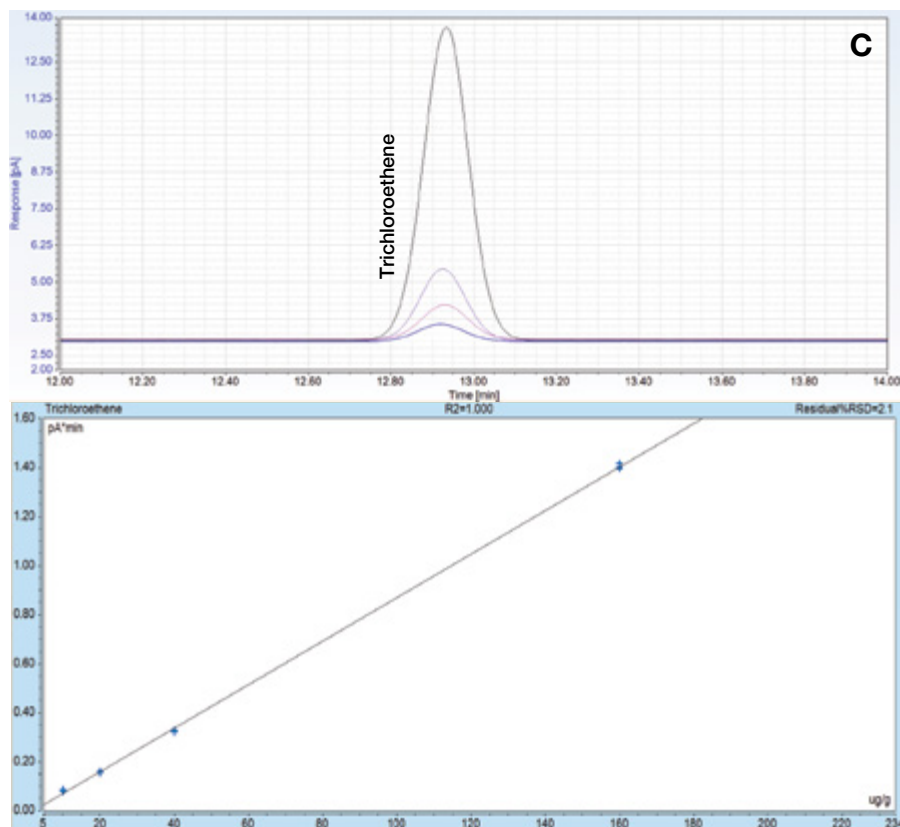
Limit of detection (LOD) and limit of quantitation (LOQ) have been calculated basing on the signal-to-noise (S/N) ratio following the ICH recommendations on the validation of analytical procedures Q2(R1).⁵ Chromeleon CDS extension pack allowed for easy calculation of ICH method validation processes providing templates to automate the complete analysis workflow from the sequence to the validation reports. Calculated LODs and LOQs are reported in Table 1.

Table 1. Calibration ranges ($\mu\text{g/g}$), coefficient of determination (R^2), calibration residuals (%RSD) and calculated limit of detections (LOD, $\mu\text{g/g}$) and limit of quantitation (LOQ, $\mu\text{g/g}$) for spiked samples.

Compound name	Concentration Range ($\mu\text{g/g}$)	Correlation Coefficient (R^2)	Residual Standard Deviation (% RSD)	LOD ($\mu\text{g/g}$)	LOQ ($\mu\text{g/g}$)
Class 1					
1,1-Dichloroethene	1–16	0.998	7.9	0.5	0.8
1,1,1-Trichloroethane	188–3000	0.999	5.6	80	280
Carbon Tetrachloride	0.5–8.0	0.999	5.6	2.0	6.0
Benzene	0.3–4.0	1.000	1.9	0.2	0.6
1,2-Dichloroethane	0.6–10	0.999	3.6	2.0	5.0
Class 2A					
Methanol	375–6000	1.000	1.6	26	87
Acetonitrile	51–820	1.000	0.6	7.0	22
Dichloromethane	75–1200	1.000	2.6	6.0	20
<i>trans</i> -1,2-Dichloroethene	234–3740	0.999	6.9	0.5	2.0
<i>cis</i> -1,2-Dichloroethene	234–3740	1.000	1.9	2.0	6.0
Tetrahydrofuran	90–1440	1.000	0.7	2.5	8.0
Cyclohexane	422–6760	0.997	11.0	0.1	0.2
Methylcyclohexane	148–2360	0.997	11.7	0.5	2.0
1,4-Dioxane	48–760	1.000	1.5	20	60
Toluene	111–1780	1.000	2.2	1.0	4.0
Chlorobenzene	45–720	0.998	6.8	0.1	20
Ethylbenzene	46–738	1.000	2.4	0.05	0.1
<i>m</i> -Xylene/ <i>p</i> -Xylene	163–2604	1.000	3.2	0.05	0.1
<i>o</i> -Xylene	24–390	0.999	5.6	0.05	0.1
Class 2B					
Hexane	36–580	0.998	9.0	0.01	0.3
Nitromethane	6–100	0.999	6.1	6.0	20
Chloroform	8–120	1.000	0.9	2.0	7.0
1,2-Dimethoxyethane	12.5–200	0.998	9.6	30	90
Trichloroethene	10–160	1.000	2.1	1.0	2.0
2-Hexanone	6–100	0.999	4.4	1.0	3.0

Figure 1. Calibration curves for some of the Class 1 (A), Class 2A (B) and Class 2B (C) solvents. Calibration curves were obtained over four concentration levels (at 12.5%, 25%, 50% and 200% of the concentration limit). R^2 as well as response factors residual standard deviations (% RSD) are shown. Each calibration level was prepared and analyzed in triplicate ($n=3$).





Conclusions

- The results obtained in this study demonstrate excellent linear response for all the solvents included in the USP <467> with an average coefficient of determination $R^2 > 0.999$ and average response factor %RSDs <12%. This analytical configuration represents a reliable tool for routine analysis of residual solvents in pharmaceutical products.
- The Instant Connect FID allows for sensitive detection of organic compounds over a wide linear dynamic range.
- Chromeleon CDS software (compliant with the FDA Title 21 CFR Part 11 requirements) ensures data integrity, traceability, and effective data management allowing for easy and fast data processing, quantitation and reporting.

Learn More Today

For more information about the TriPlus 500 Headspace Autosampler, to request a demo, or to discuss your GC/GC-MS needs, please contact your Thermo Scientific representative today.

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