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Application of Routine Analysis Procedures to a Direct Mass Spectrometry Technique: Selected Ion Flow Tube Mass Spectrometry (SIFT-MS)

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ABSTRACT

In recent years the environmental and human health impacts of volatile organic compounds (VOCs) have become more apparent, resulting in increased analysis demand. The gold-standard chromatographic techniques continue to be employed for most laboratory analyses. However, they have made only modest gains in productivity over the years, and these gains are primarily due to automated sample preparation and injection. Alternatively, significant productivity gains for VOC analysis through faster sample analysis and reduced instrument maintenance could be achieved by adopting direct mass spectrometry techniques such as selected ion flow tube mass spectrometry (SIFT-MS). This article demonstrates that routine analysis techniques such as quality control checks, method validation, the method of standard additions, and internal standards are readily applied to SIFT-MS, simplifying adoption of the technique. In addition, workflows for analysis of chromatographically challenging species are simplified by using SIFT-MS. Sample throughputs are increased two- to 25-fold depending on the analytical procedure.

KEYWORDS: SIFT-MS, headspace analysis, method validation, soil, water, air, volatile compound.

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1.0 Introduction

Chromatographic methods have been the mainstay of the volatile organic compound (VOC) analyses conducted by routine laboratories and contract research organizations (CROs) for decades. Gas chromatography (GC) methods (with various detector options) are the most widely employed for analysis of VOCs. Examples include the United States Environmental Protection Agency (US EPA) methods for environmental monitoring [1-4], US NIOSH methods for workplace exposure to VOCs [5,6], International Standards Organization (ISO) methods for indoor air quality [7,8], and United States Pharmacopeia (USP) methods such as that for residual solvents [9]. Liquid chromatography (LC) mainly finds application in analysis of semi- and non-volatile organics (especially for biomolecules) [10], but is sometimes applied to VOCs–especially those of higher polarity. An example is the analysis of low molecular weight aldehydes (following derivatization) using high-performance liquid chromatography (HPLC) in the widely used US EPA Method TO-11A [11].

As demand for routine VOC analyses increases, sample throughputs on a given analytical system are not increasing proportionately because the chromatographic separation that underpins GC and HPLC methods remains the most significant limitation on maximum throughput. Depending on the analytical method, typical chromatographic analyses range from 10 to 50 minutes each. A solution that would shorten

analysis times could be achieved by adoption of direct mass spectrometry (DMS) into routine analysis workflows at a minimum to provide rapid screening. DMS methods specifically developed for VOC analysis include atmospheric pressure chemical ionization-MS (APCI-MS) [12], proton transfer reaction-MS (PTR-MS) [13,14], and selected ion flow tube MS (SIFT-MS) [15,16]. Although all techniques date from the 1990s and a significant body of research has developed for each [17], only SIFT-MS is currently a serious contender for routine analysis alongside the chromatographic methods. Compared to PTR-MS and APCI-MS, the combination of very highly controlled soft chemical ionization (enabling a compound library to be provided for both identification and quantification), rapid reagent ion switching, and stable quantitation, make SIFT-MS the best-suited technique for the routine analysis laboratory [17,18].

However, for those investigators new to direct MS who are considering its adoption into routine analysis or a contract research organization (CRO), some adaptation of routine techniques is required.

This "how-to" article reviews work conducted since 2015 to apply common routine analysis procedures developed for separation-based analytical approaches to direct-injection analysis using SIFT-MS. First, it introduces the SIFT-MS technique and its automation. Second, it considers the nuances of method development, method transfer, and method validation as applied to SIFT-MS. Then it describes how SIFT-MS fits comfortably into routine analysis workflows and can have chromatographic quantitation approaches applied to it. The article concludes with a discussion of how SIFT-MS can also simplify the analysis of chromatographically challenging compounds across diverse [19-23] and novel [24-28] applications.

2.0 SIFT-MS and its Automation for Routine Analysis

SIFT-MS is an emerging, direct mass spectrometric analytical technique that is well suited to the routine analysis laboratory. The SIFT-MS technique itself has been described in detail elsewhere [15-18]. Briefly, SIFT-MS uses controlled, soft chemical ionization coupled with mass spectrometric detection (**Figure 1**) to rapidly quantify VOCs in air and headspace to part-per-trillion concentrations by volume (pptV). Up to eight chemical ionization agents (reagent ions) are available in commercial SIFT-MS instruments (H_3O^+, NO^+, O_2^+, O^-, O_2^-, OH^-, NO_2^-, and NO_3^-) [20], but the positive ions are the standard configuration. The reagent ions react with VOCs and inorganic gases in well-controlled ion-molecule reactions, but they do not react with the major components of air (e.g. N_2, O_2, and Ar) and only slowly with water, facilitating trace analysis without pre-concentration or drying of samples. Rapid switching of reagent ions using a quadrupole mass filter provides high selectivity in the absence of chromatographic pre-separation. Data obtained here utilized a Syft Technologies Voice200*ultra* SIFT-MS instrument (Syft Technologies, Christchurch, New Zealand; www.syft.com). The units presented for headspace concentration determinations using SIFT-MS are parts-per-million by volume (ppmV). Although volume units are the "natural" units for SIFT-MS quantification indirect gas phase analysis, in the context of headspace they can also be viewed as a response factor from which concentrations in solution can be derived via a calibration curve.

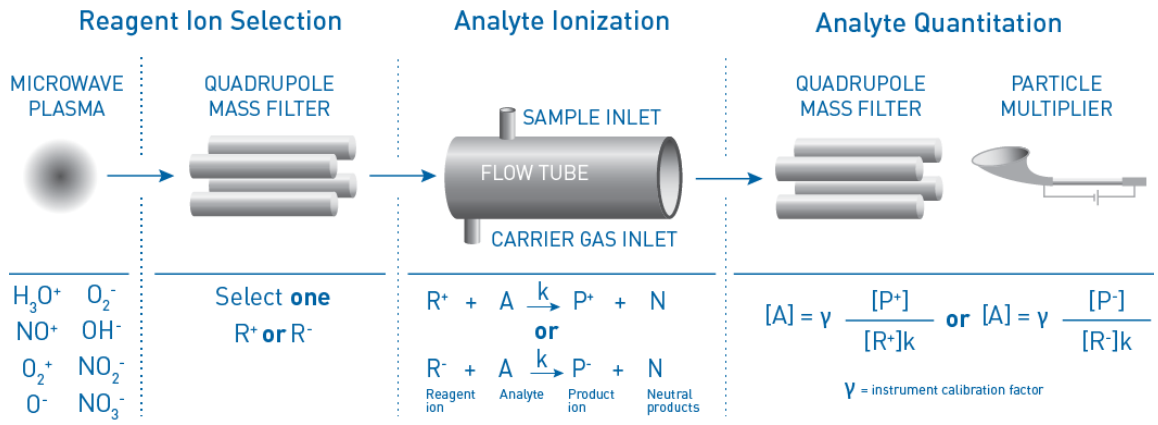

Figure 1. Schematic representation of the SIFT-MS technique. For an overview of operation, see the text.

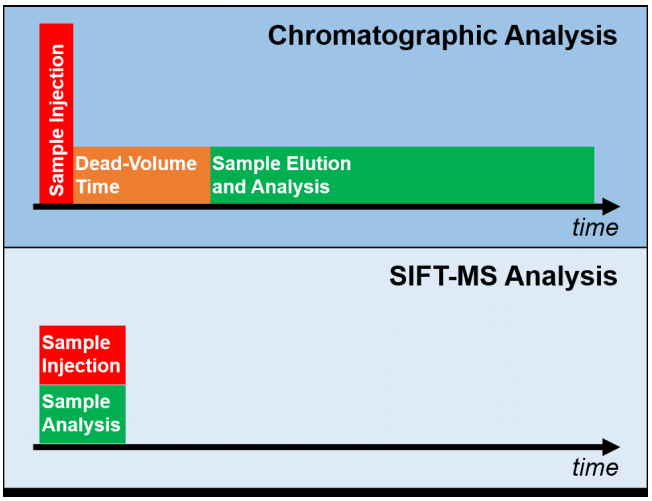

Figure 2. Schematic representation of the different sample-injection and analysis requirements of chromatographic techniques and SIFT-MS.

SIFT-MS headspace analysis is automated using a syringe-injection autosampler (for example, the Multipurpose Sampler (MPS) from GERSTEL, Mülheim an der Ruhr, Germany; www.gerstel.com), which provides slow, precisely controlled injection for the duration of the analysis. Syringe-injection autosamplers are essential for direct MS techniques such as SIFT-MS because–in contrast to chromatographic methods–sample analysis occurs synchronously with sample introduction (**Figure 2**) [29]. Headspace analysis is most commonly conducted from 20 mL sample vials on a standard GERSTEL vial rack.

3.0. SIFT-MS Method Development

Direct sample analysis without chromatographic separation introduces some significant differences for SIFT-MS method development compared to conventional chromatographic techniques. It is outside the scope of this article to discuss the details here, so the key differences are summarized.

3.1 Matrix Effects

Since the SIFT-MS technique has no chromatographic column to separate solvents and other dominant matrix species from the analytes, the total load of reactive compound in samples needs to be considered. If samples need to be diluted to avoid overloading the SIFT-MS instrument (i.e. to keep it within its dynamic range), then the LOQs of target compounds will be affected proportionally. An example of coping with the matrix is summarized below in a case study where a methanolic extraction method developed for GC/MS is transferred to SIFT-MS.

3.2 Specificity

Since SIFT-MS does not resolve compounds chromatographically, selectivity is achieved by using a combination of chemical separation (provided by multiple soft chemical ionization agents) and mass spectrometric detection [17,18]. Software tools assist the user with resolving compounds [18]. Additionally, a calibration approach [30,31] sometimes aids resolution of certain isomeric species – in this approach, ethylbenzene is distinguished from the measurement of total xylenes based on different fragmentation patterns with the O_2^+ reagent ion [32].

If both positively and negatively charged reagent ions are utilized, the current commercial option is unable to instantly switch polarities (the switch takes about 30 seconds due to a change in ion source pressure, because higher pressures are required to form negative reagent ions through the electron attachment process). However, with automation, the preparation of duplicate samples is obviated: duplicate or dual sampling of each sample vial is readily undertaken. A recent study [31] has successfully applied and validated dual sampling of single vials for the first time with SIFT-MS. Data from a dual-sampling analytical approach is shown in

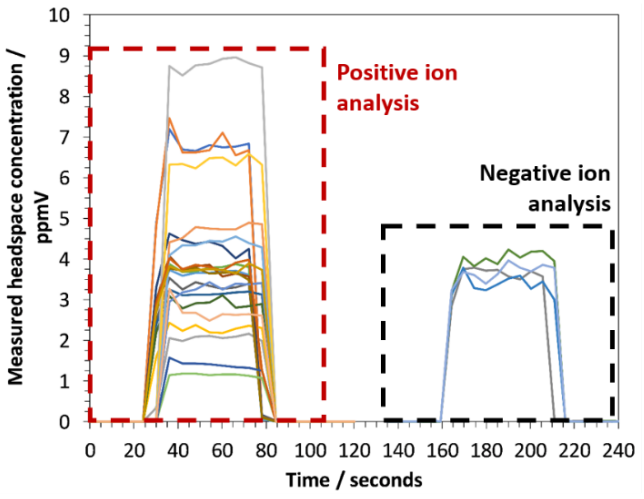

Figure 3. Example injections for dual sampling of a single vial, enabling both positive and negative ion SIFT-MS analysis in a single run. Each trace represents real-time measurement of a given quantitation ion.

Figure 3, where all positive quantitation ions are analyzed on the first injection and negative ions on the second. For static headspace analysis, this approach yields a throughput of about 180 samples per day, compared with approximately 280 per day with single sampling and reduced specificity. For comparison, the Anatune "VOC analyzer" has a throughput of 97 samples per day [33].

3.3 Limits of Detection and Quantitation

In SIFT-MS, the LODs and LOQs are improved by increasing one or more of (i) reagent ion signal, (ii) flow of sample into the flow tube, and (iii) the measurement time for target compounds [34], which contribute to improved measurement statistics. This means that limitations may be imposed on the number of compounds that can be analyzed to the required LOQ or LOD for a given sample injection due to the limited sample volume of the headspace syringe coupled with the injection rate into the SIFT-MS instrument (see, for example [23]). This contrasts with chromatographic methods, where higher sensitivities and hence improved LODs and LOQs are obtained by injecting more sample on the column [35].

3.4 Sample Delivery

As described elsewhere [29], the direct sample analysis in SIFT-MS requires that sample be introduced continuously and steadily while the instrument is analyzing the sample. As noted above, automated SIFT-MS headspace analysis is most readily achieved using autosamplers based on the syringe-injection technique, and the injection window is averaged to determine the headspace concentration, since it is constant throughout the injection (**Figure 3**). For thermal desorption or thermal extraction analyses using SIFT-MS detection, a constant desorption flow rate is utilized, but data are integrated to determine the concentration due to the time-dependent nature of the desorption profile.

4.0 Method Transfer and Validation

The direct analysis inherent to SIFT-MS yields increased sample throughputs compared to chromatographic methods. Hence, when the matrix is compatible with SIFT-MS and the target compounds are amenable to detection, method transfer from chromatographic techniques to SIFT-MS may be feasible. If the method is automated for chromatographic analysis, then the transfer to SIFT-MS is likely to be straightforward, as demonstrated in the case study below. Validation of SIFT-MS methods is achieved using an approach developed from the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline document Validation of Analytical Procedures: Text and Methodology Q2(R1) [36] as demonstrated elsewhere for gas [37] and headspace [31] analyses.

4.1 Case study: Methanolic Extraction of BTEX from Soil

Methanolic extraction is a widely used preparation technique for the analysis of benzene, toluene, ethylbenzene, and xylene (BTEX) in contaminated soils [38,39]. The two most used sample introduction techniques for GC/MS are closed-system purge-and-trap and static headspace. Single quadrupole GC/MS is the main chromatographic and detection method, but all conventional methods have drawbacks. It has been shown previously that the headspace methodology can be automated using the GERSTEL MPS sampler on GC/MS [40]. Whilst the sample preparation time remains the same in transferring the method to SIFT-MS, the analysis time is reduced threefold. Full details on the sample preparation and the results obtained are provided elsewhere [41] so a summary of results is provided here.

There were several factors to consider in transferring this method to SIFT-MS. First, the methanol used to extract the VOC residues from soil reacts rapidly with both the H_3O^+ and O_2^+ reagent ions, but about 100-fold slower with NO^+ [42] This means that – due to residual methanol in headspace samples – only the NO^+ reagent ion can be utilized. This is entirely satisfactory for benzene and toluene, but it means that ethylbenzene cannot be resolved from the xylenes using the O_2^+ reagent ion with the approach described elsewhere [30,31]. Second, more contaminated samples may cause the linear range of the instrument to be exceeded when a 2.0-g soil sample is used. Linear response was observed over the evaluated range from 0.25 g to 2.0 g, providing flexibility to the analyst in handling more contaminated soils. Finally, it is possible that residual extraction solvent could overwhelm the NO^+ reagent ion. Hence the effect of different extract spike volumes (from 25 to 500 μL) was evaluated, also giving a linear response.

Validation of the transferred method was conducted using the approach described elsewhere [31]. The results of validation are summarized in **Table 1** with full data in [41]. Three soil samples (proficiency test samples 'loamy sand', 'silt loam', and 'BTEX in soil' from Sigma-Aldrich, Gillingham, UK) were used to determine analytical precision. Recovery was evaluated in triplicate on the 'silt loam' and 'BTEX in soil' samples. Except for several 'BTEX in soil' samples over-recovering, all acceptance criteria (from [36]) were met.

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5.0 Routine Analysis Workflow

In this section, recommended procedures for implementing routine calibration, system suitability tests, and quality control checks are discussed.

5.1 Calibration Approaches for SIFT-MS

Regular calibration of SIFT-MS instrumentation is a departure from the conventional SIFT-MS approach, where the quantitation based on pseudo-first-order gas-phase reaction kinetics [15,16] and instrument stability deem calibration uncommon. However, calibration is simple and rapid for automated SIFT-MS instruments, so transferring routine chromatography calibration procedures to the SIFT-MS workflow is recommended.

Conventional applications of SIFT-MS instruments frequently involve continuous, real-time analysis. These have utilized gas-phase calibration from gas calibration standards (cylinders and permeation tubes being commonly used). In contrast, automation greatly simplifies calibration, enabling more cost-effective, easy-to-handle solution-based standards to be utilized. The most important consideration is that because SIFT-MS is a direct analysis method, criteria determining solvent compatibility differ from GC/MS. For SIFT-MS, the solvent must be non-reactive or react only very slowly with one or more SIFT-MS reagent ions. In contrast to GC/MS, water is the preferred solvent for SIFT-MS. However, in various applications methanol (see the case study in the preceding section), chloroform, dichloromethane, and dimethylsulfoxide (DMSO) [31,43] have all been utilized successfully.

Calibration standards can be prepared automatically on the autosampler platform if a compatible model is used (for example, the GERSTEL MultiPurpose Sampler (MPS) Robotic-Pro with tool change, or the GERSTEL dual-head MPS XT). If either GERSTEL platform is used, then the GERSTEL Maestro PrepAhead functionality enables this preparative work to be done very efficiently, in addition to the calibration sequence itself.

Analogous to GC/MS, multiple-point calibration curves covering the range of the analysis and single-point calibrations are both supported by automated SIFT-MS.

Table 1. Results of SIFT-MS method validation for methanolic extraction from soil of benzene, toluene, and ethylbenzene plus the xylenes.

Validation parameters	Acceptance criteria*	Benzene	Toluene	Et-B + Xylenes
Linearity	$R^2 > 0.99$	0.9993	0.9997	0.9979
Range		10 – 5000 ppb in solution	10 – 5000 ppb in solution	10 – 5000 ppb in solution
System precision (% RSD) • 500 ppb • 1500 ppb • 3000 ppb	< 10%	 1.2% 3.6% 2.3%	 1.5% 3.7% 2.9%	 2.7% 5.6% 4.5%
Analytical precision • 'Loamy sand' • 'Silt loam' • 'BTEX in soil'	< 10%	 1.8% RSD 1.7% RSD 2.7% RSD	 1.6% RSD 2.0% RSD 0.9% RSD	 1.2% RSD 1.6% RSD 1.0% RSD
Accuracy (% RSD)** Unspiked • 250 µL • 500 µL • 750 µL	< 10%	 0.3-0.7% 1.9-2.7% 0.2-1.8% 0.7-0.9%	 0.3% 1.2-1.5% 0.9-1.3% 0.5-1.0%	 0.6-0.8% 1.0-1.2% 0.7-2.0% 0.3-0.6%
Recovery • Calibrations Crosscheck • 'Silt loam' • 'BTEX in soil'	 < 10% 10% 80 < x < 120%	 0.8% 96.6% 101.3% 124.3%	 0.9% 95.4% 88.4% 115.7%	 0.9% 94.9% 105.9% 106.9%

* Acceptance criteria are derived from [36].
** Accuracy: range of values indicates values for 'silt loam' and 'BTEX in soil'.

Multiple-point calibrations. Multiple-point calibrations have been implemented regularly in automated SIFT-MS analyses. **Figure 4** shows an example for BTEX and chloroform analysis in the headspace of water at 60°C, demonstrating the excellent linearity of aqueous headspace analysis using automated SIFT-MS. Similar results were obtained for soil headspace analysis (described above) and gas-phase analysis [37,44].

Single-point calibrations. Automated SIFT-MS provides extremely repeatable analysis, even for headspace measurements when no internal standard is utilized (see 'Internal Standards for SIFT-MS' below). This means that single-point calibration is justified for certain methods. **Table 2** summarizes repeatability for six water headspace measurements; all analytes have RSDs less than 2.5%.

5.2 System Suitability Tests for SIFT-MS

System suitability tests (SSTs) verify that the analytical system will perform in accordance with the criteria set forth in the method [9]. SSTs are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. Here, an example SST for SIFT-MS is presented that was utilized in a regulatory submission for formaldehyde analysis in novel drug delivery devices.

The manufacturer of the SIFT-MS instruments utilized in this work recommends running an automated daily qualification routine on their SIFT-MS instrument(s) that utilizes an eight-component certified gas mixture [45]. (This can be considered equivalent to the autotune procedure run on a GC/MS.) This gas standard is utilized here for a generic SST.

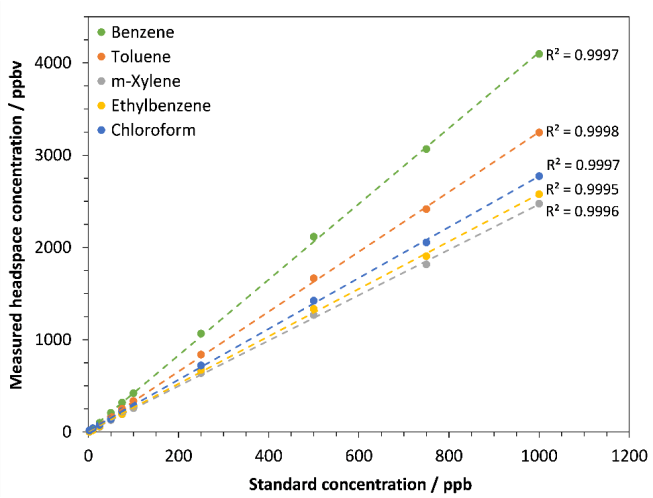

Figure 4. Linear calibration of benzene, toluene, ethylbenzene, m-xylene (BTEX), and chloroform from 2.5 to 1,000 ppb in water.

After running the full daily qualification routine, the quantitation test was performed in replicate several times. In this example, it was run 10 times and four compounds (benzene, ethylene, isobutane, and toluene) were used to assess performance. These replicate measurements took less than seven minutes to obtain. **Figure 5(a)** shows the replicates and means for 10 replicates, with RSDs of ca. 2% or less shown in red. However, this rapid SST can be further reduced to little more than two minutes by simply making triplicate measurements **Figure 5(b)**, since RSDs are still well within typical acceptance criteria [36].

Table 2. Six replicate SIFT-MS measurements of single-point calibration from an aqueous calibration standard. SIFT-MS measurements are ppmV in headspace. Solution concentration was 1 ppm for each analyte.

Samples and Statistics	Benzene	Toluene	Xylenes + Ethylbenzene	Chloroform
Rep 1	2.25	3.00	5.22	3.02
Rep 2	2.31	3.06	5.25	2.98
Rep 3	2.19	2.92	5.08	2.90
Rep 4	2.25	2.94	5.09	2.94
Rep 5	2.32	2.99	5.16	3.00
Rep 6	2.18	2.84	4.97	2.89
Mean	2.25	2.96	5.13	2.96
St. Dev.	0.053	0.069	0.094	0.049
%RSD	2.4	2.3	1.8	1.7

Following the principles described for developing a generic SST, rapid SSTs for specific methods can be created. In the context of this regulatory submission [37], a rapid specific SST was developed in which formaldehyde was analyzed from a permeation tube standard.

5.3 Quality Control Checks for SIFT-MS

Some methods require inclusion of quality control check (QCC) standards to provide within-sequence assurance that the method continues to perform properly. Analytical instrument qualification, analytical method validation, and SSTs contribute to quality assurance of the analysis before samples are analyzed. The QCCs assure quality analytical results are obtained during the sample analysis sequence.

QCCs are easily implemented and the samples are rapidly analyzed with automated SIFT-MS. **Table 3** summarizes results obtained from a short demonstration sequence for methanolic extraction of BTEX from soil (summarized in the previous section and described fully in [41]). The QCC results all lie within 1.2% of the original triplicate calibration, so acceptance criteria are met [36].

The rapid analysis provided by SIFT-MS means that more QCCs can be added in the sequence and additional QA checks can be made. For example, regular interleaving of blanks ensures that carryover is within acceptable limits.

6.0 Applying Quantitation Approaches used with Chromatograpic Methods

For certain methods, routine calibration has proved inadequate for chromatographic methods, so internal standards and/or the method of standard additions are incorporated. In this section, SIFT-MS approaches to applying these procedures are described.

6.1 Internal Standards for SIFT-MS Analysis

For most applications of automated SIFT-MS, the use of internal standards has been unnecessary (cf. **Figure 4** for aqueous headspace analysis with SIFT-MS). In contrast to headspace-GC/MS, where there is significant variability and internal standards are essential, headspace-SIFT-MS measurements are routinely very precise (**Figure 6**). It appears that the reason for this difference is that the steady, slow injection into the sample inlet of the SIFT-MS instrument yields much less variability in headspace-SIFT-MS (see **Table 4** for

Table 3. Example data for standards, blanks, and samples analyzed using the transferred automated methanolic extraction method. Data are organized as they were in the run's sequence table and illustrate the use of a QCC in the SIFT-MS workflow.

Parameter	Headspace concentrations/ ppbV		
	Benzene	Toluene	EtB + m-X*
Calibration 1	63.9	58.8	131
Calibration 2	64.9	60.6	135
Calibration 3	67.5	61.0	136
Mean	65.4	60.1	134
SD	1.5	0.96	2.2
%RSD	2.3%	1.6%	1.6%
Soil blank	0.14	0.58	0.00
Spike: 16.7 ppb (43 ng/g)	4.34	4.67	8.46
Spike: 41.7 ppb (108 ng/g)	13.6	13.9	27.6
Spike: 83.3 ppb (216 ng/g)	24.6	24.4	53.9
Spike: 167 ppb (432 ng/g)	50.7	51.5	118
Spike: 333 ppb (864 ng/g)	104	97.2	222
Quality control check (QCC)	66.2	60.3	134
% Difference QCC to Cal. Mean	1.2	0.33	0

* "EtB + m-X" is the sum of ethylbenzene and m-xylene.

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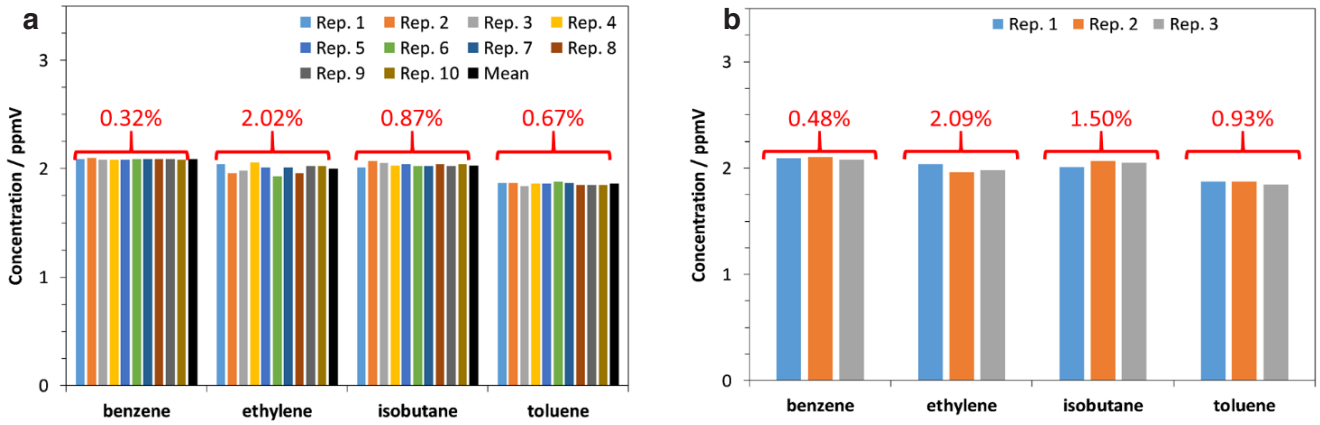

Figure 5. Data from (a) ten and (b) three replicate analyses for benzene, ethylene, isobutane, and toluene of the "Syft Calibrant Standard". RSDs are annotated on the graphs.

the results summary for 50 replicate injections from a Tedlar bag sample). In contrast, for headspace-GC/MS, a relatively large headspace volume is injected into a small liner volume very rapidly, likely introducing greater variability.

Although SIFT-MS methods do not ordinarily require internal standards, the procedure is readily applied to SIFT-MS – albeit with some modifications compared to GC/MS. Because SIFT-MS analysis has no chromatographic separation, application of the internal standards used in chromatographic methods (e.g. deuterated standards) may not give good results for SIFT-MS. Selection of an internal standard for a SIFT-MS method requires that the matrix and the target compound list be evaluated in detail to ensure (1) that the internal standard does not interfere with other analytes, and (2) that the standard is not interfered with by other analytes or the matrix. That is, the internal standard needs to have product ions in regions of the mass spectra where there are no matrix or analyte peaks.

Consider a simple example: the analysis of two industrial solvents: toluene and methyl isobutyl ketone (MIBK). These compounds have molecular weights of 92 and 100 Da respectively. Their SIFT-MS positive reagent ion scan spectra are shown in **Figure 7(a)**. if toluene-D8, a conventional internal standard for GC/MS, is used, then a significant interference issue results with two of the available quantitation ions for MIBK (as shown in **Figure 7(b)**: with H_3O^+, m/z 101 and with O_2^+, m/z 100). However, fluorinated internal standards provide a promising alternative. Consider perfluorotoluene (or toluene-F_8; **Figure 7(c)**): its product ion is shown overlaid on the spectrum and cause no problems.

6.2 Case study: Solvents in Plasma

Early method development in a recent study [48] investigating cyclohexanone and its metabolite cyclohexanol in porcine plasma utilized acetone-D_6 as an internal standard (100-ppm in solution) due to some variability in the headspace data [49]. This preliminary method development work utilized standards in 0.1 M saline solution, not plasma. **Figure 8(a)** shows the calibration curves for cyclohexanone and cyclohexanol uncorrected, while **Figure 8(b)** shows the points corrected by the acetone-D_6 internal standard's response – illustrating a significant improvement. Interestingly, as method

Table 4. Results summary for 50 replicate injections of sample from a Tedlar sample bag over a 36-minute period. Mean concentrations and standard deviations are in ppmV, and RSDs are a percentage.

Statistics	Acetone	Butyl acetate	Isoprene	Limonene	Toluene
Mean	0.368	0.021	0.046	0.182	6.028
St. Dev.	0.008	0.001	0.001	0.004	0.041
%RSD	2.3	5.6	2.8	1.9	0.7

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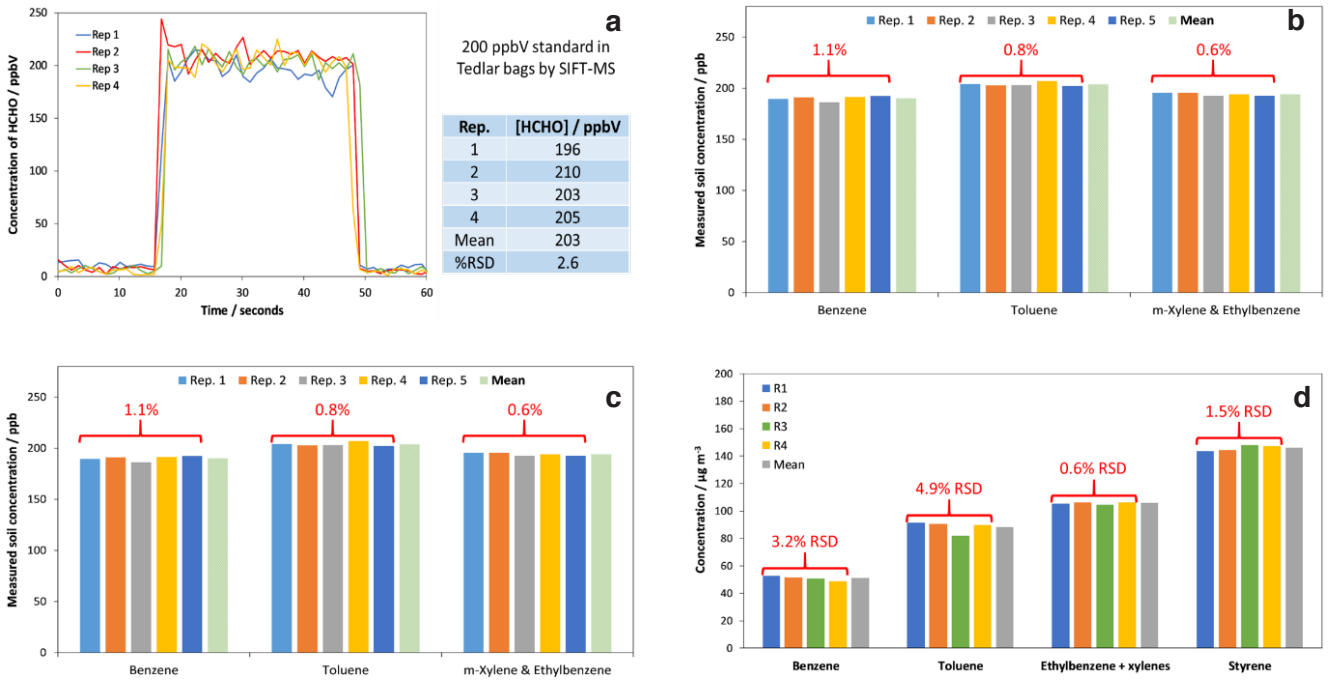

Figure 6. Examples of highly repeatable measurements made using SIFT-MS without using an internal standard. (a) Formaldehyde (HCHO) analysis from sample bags, showing repeatable sample injection profiles [19]. (b) BTEX and chloroform in water headspace [46]. (c) BTEX analysis following methanolic extraction from soil [41]. (d) BTEX and styrene from thermal desorption tubes (TDTs) [47]. RSDs are annotated for (b) – (d)

development progressed inclusion of an internal standard for the SIFT-MS analysis was deemed unnecessary based on method performance criteria being met without it [48].

6.3 Standard Additions for SIFT-MS

The method of standard additions is really the "gold standard" analytical method, because each sample carries its own calibration curve and thus any drift in the method over time is mitigated [50-52]. However, performing the method of standard additions analysis is expensive due to multiple analyses being conducted per sample and it is typically only utilized when essential. Examples of such usage include when the matrix effects prevent good chromatography, or when the matrix modifies the partitioning of the analyte in headspace analysis. Mitigation of matrix effects has seen it applied in SIFT-MS analysis. Sample throughput using SIFT-MS is reduced compared to routine headspace analysis, but it is still significantly faster than the method of standard additions utilized with GC/MS.

To apply the method of standard additions to SIFT-MS, automation is recommended. When developing the method, the spike volumes of standards should be kept as small as possible so that additional matrix effects are not introduced; typically, this means using 1-10 µL spikes. The method developer should also ensure that headspace partitioning is not perturbed through multiple cycling of spikes and analysis; if perturbation of headspace partitioning is observed, multiple vials per sample should be prepared (one for each spike level). If method development shows that multiple sampling of the headspace from the same vial can be conducted, then the process is (1) incubate, (2) inject, (3) add spike, repeating for the number of standard additions that will be made. For a curve with three spike additions, the sequence for one sample is shown in **Figure 9(a)**. Because the time for analysis is not the rate-limiting step with SIFT-MS (as it is for GC/MS), three additional samples (or if the standard additions samples need to be prepared separately) increase the analysis time by only 16 minutes (or 17%; **Figure 9(b)**).

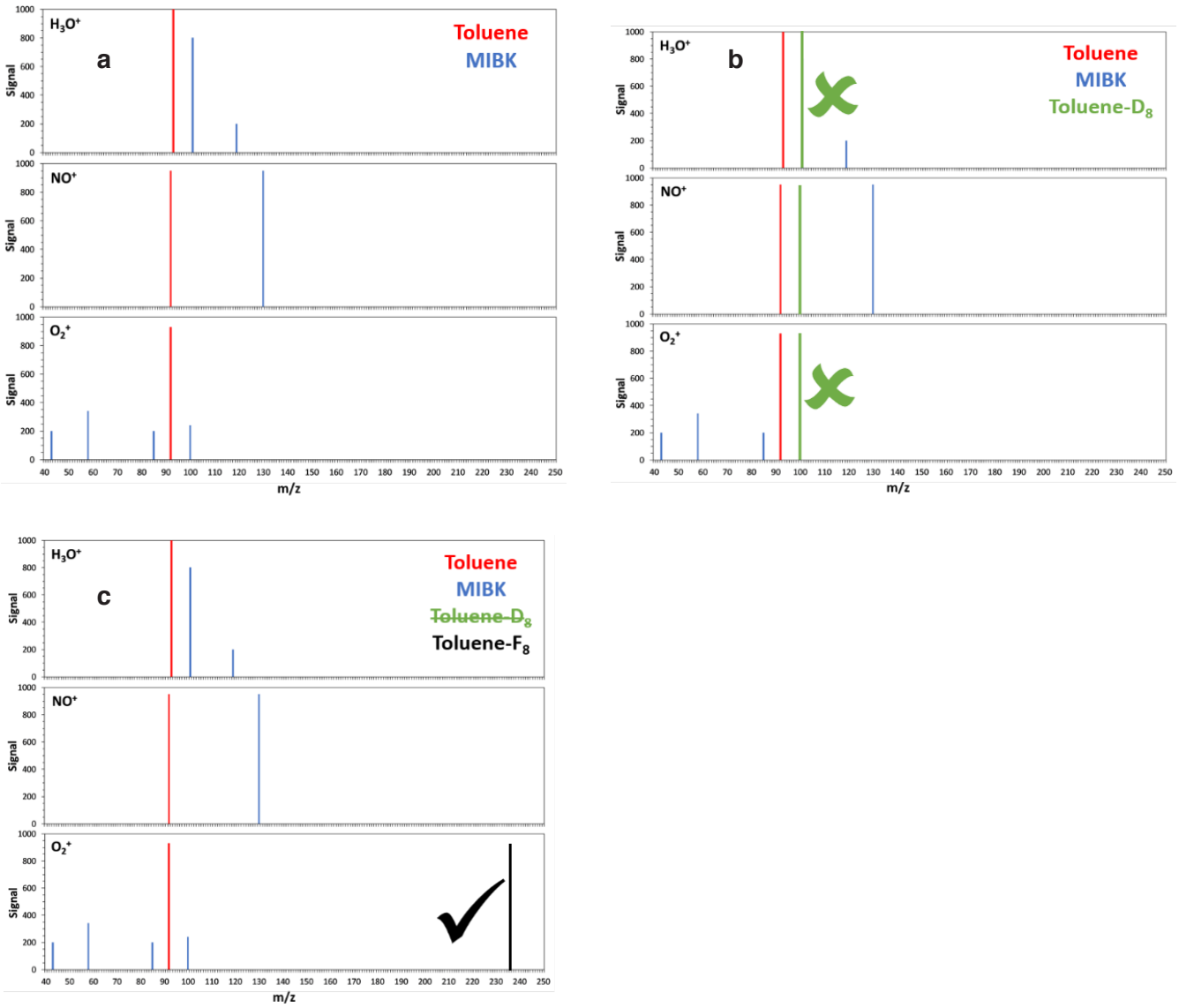

Figure 7. Selecting an appropriate internal standard for automated SIFT-MS. (a) Positive reagent ion mass spectra for analytes toluene and MIBK. (b) Toluene-D8 interferes with two MIBK quantitation ions, so does not work well for direct analysis for SIFT-MS. (c) Toluene-F8 is a much better choice as an internal standard for this SIFT-MS analysis.

6.4 Case study: Formaldehyde Analysis in Fragrance Matrices

Variability in fragrance matrices means that formaldehyde cannot be analyzed reliably using the routine headspace-SIFT-MS approach. Two significant contributors are (1) partitioning of formaldehyde from aqueous solutions is relatively low – resulting in relatively poor sensitivity (~0.1 μg/mL), and (2) high levels of VOCs in the fragrance matrix consumed reagent ion signals but were not consistent from one sample to the next, leading to overestimation of concentration. Hence the method of standard additions was employed to address this.

A simple aqueous calibration set for formaldehyde quantitation did not match the complex fragrance matrix adequately,

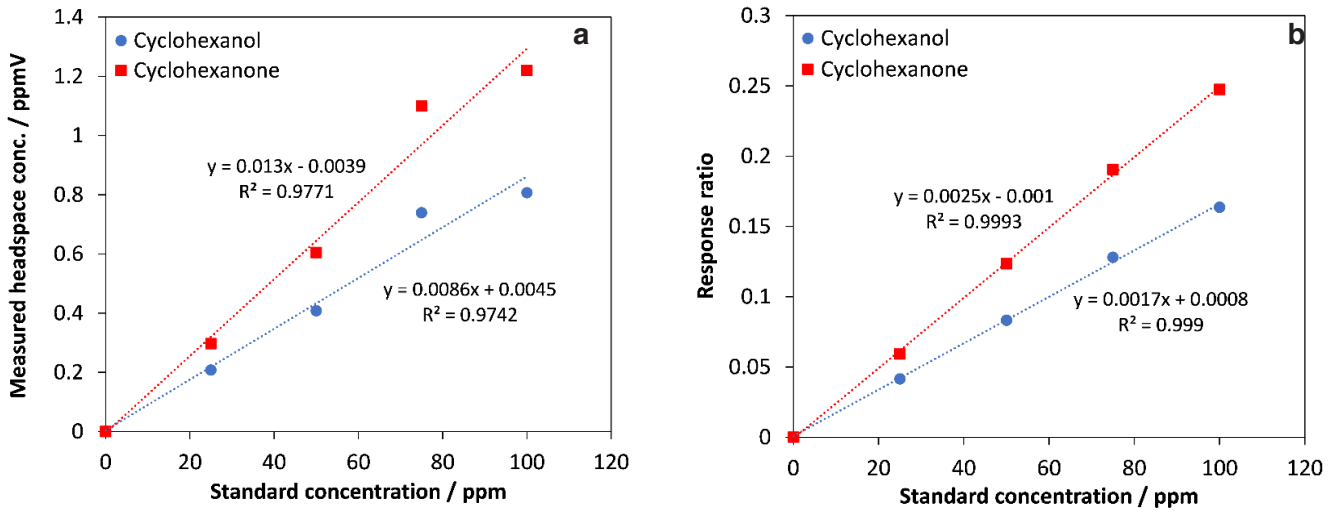

Figure 8. Calibration curves for cyclohexanone and its metabolite cyclohexanol in 0.1 M saline solution: (a) response as measured (uncorrected for internal standard response), and (b) target compound responses corrected by acetone-D6 response.

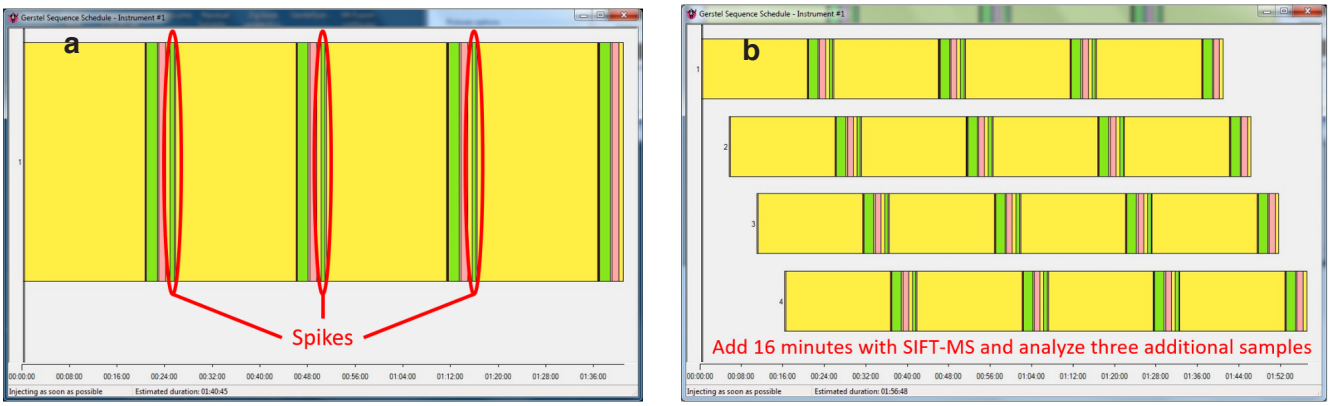

Figure 9. Sequence schedules from the GERSTEL Maestro software package, illustrating the sequences for (a) one and (b) four samples being analyzed using the method standard additions on an automated SIFT-MS instrument.

so the method of standard additions was utilized to overcome this issue. In this case study, 1 mL of sample was added to a 20 mL vial and it was incubated for 15 minutes at 75°C. After the headspace was analyzed, standard additions were made at 10, 20 and 30 µg/mL from a 1000 µg/mL standard. **Figure 10** shows the linearity across the standard additions range in (a) water and (b) a fragrance sample. For the fragrance sample, extrapolation revealed the presence of 65 µg/L of formaldehyde.

7.0 Simplified and novel routine analysis with SIFT-MS

The SIFT-MS technique applies very soft chemical ionization that enables analysis of a wide range of volatile compounds in a single analysis with high selectivity, due to the diverse ionization mechanisms provided by the reagent ions [53]. This means that some of the common limitations of GC methods for gas and headspace analysis are addressed by implementing chromatography-free SIFT-MS analysis, as summarized in **Table 5**. Additionally, the speed with which

Table 5. Challenges for GC methods that are addressed by SIFT-MS and the benefit obtained by utilizing SIFT-MS.

Challenge for GC Methods	How SIFT-MS Addresses Challenge	Benefit of SIFT-MS to Routine Analysis*
Throughput is primarily limited by the chromatographic separation	No chromatographic separation	Significant throughput advantage
Time-resolved measurements require repeat sampling followed by off-line analysis	No column, direct ionization enables real-time analysis	Process dynamics can be followed
Column discriminates, so multiple analyses may be required (e.g. special columns for amines and glycols)	No column – direct, soft chemical ionization	All-in-one volatile compound analysis, including amines [54] and glycols [55]
High polarity compounds need to be derivatized	Reagent ions react with polar and non-polar compounds	Direct analysis of polar species such as aldehydes [56], nitrosamines [57], volatile fatty acids [58], etc.
Samples must be dried due to (1) high coefficient of expansion of water, and (2) impact on ionization for MS detectors	Sample is introduced slowly into SIFT-MS inlet and ionization is robust to water	Simplified workflow and better repeatability because no drying step required
Thermally labile species are challenging due to high injector temperatures	SIFT-MS uses lower inlet temperatures as a dedicated gas and headspace technique	Thermally labile compounds (e.g. hydrogen sulfide and organosulfur compounds [59]) are analyzed straightforwardly
Air and water checks on the MS because these lead to poor chromatography and more noise	SIFT-MS ionization is unaffected by oxygen	Simplified workflow and better repeatability because air does not need to be removed
Non-zero dead volume time on the column means there is a minimum time needed (typically minutes) before analysis even begins	Dead volume is negligible for SIFT-MS; instrument responds to sample injection in <1 s	Contributing factor to high sample throughput
Column clear-out times lengthens analysis of very volatile compounds in presence of less volatile components	No column – all volatilities analyzed simultaneously without clear-out times	Significant throughput advantage (e.g. see the discussion under fruit application)
Siloxane bleed from septa and columns makes their analysis challenging	Siloxane-leaching materials and system temperatures are much lower	Siloxane analysis [60,61] is simplified, and their volatility used to advantage

* Note that realization of the benefit of SIFT-MS in routine analysis still requires evaluation of effective sample delivery to the instrument

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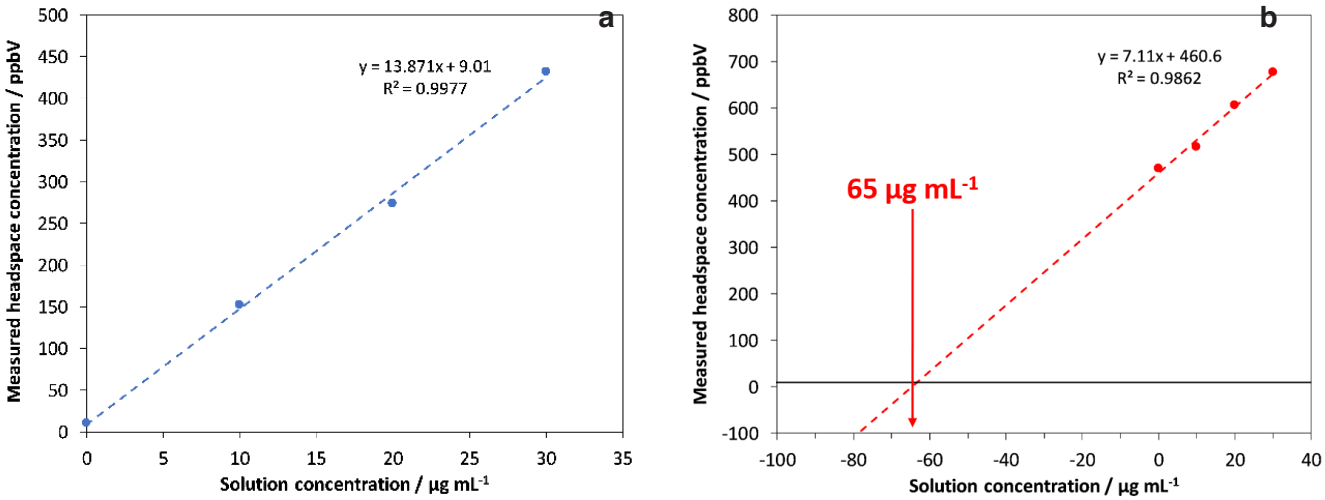

Figure 10. Standard additions calibration curves determined using automated SIFT-MS for (a) water and (b) a fragrance sample respectively.

static headspace analysis can be conducted with SIFT-MS [31] means that it can also be applied in support of method development for the other techniques for which headspace parameter optimization is ordinarily a protracted procedure and may be ignored.

In this section, two novel applications of SIFT-MS are briefly described that illustrate some of these benefits: (1) continuous headspace analysis of formaldehyde from polyoxymethylene polymer (POM) pellets, and (2) analysis of ethylene in fruit.

7.1 Case Study 1: Continuous Headspace Analysis (CHA)

CHA is a novel technique made possible by direct headspace analysis, such as that provided by SIFT-MS [62]. It enables emissions of volatile compounds to be probed in a dynamic, controlled manner, which is very challenging for conventional chromatographic methods. CHA differs from dynamic headspace analysis (DHA) in that real-time measurement of volatile emissions in the headspace is made throughout the process, whereas in DHA emissions are continuously trapped on a sorbent, then later thermally desorbed to give a single time-averaged measurement for the sample.

CHA is straightforward when using a SIFT-MS instrument integrated with a GERSTEL MPS autosampler equipped with a GERSTEL purge tool. **Figure 11** shows replicate analyses of 22-mg samples of polyoxymethylene (POM) polymer pellets in standard 20-mL sample vials incubated at 60°C for 20 minutes. Data points have 2.7-s time resolution. Under dry purge conditions (zero air), formaldehyde concentrations demonstrate the expected decay. However, prior addition of water (2 µL) to the sample results in new structure (dotted curve in **Figure 11**). The area under each curve is very similar, indicating that the same amount of formaldehyde is being released from each sample. Addition of water hydrates the emitted formaldehyde, which then condenses on the vial walls for a short period before being released in a burst, producing the observed (and repeatable) spike in concentration at 3.25 minutes.

Similar principles apply to direct measurement of formaldehyde during thermal extraction of POM [63] and more general applications of SIFT-MS to formaldehyde analysis [19,37]. In summary, formaldehyde can be analyzed directly from just a few sccm in real-time and at high sensitivity using SIFT-MS, substantially simplifying sampling and analysis workflows.

7.2 Case Study 2: Rapid, Simple Analysis of Ethylene in Fruit

During ripening, fruits emit a diverse range of low molecular weight compounds arising from various hormonal and metabolic processes. The relative abundances of these volatiles change over time. Ethylene – because it promotes ripening – is usually of particular importance [64]. Conventional GC methodologies are usually applied, but this is challenging for ethylene and the solvent-like compounds emitted from fruits [65]. Direct analysis using SIFT-MS enables poorly retained compounds, such as ethylene, to be analyzed synchronously

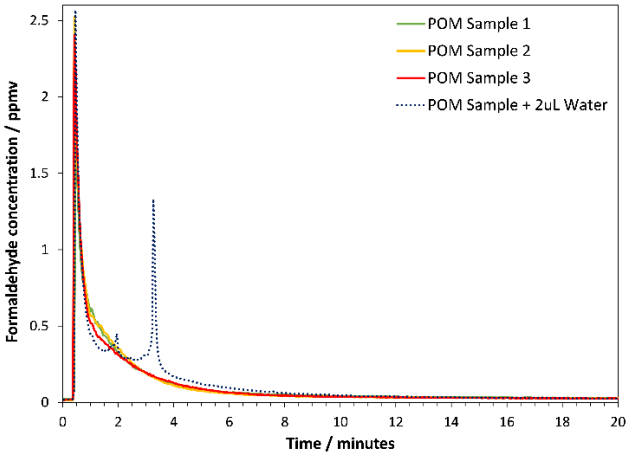

Figure 11. CHA-SIFT-MS analysis of formaldehyde direct from POM polymer headspace under dry (solid traces) and humidified (dotted trace) conditions.

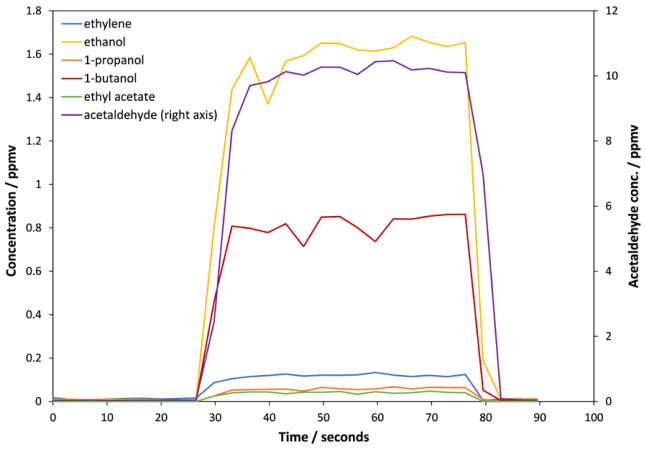

Figure 12. SIFT-MS headspace analysis of an apple sample. More details are given in the text.

with the more retained volatiles in a GC analysis, eliminating the extended run time necessary in GC to clear the column of the less volatile, non-target compounds.

Application of SIFT-MS utilized 2-g apple samples in 20-mL autosampler vials, and an incubation temperature of 60 C for 15 minutes [66]. Efficient scheduling of samples for analysis was achieved using commercially available software (GERSTEL Maestro; GERSTEL GmbH, Mülheim an der Ruhr, Germany). **Figure 12** shows SIFT-MS data obtained for an apple sample, with all compound traces measured during the same injection. The background is visible at the start and end, and the rapid rise in headspace to a steady value occurs as the headspace sample is injected steadily into the SIFT-MS instrument's inlet from the autosampler syringe. Comparing the SIFT-MS results with those in the GC/MS application data sheet [65] the relative levels are the same for both techniques. However, the analysis time is very different: compared to GC/MS, each SIFT-MS data point represents acquisition of results equivalent to an entire chromatogram in just a matter of seconds. Because SIFT-MS limits of quantitation improve with increased acquisition time [34], sample averaging over a total analysis time of several tens of seconds is employed. The concentration of each compound is derived from the mean value across the headspace injection.

SIFT-MS provides simple and highly sensitive and selective analysis of a poorly retained volatiles from fruits, with no delays due to late elution of non-targeted, less volatile compounds. Hence SIFT-MS addresses the rate limiting step in the conventional analysis: the chromatographic separation. The SIFT-MS method can analyze over six times more samples than the GC/MS method in a 24-hour period.

8.0 Conclusion

Chromatography-based test methods have been the gold standard and workhorse for VOC analysis in routine testing laboratories and CROs for many years. However, they are not without their challenges – especially in terms of sample throughput, sample preparation (especially for polar compounds or wet samples), and discrimination introduced by the column or detector. Adoption of SIFT-MS has the potential to address these challenges through direct, soft CI of the sample gas or headspace by the reagent ions, while eliminating chromatographic separation. High specificity in real-time is achieved uniquely in SIFT-MS: multiple rapidly switchable chemical ionization agents (reagent ions) are utilized that often have different ionization mechanisms with different classes of VOCs. Throughput increases for room temperature analyses are up to 25-fold, incubated headspace analysis from 2 to 10-fold, and for the method or standard additions and multiple headspace extraction are from 2 to 6-fold.

This article has demonstrated how SIFT-MS fits comfortably in the routine testing laboratory and CRO, because routine analysis techniques developed for the chromatographic methods are readily adapted to suit it. Calibration and method validation approaches are increasingly utilized with SIFT-MS.

However, some of the routine analysis procedures – in particular, use of internal standards and the method of standard additions – have not been utilized significantly with SIFT-MS due to the nature of the instrument (e.g. stability leading to high precision) and the predominant analyses that have been conducted (e.g. headspace). However, when needed they are easily implemented.

SIFT-MS will not replace the chromatographic methods in the routine analysis laboratory; rather, it complements them. It offers potential for high-throughput, economic screening prior to regulatory analyses, plus readily tackles a variety of compounds that are very challenging for conventional methods – especially species of low molecular weight that are polar and/or thermally labile.

9.0. References

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