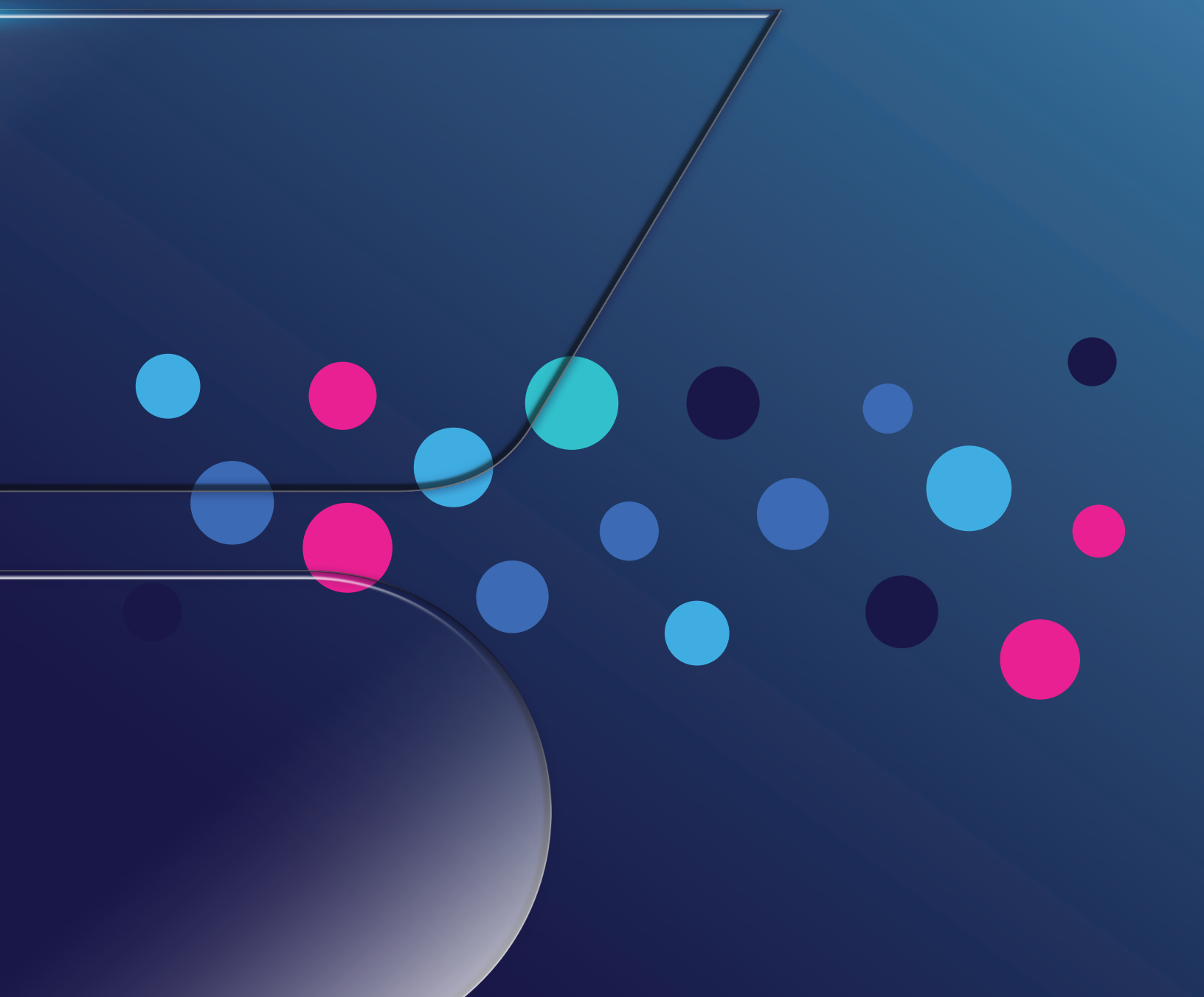
HIGH-THROUGHPUT SIFT-MS

ANALYSIS OF FORMALDEHYDE IN FRAGRANCES USING THE METHOD OF STANDARD ADDITIONS

Mark J. Perkins[1] and Vaughan S. Langford[2]
[1]Element Materials Technology, Cambridge, United Kingdom
[2] Syft Technologies Limited, Christchurch, New Zealand



Abstract

Selected ion flow tube mass spectrometry (SIFT-MS) provides rapid, sensitive quantitation of formaldehyde in fragrance samples via headspace analysis. Matrix effects due to the variable headspace compositions of the fragrance mixes were effectively addressed through utilization of the method of standard additions. In this study, three aqueous fragrances were analyzed for formaldehyde content with results ranging from 7 to 85 µg mL^{-1}. The high sample throughput of SIFT-MS means that calibration curves for each matrix are generated rapidly, making the standard additions approach more economic when using SIFT-MS than for chromatographic approaches. This enables SIFT-MS to reduce the time for reporting the first result while increasing the daily throughput. For full standard additions on every sample, three complete analyses (including standards) can be achieved per hour. If the matrix is consistent, then 12 samples can be screened per hour. The ease with which SIFT-MS rapidly analyzes formaldehyde means that it is ideally suited to product quality control – both in the testing laboratory and on the process line.

Introduction

Volatile compounds can be harmful to human health if present in consumer or drug products at levels that represent a toxicological risk. Formaldehyde is of particular concern, because it is a known human carcinogen (e.g., US NTP (2011), European Commission (2018))) and can arise from impurities in, or degradation of, ingredients, or from residual impurities in packaging materials. Formaldehyde is, however, challenging to analyze using conventional chromatographic techniques (both gas and liquid chromatography; GC and LC) due to its high polarity, high reactivity, and the need for sample preconcentration and solvent extraction. Alternatively, selected ion flow tube mass spectrometry (SIFT-MS) can analyze formaldehyde directly in headspace at toxicologically relevant concentrations.

This application note applies SIFT-MS to the analysis of formaldehyde in three fragrance mixes. These mixes have different compositions, but all pose a challenge to SIFT-MS as used conventionally because the total concentration of matrix volatile organic compounds (VOCs) exceeds the dynamic range of the instrument (Smith et al. (2023), Langford (2023)). This complication arises due to the direct, chromatography-free analysis achieved using SIFT-MS, which means that analytes and other matrix volatiles pass through the instrument ionization region simultaneously.

The challenge is addressed through application of the method of standard additions to SIFT-MS (Perkins and Langford (2021), Silva and Langford (2022)). This procedure, which is used in conjunction with chromatographic methods when analyzing complex matrices, provides a means by which the SIFT-MS instrument can quantify trace components even when the instrument is operating above its conventional dynamic range. As demonstrated below, formaldehyde is successfully quantified in the fragrance matrix by using this approach. Moreover, by applying automated headspace-SIFT-MS, significant workflow benefits are realized compared to utilizing standard additions with chromatographic methods. These include reporting first the results greater than 1.8-fold faster and delivering over 2.9-fold higher sample throughput. This serves to make the method of standard additions a viable and economic analytical approach in the broader SIFT-MS analysis toolkit.

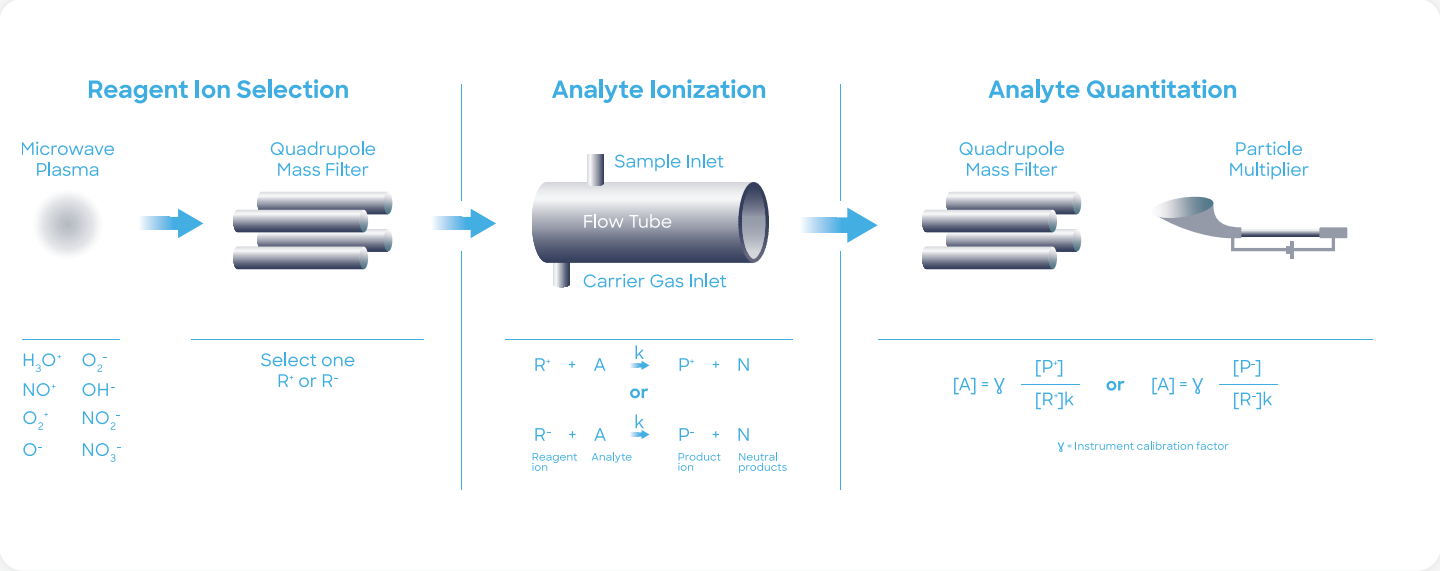
Method

1. The SIFT-MS technique

This work utilized a Syft Tracer™ SIFT-MS instrument operating on helium carrier gas. SIFT-MS (Figure 1) uses soft chemical ionization (CI) to generate mass-selected reagent ions (Smith et al. (2023)) 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 available on Syft Tracer™ instruments. 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 (Langford (2023)). The multiple reagent ions frequently remove uncertainty from isobaric overlaps in mixtures containing multiple analytes. Hence Syft Tracer™ sets the standard for sensitive and selective real-time analysis of volatile compounds.

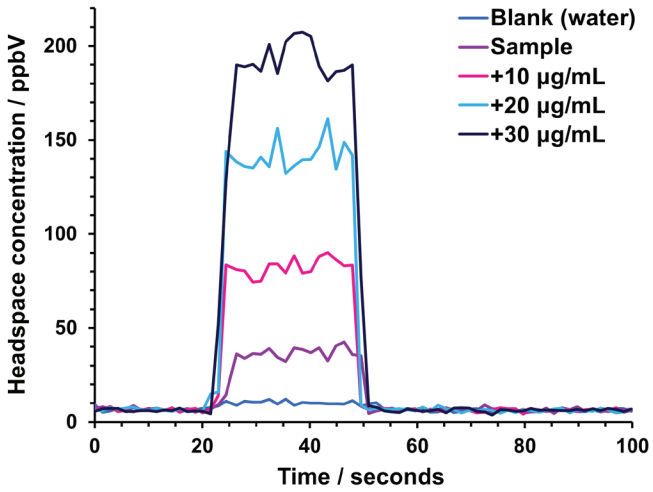
Automated analysis was carried out using a Syft Tracer™ coupled with a multipurpose autosampler (MPS Robotic Pro, GERSTEL; Mülheim, Germany). [Note that the best configuration is a dual-head GERSTEL MPS Robotic Pro, while the single-head GERSTEL MPS Robotic Pro with tool change capability is next best.] The autosampler was controlled using GERSTEL's Maestro software and incubation was carried out in a GERSTEL agitator. Headspace was sampled using a 2.5-mL headspace syringe (heated to 150 °C) and subsequently injected at a flow rate of 100 µL s^{-1} into the SIFT-MS instrument's autosampler inlet (heated to 150 °C) via a self-sealing GERSTEL septumless sampling head. Since the nominal sample flow into the SIFT-MS instrument is 420 µL s^{-1}, a make-up gas flow (ultra-high purity nitrogen) is also introduced through the sampling head. Figure 2 shows the synchronous sample injection and analysis of formaldehyde for the sample and three standard

Figure 1. Schematic diagram of the SIFT-MS technique, which utilizes soft chemical-ionization for direct analysis of samples.



additions. The analysis time for each sample was 100 seconds and reported concentrations are obtained from the mean of measurements made during injection (i.e., between about 40 and 60 s in Figure 2).

Figure 2. Real-time SIFT-MS analysis of formaldehyde: the headspace injections shown are from Sample 1 and show the measurement made on the sample itself and the three standard additions. Data for a blank measurement are shown for comparison



2. SIFT-MS analysis of formaldehyde

SIFT-MS selectively detects formaldehyde via the proton-transfer reaction shown in Eqn. 1 (Španěl and Smith (2008)).

$$H_3O^+ + H_2CO \longrightarrow H_3CO^+ + H_2O \qquad k = 3\times10^{-9}\ cm^3\ s^{-1}$$

The H_3CO^+ product ion is detected at a mass-to-charge ratio (m/z) of 31. This product ion m/z is specific to detection of formaldehyde due to the soft ionization in SIFT-MS and its infrequent occurrence for other volatiles. Formaldehyde quantitation was conducted using the literature reaction rate coefficient (*k*) above. Note that no internal standard was utilized.

3. Samples

Three anonymized samples were supplied by a customer for determination of formaldehyde impurity concentrations. The samples were aqueous but contained significant concentrations of proprietary fragrance components and solvent carrier. For SIFT-MS headspace analysis, 1 mL of fragrance mix was sampled into 20-mL headspace vials. Samples were incubated for 20 min at 75 °C.

4. Standard additions utilized with SIFT-MS

The volume of spiked standard was kept as small as possible to mitigate introduction of matrix effects (10 µL). During method development it was determined that headspace partitioning was not perturbed through multiple cycling of standard spikes and analyses. [Note: If headspace partitioning is perturbed, then multiple vials per sample should be prepared – one for each spike level.] Hence the process for each test sample was:

A. incubate,
B. inject headspace into SIFT-MS instrument, and
C. add spike.

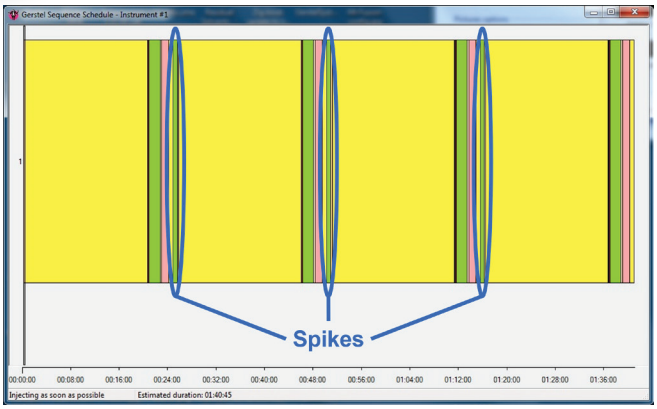
This was repeated for the number of standard additions that were made (three or four). Standard additions were made at 10, 20, and 30 µg mL^{-1} from a 1000-µg mL^{-1} standard.

For a method using three standard additions (here, water and samples 1 and 3), the sequence for one sample is shown in Figure 3(a). Because analysis is not the rate-limiting step in SIFT-MS analysis (as it is frequently for chromatographic analysis), running three additional samples in parallel increases the total analysis

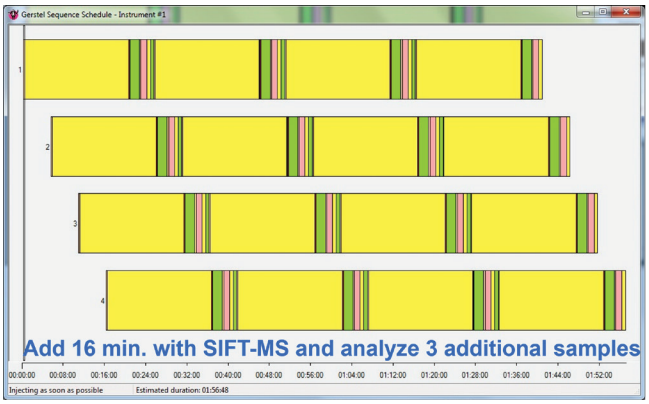
time by only 16 min. (or 17%; Figure 3(b)). Note, however, that this approach does not utilize the analytical instrument as efficiently as does the preparation of individual samples at different spike levels, since this approach reverts to static headspace throughputs (see the next section).

Figure 3. Sequence schedules from the GERSTEL Maestro software package, illustrating the sequences for (a) one and (b) four samples being analyzed using the method of standard additions on an automated SIFT-MS instrument.

(a)



(b)



Results and Discussion

Fragrance matrices of variable composition, coupled with total VOC concentrations that exceeded the instrument's linear range, meant that formaldehyde could not be analyzed reliably using static headspace-SIFT-MS analysis. Two factors were particularly significant:

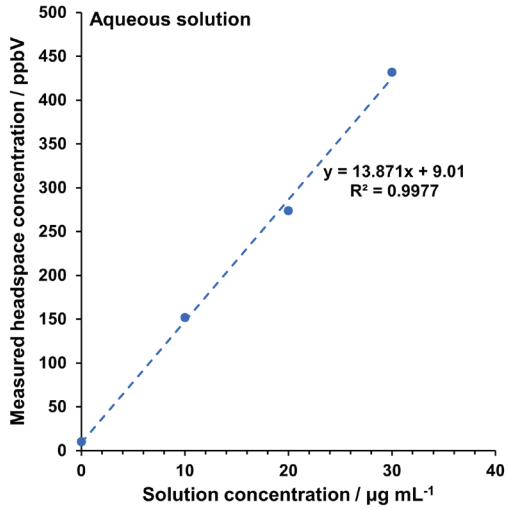
1. Partitioning of formaldehyde from aqueous solutions is relatively low – resulting in relatively poor sensitivity (a limit of quantitation (LOQ) of approximately 0.1 µg mL^{-1}), and
2. High levels of VOCs in the matrix consumed reagent ion signals but were not consistent from one sample to the other, leading to overestimation of concentration.

A simple aqueous calibration set for formaldehyde quantitation could not be utilized and the method of standard additions was employed. The method was developed on sample 2 using four additions (at 10, 20, 30, and 40 µg mL^{-1}), as shown in Figure 4(c). However, three additions from 10 – 30 µg mL^{-1} were adequate for this method (Figure 4(a),(b),(d)).

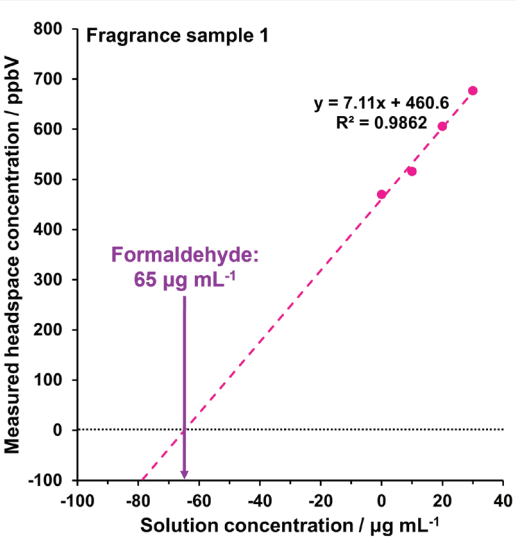
Figure 4 shows the linearity across the range of standard additions in (a) water and in (b) to (d) for the fragrance samples 1, 2 and 3, respectively. Extrapolation of the standard addition curves determined formaldehyde at 65 µg L^{-1}, 87 µg L^{-1}, and 7 µg L^{-1} in the respective fragrance samples.

Figure 4. Standard additions calibration curves determined using automated headspace-SIFT-MS for (a) water and (b) – (d) fragrance samples 1 to 3, respectively.

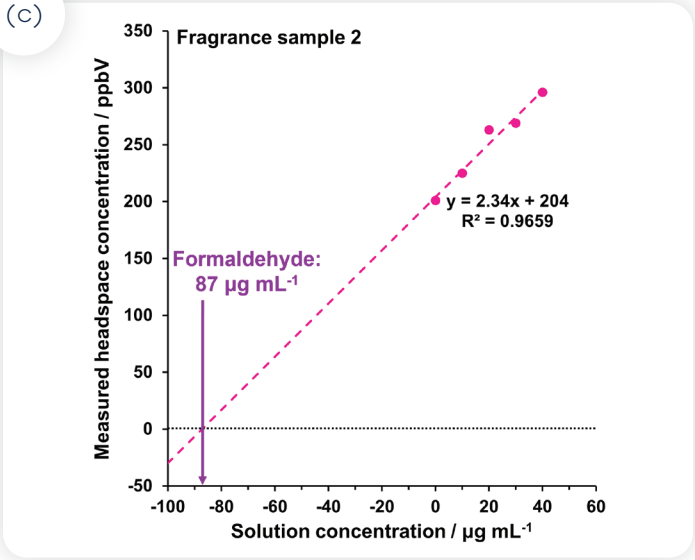
(a)



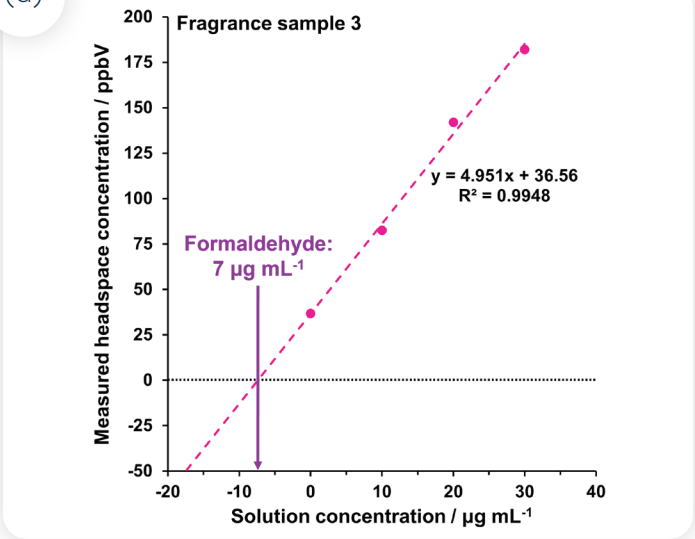
(b)



(c)



(d)



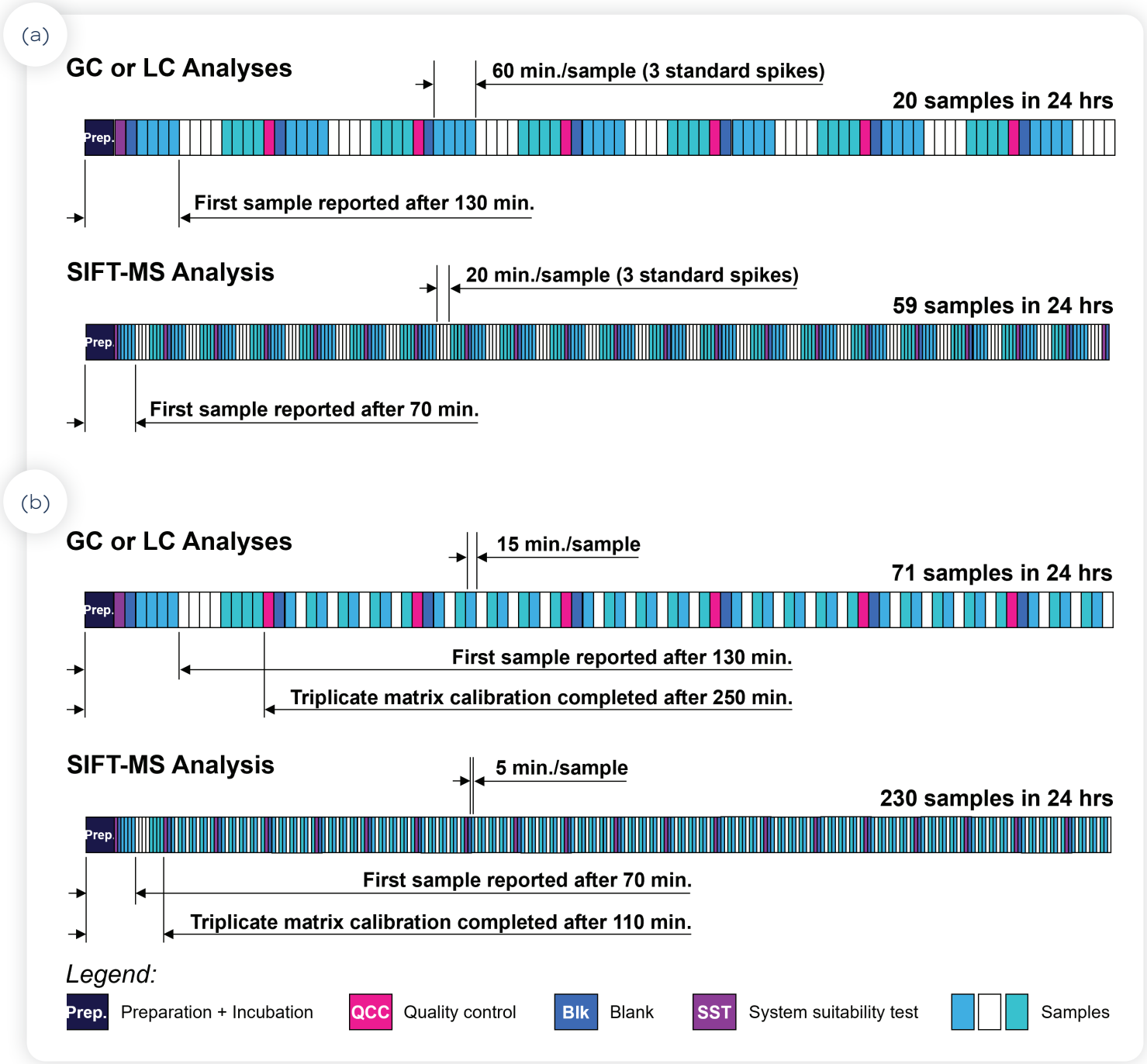
These results demonstrate that the method of standard additions is readily applied to SIFT-MS for systems in which static headspace analysis is problematic, but for which homogeneous spiked solutions can be prepared. Where this requirement cannot be met, multiple headspace extraction (MHE) may be required (Perkins and Langford (2022)).

However, although the sample preparation approach used here is conceptually elegant – it uses just one vial per sample and the standard additions are spiked sequentially – it is not the most efficient approach. For SIFT-MS, it takes just over 100 min. to produce a result for the first sample (with 20-min. incubation) and analyzes approx. 48 samples per day (Figure 3). For a GC- or LC-based approach, based on a run-time of 15 min. less than 10 samples per day can be analyzed since there is no option to run samples in parallel, unlike SIFT-MS with its shorter run-times (Figure 3b).

A more efficient approach to running standard additions on both conventional and SIFT-MS platforms involves preparing individual samples for each spike level up-front using the autosampler, then conducting the sequence as if it were conventional static headspace analysis. This approach is illustrated in Figure 5(a) assuming that every sample requires full standard additions and ignoring any other time taken for GC or LC sample prep. GC benefits most in terms of daily throughput (but it is still only around one-third of the throughput of SIFT-MS), whereas the time to report the first result is reduced by 30% for SIFT-MS (to 70 min., including preparation time). If the analysis is conducted repeatedly on the same matrix, then for both techniques subsequent analyses can be conducted from a single static headspace analysis every 15 min. for GC and LC and 5 min. for SIFT-MS. Figure 5(b) illustrates this approach and includes triplicate calibration on three samples to provide improved reliability of the standard additions curve that is applied to the subsequent samples.

Finally, the flexibility of the Syft Tracer™ platform applies equally to routine static headspace analysis and the method of standard additions. That is, analyses using standard additions can be accommodated seamlessly into a routine analysis workflow with no instrument configuration changes (Langford *et al.* (2023)). Moreover, where the same matrix is tested repeatedly Syft Tracer™ can provide high-throughput screening over extended periods without the need for frequent recalibration, further enhancing its application to quality control (QC) applications (Langford and Perkins (2023)).

Figure 5. Efficient 24-hour chromatographic and SIFT-MS sequence schedules for analysis of formaldehyde (with 20 min. incubation) using (a) the full method of standard additions on separate spiked samples for every sample tested, and (b) triplicate calibration using standard additions followed by headspace analysis. In both scenarios, three calibration spikes are assumed and these plus the sample are indicated back-to-back using the same fill color.



Conclusions

- Ultra-soft chemical ionization enables direct analysis of formaldehyde to be conducted without derivatization or other sample preparation or preconcentration.
- The method of standard additions is compatible with direct sample analysis in SIFT-MS and enables VOC to be analyzed quantitatively in more challenging matrices.
- SIFT-MS analyzes formaldehyde with a throughput of 12 samples/hr for static headspace and 3 samples/hr (including standards) for the full method of standard additions.
- The SIFT-MS approach delivers productivity benefits, reporting the first result >1.8-fold faster than chromatographic methods and providing 2.9 – 4.8-fold daily throughput increase.
- Seamless transitions between test methods make Syft Tracer™ the most efficient and flexible instrument for analysis of volatile impurities, including in QC applications.

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Syft Technologies Ltd
New Zealand | +64-3-3386701

Syft Technologies GmbH
Germany | +49-6151-5201341

Syft Technologies Inc.
North America | +1-818-4504270

Syft Technologies Korea
Korea | +82-31-7056701

W: www.syft.com E: info@syft.com

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