RAPID RESIDUAL SOLVENT ANALYSIS

VALIDATION OF AN ALTERNATIVE PROCEDURE FOR USP METHOD <467> USING SIFT-MS

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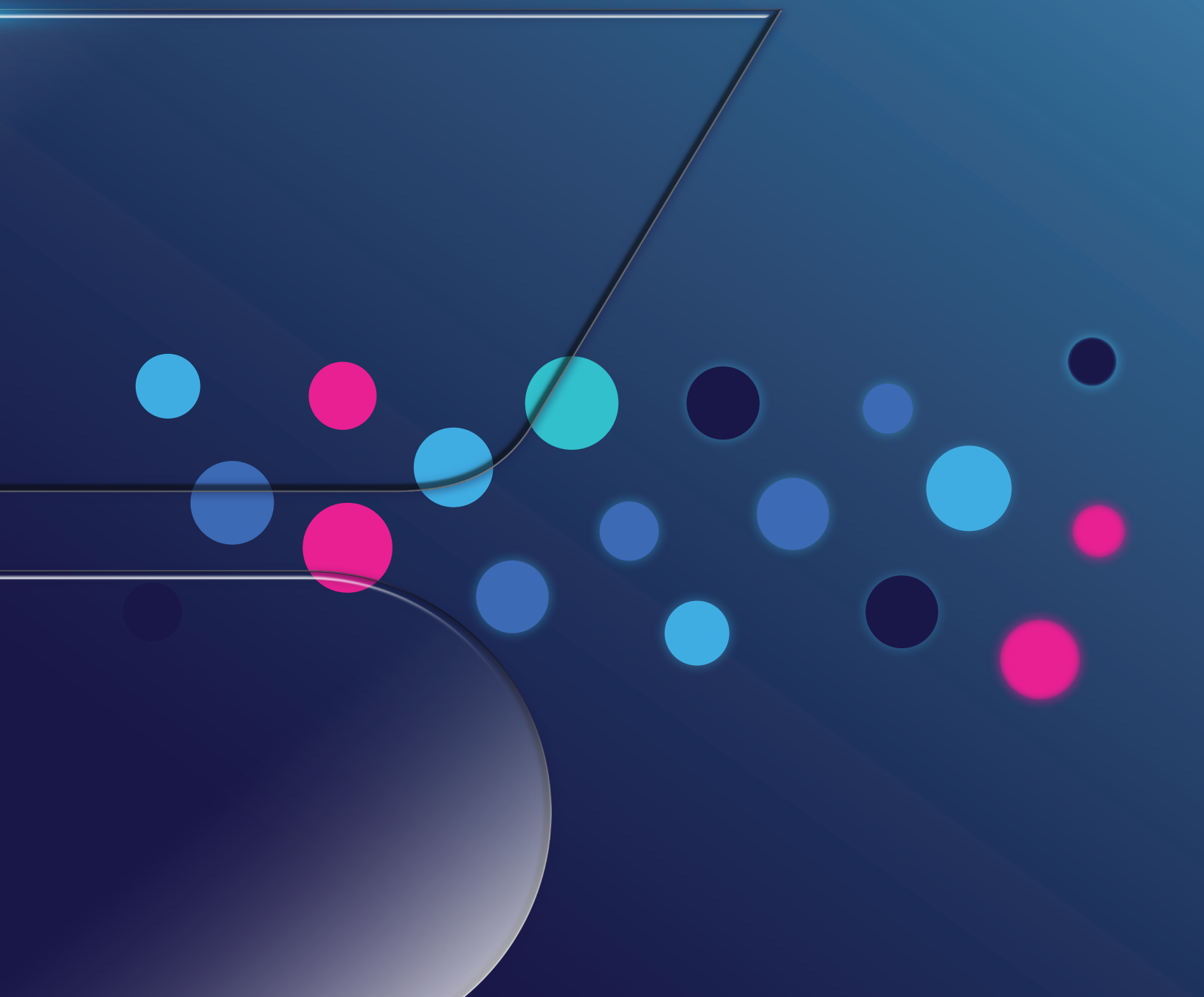


This application note describes the successful validation of selected ion flow tube mass spectrometry (SIFT-MS) as an alternative procedure for United States Pharmacopeia (USP) General Chapter <467> Residual Solvents (USP<467>) according to USP guideline Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures <1467> (USP<1467>). The validated SIFT-MS procedure meets the acceptance criteria in USP<1467>, and with 17-fold higher sample throughput addresses current scale-up issues for residual solvent testing in the pharmaceutical industry. Furthermore, due to simplified, direct, chromatography-free sample analysis, SIFT-MS can also be applied for online monitoring of residual solvents in continuous manufacturing.

Important notice:
*The results and discussion in this application note are based on the work published in Pharmacopeia Forum Volume 47, Issue 6 – Stimuli to the Revision Process article: High-throughput residual solvent analysis using selected ion flow tube mass spectrometry (SIFT-MS) (Biba et al. (2021)).**
** Any omissions from the original text were not decided by the United States Pharmacopeia (USP).*

INTRODUCTION

Residual solvents are defined as "organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques" (page 1, International Committee on Harmonization (ICH) (2021)). Residual solvents are further classified in three classes based on their toxicity:

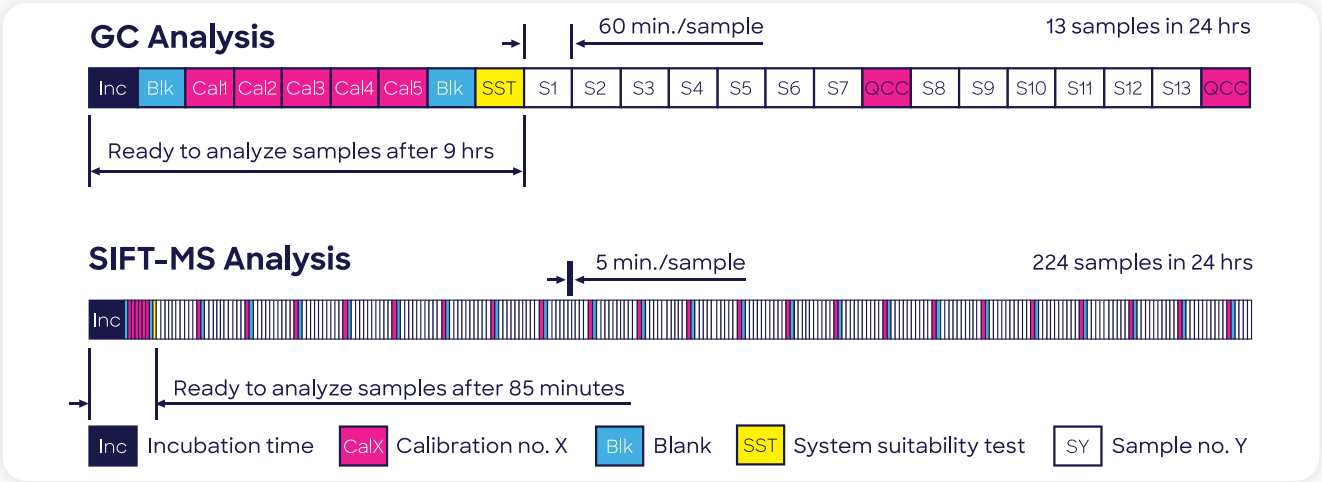
- Class 1: Solvents that are known to cause unacceptable toxicities and should be avoided (the exception is 1,1,1-trichloroethane, which is an environmental hazard)
- Class 2: Solvents associated with less severe toxicity, should be limited to protect the patients
- Class 3: Solvents with low toxic potential – should be used where practical.

The content of Class 1 and Class 2 Residual Solvents in drug products must be limited to ensure that they are below the permitted daily exposure (PDE) (ICH (2021), (USP<467>).

The ICH Q3C guideline (ICH (2021)) is not limited to certain analytical procedures. It states (p4), "Any harmonized procedure for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible." Three analytical procedures are described in the United States Pharmacopeia (USP) General Chapter <467> *Residual Solvents* (USP<467>). These procedures enable the levels of all Class 1 and most Class 2 residual solvents to be evaluated using gas chromatography with flame ionization detection (GC-FID).

For pharmaceutical companies investing in scale-up of their manufacturing processes, the associated scaling of residual solvent testing using the USP<467> procedure requires significant upscaling of analysis capacities. This involves increased investments in qualified personnel, lab space, validation procedures and maintenance as well as higher overall instrument acquisition and running costs. Selected ion flow tube mass spectrometry (SIFT-MS) offers an alternative approach to GC-FID by providing sample throughputs that are 17-fold higher per day and faster time to sample analysis (Figure 1). Since SIFT-MS uses direct, chromatography-free analysis, practical issues for the front-end separation are eliminated, resulting in a robust and reliable analytical result that is easily obtained and requires less qualified personnel. Capacity increase can thus be reached with just a single automated SIFT-MS instrument.

Figure 1. *Daily sample schedules for gas chromatography and SIFT-MS analysis of Class 2 residual solvents. The SIFT-MS schedule applies to any headspace sample.*



In SIFT-MS, specificity in real-time is maximized by the combination of rapidly switchable reagent ions with various reaction mechanisms to distinguish multiple compounds simultaneously in a single analysis. Reliable quantification of target compounds is provided by mass spectrometric detection combined with library records. The suitability of SIFT-MS for routine analysis has been demonstrated for a wide range of applications (Perkins and Langford (2021a, 2021b)).

Validation of SIFT-MS as an alternative procedure for USP<467> residual solvent analysis was conducted according to *Residual Solvents—Verification of Compendial Procedures and Validation of Alternative Procedures <1467>* (USP<1467>). This application note summarizes the successful outcome of the validation study for Class 2 residual solvents, together with a feasibility assessment for Class 1. Full details of these studies are given in the stimuli article on the *Pharmacopeial Forum* (Biba et al. (2021)).

METHODS

1. AUTOMATED SIFT-MS ANALYSIS

This work utilized a Syft Technologies Voice200*ultra* SIFT-MS instrument operating on helium carrier gas. SIFT-MS (Figure 2) uses soft chemical ionization (CI) to generate mass-selected reagent ions (Smith et al. (2020)) that can rapidly react with and quantify VOCs down to part-per-trillion concentrations (by volume, pptV). Up to eight reagent ions (H_3O^+, NO^+, O_2^+, O^-, OH^-, O_2^-, NO_2^- and NO_3^-) obtained from a microwave discharge in air are now applied in commercial SIFT-MS instruments (Hera et al. (2017)). These reagent ions react with VOCs and other trace analytes in well-controlled ion-molecule reactions, but they do not react with the major components of air (N_2, O_2 and Ar). This enables direct, real-time analysis of air samples to be achieved at trace and ultra-trace levels without pre-concentration. Rapid switching between reagent ions provides high selectivity because the multiple reaction mechanisms give independent measurements of each analyte. The multiple reagent ions frequently remove uncertainty from isobaric overlaps in mixtures containing multiple analytes.

The SIFT-MS instrument was equipped with a GERSTEL MPS autosampler (Robotic Pro; Mülheim, Germany). Samples were incubated in a virtual twelve-place GERSTEL agitator (comprised of two physical six-place agitators) prior to sampling of the headspace and subsequent injection into the SIFT-MS instrument through a GERSTEL septumless sampling head.

Residual solvents reported in this application note were analyzed using the quantitation ions summarized in Table 1 of the Stimuli Article (Biba et al. (2021)). Because reagent ions are rapidly switchable in SIFT-MS, all positively charged ions were used in the method to provide the best combination of specificity and sensitivity.

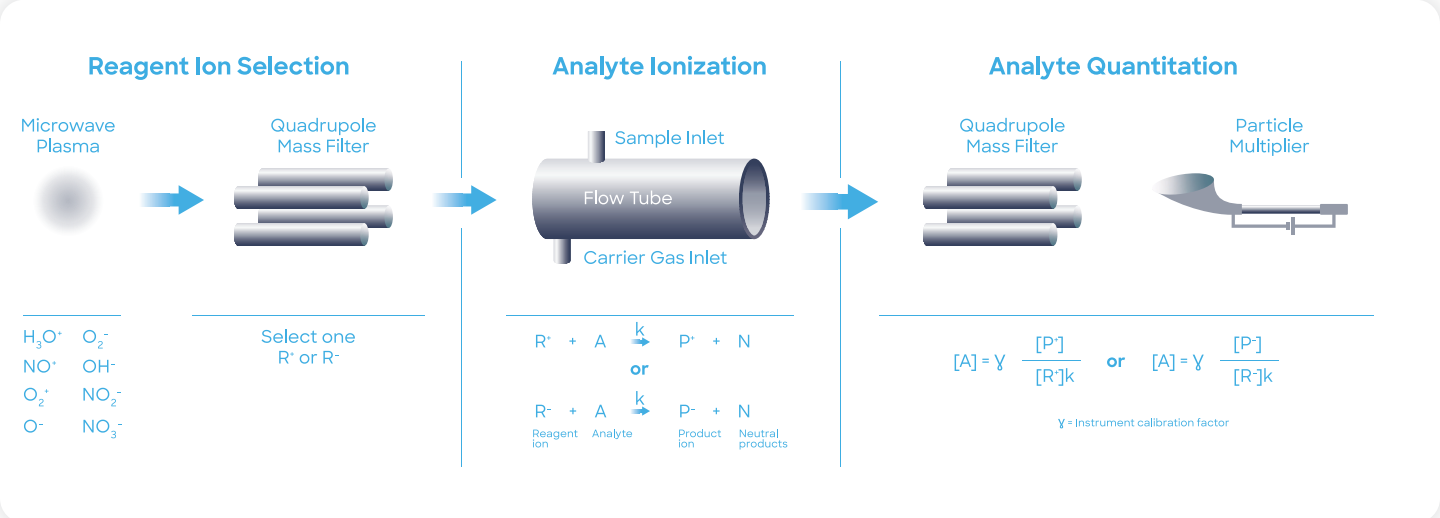
The headspace conditions for all analyses used 6 mL of solution in a 20-mL headspace vial incubated at 60 °C for 45 min. A 2.5-mL aliquot of headspace was removed via a heated syringe (150 °C) and injected into the SIFT-MS at 50 µL s^{-1}, with a zero-air make-up flow through the inlet to ensure that the total flow into the instrument was 25 mL min^{-1}. After the injection, the syringe was flushed with zero-grade air for 1 min. at 200 mL min^{-1}.

2. SAMPLES

Official USP reference standards (USP, Bethesda, MD, USA) were utilized in this validation study: USP Residual Solvents Mixture — Class 1 RS, USP Residual Solvents Class 2 —Mixture A RS, and USP Residual Solvents Class 2— Mixture B RS. The Class 2 Mixture A standard solution and the Class 2 Mixture B standard solution were prepared as described in Procedure C (quantitative test) of USP<467>. The Class 1 standard stock solution and Class 1 system suitability solution were prepared as described for Procedures A and B (limit tests) of USP<467>.

The Stimuli Article (Biba et al. (2021)) describes preparation of samples for the feasibility study and the results obtained. In that study, the linear dynamic range was investigated for many Class 1 and 2 compounds, with only N,N-dimethylformamide, formamide, pyridine,

Figure 2. Schematic representation of SIFT-MS – a direct-injection, chemical-ionization technique.



and sulfolane having linear regression coefficients (R^2) less than 0.99 (all fell within 0.931 to 0.986 range). Several examples are shown in Figure 3. This application note focuses on the validation phase.

1. VALIDATION OF A QUANTITATIVE PROCEDURE FOR CLASS 2 RESIDUAL SOLVENTS

Validation of an alternative procedure to those of USP<467>, which utilizes SIFT-MS, was conducted according to USP<1467> using the official reference standards (above) for the preparation of standard solutions and spiked sample solutions. USP<467> states "Spiked sample solutions [were prepared] with the sample matrix and spiked with each sample [likely to be present] at [not less than] 5 levels covering the range of interest." Spiked sample solutions were prepared here at 50%, 75%, 100%, 120%, and 150% of the control limit defined by the permitted daily exposure (PDE) for a given solvent.

The acceptance criteria for an alternative procedure for the quantitation test (Procedure C), together with the results obtained using SIFT-MS, are summarized in Table 1. Full data are provided in the Stimuli Article (Biba et al. (2021)). The validation of the alternative procedure for Class 2-Mixture A and Class 2-Mixture B meets all acceptance criteria for Procedure C, with a few exceptions as listed in the table.

2. FEASIBILITY OF A LIMIT PROCEDURE (B) FOR CLASS 1 RESIDUAL SOLVENTS

Performance of SIFT-MS analysis of the Class 1 solvents was evaluated in terms of Limit Procedure B (USP<467>). This approach also enabled performance of SIFT-MS to be ascertained for the USP<467> system suitability test, which requires that the signal-to-noise ratio (S/N) for benzene is not lower than 5. Full validation would require demonstration of linearity and recovery from a spiked solution at a second level, both of which should be readily achieved.

Figure 3. Example linear dynamic range data from the feasibility study, demonstrating the linearity (R^2) over a wide concentration range.

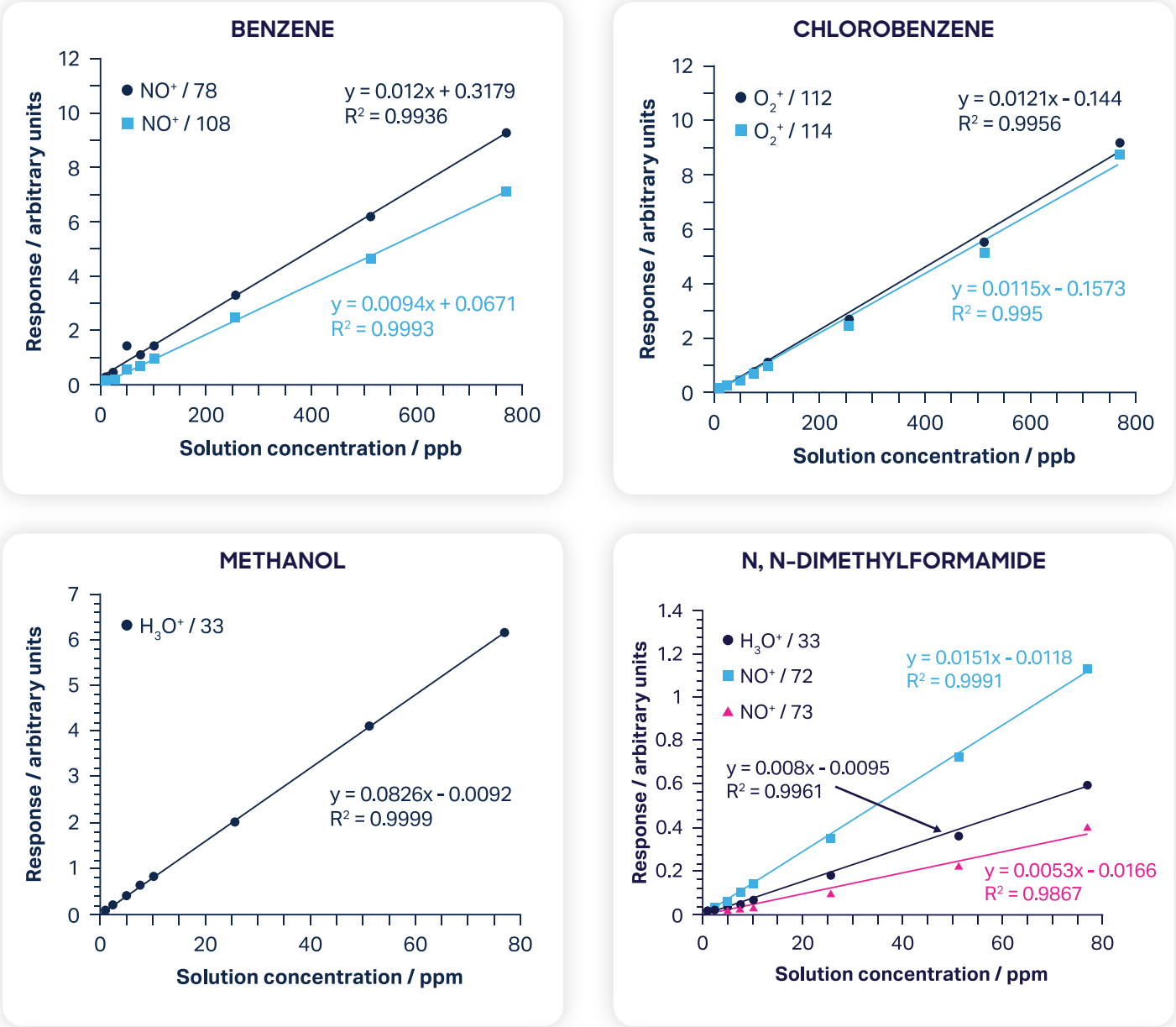


Table 2 shows the results obtained for the detection limit (LOD) and repeatability tests on the Class 1 system suitability solution prepared according to USP<1467>. Detection limits are expressed in terms of S/N for each of the individual ions. For SIFT-MS, S/N was calculated by dividing the signal obtained during the injection phase of the analysis by signal post injection, as shown in Figure 4. A S/N ≥ 13 was obtained for the critical system suitability compound benzene; other compounds in the mix generally have higher S/N than benzene. Precision (repeatability) was also excellent, with all quantitation ions giving a %RSD of <4% from the six replicate analyses.

Table 1. USP<1467> requirements for validation of an alternative procedure for the USP<467> quantitation test (Procedure C) and summary of the SIFT-MS results.

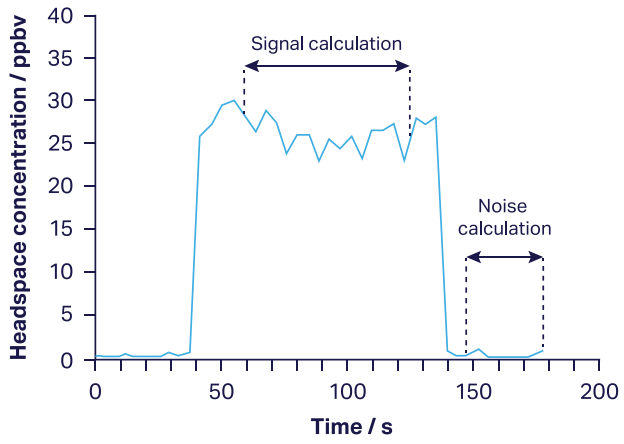
PARAMETER ACCORDING TO (1467)	ACCEPTANCE CRITERIA ACCORDING TO (1467)	RESULT OBTAINED
Specificity	"the analytical procedure must have the ability to assess unequivocally the analytes of interest in the presence of components expected to be present"	Demonstrated for three common drug products in Accuracy and Precision. See Stimuli Article for prcedure used in feasibility study
Linearity	$R^2 \geq 0.90$	$R^2 \geq 0.98$
Precision: Repeatability	Mean S/N ≥ 10 (determined from ≥ 3 replicates) OR "demonstrated by Accuracy and Precision"	Demonstrated in Accuracy and Precision*
Range	50 - 100% of limit	Pass
Accuracy (%RSD)	<20%	
1. Acetaminophen†		
· Class 2, Mix A		0.4 - 17.5
· Class 2, Mix B		0.2 - 14.3
2. Aspirin		
· Class 2, Mix A		0.3 - 13.2
· Class 2, Mix B		0.4 - 12.6
3. Ibuprofen		
· Class 2, Mix A except: 1,3-dioxane		0.2 - 14.5
· Class 2, Mix B		0.7 - 25.3
		0.6 - 14.0
Recovery	"The mean recovery for each Spiked sample solution should be 80% - 120%"	
1. Acetaminophen†		
· Class 2, Mix A		84.4 - 117.5
· Class 2, Mix B except: pyridine		88.6 - 115.3
		102.9 - 136.9
2. Aspirin		
· Class 2, Mix A		81.7 - 119.5
· Class 2, Mix B except: (i) hexane (ii) pyridine		80.5 - 111.9
		92.4 - 181.5
		51.2 - 57.8
3. Ibuprofen		
· Class 2, Mix A		80.2 - 116.5
· Class 2, Mix B except: pyridine		87.5 - 113.7
		71.5 - 94.9
Precision: Repeatability	RSD is ≤20% for "at least six independent Spiked sample solution preparations from the same lot" for each solvent present	
· Class 2, Mix A		1.4 - 6.4
· Class 2, Mix B		2.6 - 10.9

* S/N cannot be demonstrated for SIFT-MS in the manner that it is for chromatographic methods. The approach used here is described in the system suitability test.
† Outside North America, acetaminophen is known as paracetamol.

Table 2. Repeatability (instrument precision) and signal-to-noise data for Class 1 System Suitability Solution.

PARAMETER ACCORDING TO (1467)	SYSTEM SUITABILITY	RESULT OBTAINED
Detection Limit (LOD)	S/N ≥ 5 for benzene; S/N ≥ 3 for other solvents (determined from ≥ 3 replicates)	
Benzene		13 - 69
Carbon tetrachloride		24 - 466
1,2-Dichloroethane		58 - 208
1,1-Dichloroethene		25 - 365
1,1,1-Trichloroethane		43 - 503
Precision: Repeatability	RSD is ≤ 20% for "at least siz independent Spiked sample solution preparations from the same lot" for each solvent present	%RSD range for quantitation ions used, each calculated from 6 replicates
Benzene		1.1 - 3.0 %
Carbon tetrachloride		3.1 - 3.8 %
1,2-Dichloroethane		1.1 - 3.0%
1,1-Dichloroethene		0.9 - 2.2 %
1,1,1-Trichloroethane		1.2 - 2.4 %

Figure 4. Repeatability (instrument precision) and signal-to-noise data for Class 1 System Suitability Solution.



CONCLUSIONS

- This study demonstrates that SIFT-MS provides an alternative procedure to USP<467>, which describes quantitation of residual solvents in pharmaceutical products.
- The analytical performance characteristics recommended in USP<1467> for the validation of alternative procedures for determination of residual solvents were met by SIFT-MS for all Class 2A and Class 2B residual solvents in the quantitative procedure (Procedure C).
- SIFT-MS comfortably meets acceptance criteria for a chromatography limit test (Procedure B) on Class 1 residual solvents, including the system suitability test for benzene (S/N ≥ 13).
- Because SIFT-MS is inherently a rapid test technique (all sample components are simultaneously analyzed in about one minute per sample), the validated procedures can be used in organizations that require high-throughput testing, providing 17-fold daily throughput increase over GC-FID.
- No chromatographic separation is required, significantly reducing the effort and necessary qualification for high-throughput analysis.
- The validation approach is also applicable to on-line monitoring of residual solvents by SIFT-MS.

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