

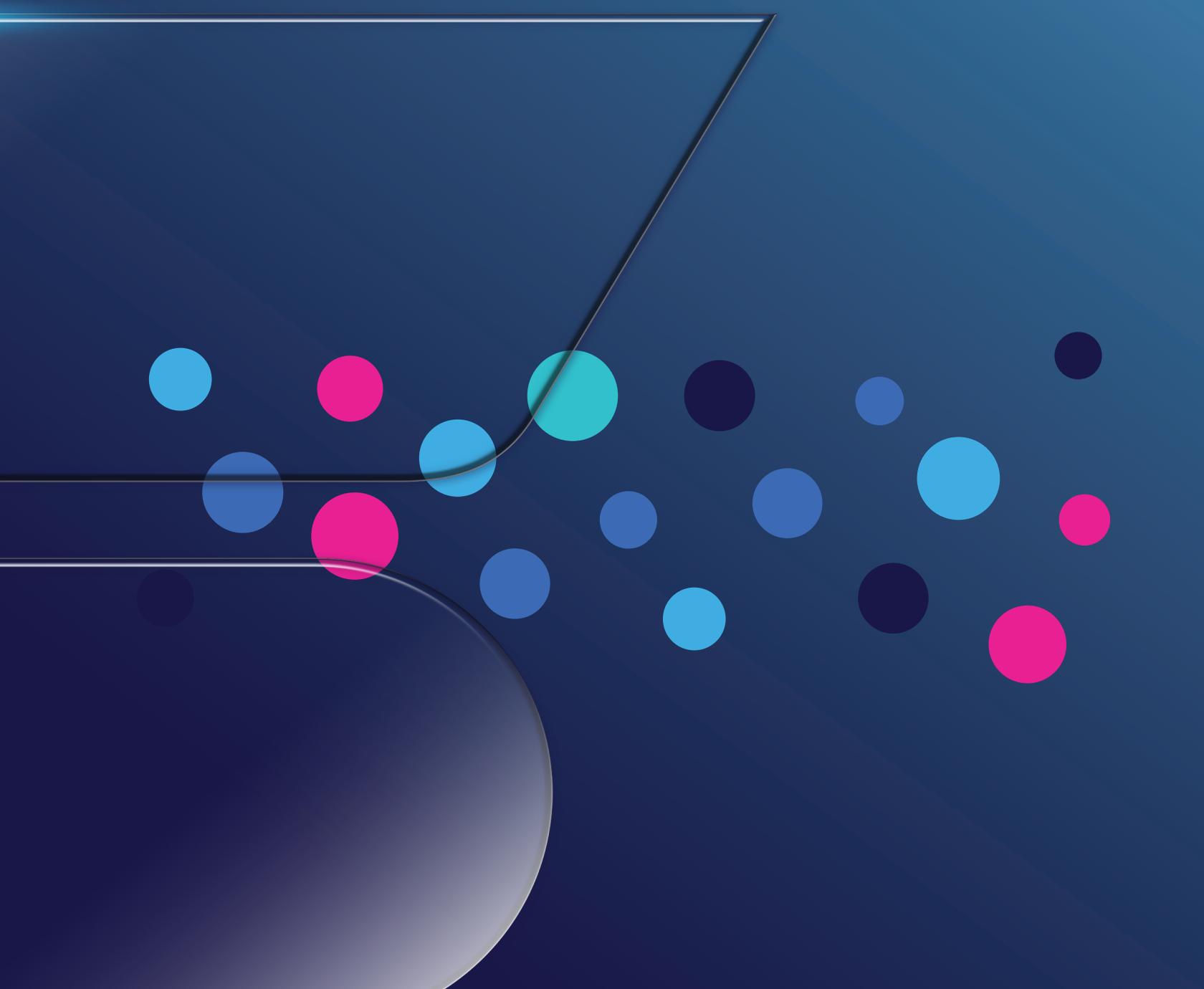
**SYFT TRACER™:**

# NEXT-GENERATION VOLATILE IMPURITIES ANALYSIS FOR ENHANCED WORKFLOWS

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## Abstract

Syft Tracer™ is the latest advancement in selected ion flow tube mass spectrometry (SIFT-MS) technology, delivering even greater stability and reproducibility. For these reasons, together with enhanced sensitivity, this next-generation instrument revolutionizes workflows. This application note describes the benefits that Syft Tracer™ brings to analysis of formaldehyde in a polyethylene glycol (PEG) excipient (Gelucire 44/14). Syft Tracer™ quantifies formaldehyde directly from the polymer headspace without dissolution and eliminates the derivatization step required by chromatographic analyses. Stable quantitation of formaldehyde is demonstrated for almost one month, enabling sample throughputs of over 220 samples/day to be achieved by reducing the calibration frequency. Additionally, Syft Tracer™ is four-fold faster reporting the first result than chromatography-based analyses.

## INTRODUCTION

Maximizing sample throughput and minimizing the time to report analytical results are key efficiency metrics in routine testing laboratories, while also acting as important enablers in research and development. Conventional chromatographic techniques have limitations on analysis times imposed by the chromatographic separation process. Furthermore, set-up times for analysis can be long, since in addition to sample preparation (which may include sample drying or derivatization) there is also significant time devoted to analysis of calibration standards. Additionally, changing between methods on chromatographic systems may require hardware configuration changes (for example, change of inlet liner or column).

Selected ion flow tube mass spectrometry (SIFT-MS), through elimination of chromatography and application of direct, ultra-soft chemical ionization to gas and headspace samples, has been demonstrated to significantly improve sample throughputs (Perkins and Langford (2021a)) while meeting method validation requirements (Perkins and Langford (2021b)) and comparing well with the conventional methods (Hastie *et al.* (2021), Perkins *et al.* (2023)). The latest advancement in SIFT-MS technology, the Syft Tracer™, extends these benefits further. Syft Tracer™ delivers greater stability and reproducibility, together with enhanced sensitivity, while retaining the specificity and flexibility for which the legacy instruments are renowned. Improvements in stability and reproducibility enable process or sample changes of even smaller magnitude to be reliably identified, while also enabling calibration cycles to be conducted less frequently.

Leveraging these enhancements enables revolutionary improvements to workflows to be achieved – especially for quantitative analysis of volatile impurities in solid-phase samples. Conventionally, quantitation based on a single static headspace measurement of the product is not possible because it is extremely difficult to create matrix-matched calibration standards. Typically, the solid product needs to be dissolved in solvent or utilization of an exhaustive procedure (such as dynamic headspace analysis (DHA) or multiple headspace extraction (MHE; Perkins and Langford (2022a))). By applying Syft Tracer™, the conventional, slow MHE approach can be replaced by a single static headspace measurement over a period of at least 27 days because

the full MHE measurement (calibration) remains stable long-term. Moreover, this is practical because of the flexibility of the Syft Tracer™ platform: it can undertake headspace analysis of virtually any volatile compound with no hardware change. The outcome: much faster time-to-result for quantitation of volatile impurities direct from the sample matrix.

This application note illustrates the benefit of adopting Syft Tracer™ for analysis of volatile impurities in solids. It does so by demonstrating the simplified quantitation of formaldehyde impurity in polyethylene glycol (PEG) excipient (Gelucire 44/14). Syft Tracer™ analyzes formaldehyde directly from headspace, eliminating the derivatization step required by chromatographic analyses (Perkins and Langford (2022b)). Sample throughputs of over 220 samples/day are achievable compared to under four samples per day for a chromatographic analysis. Moreover, the time to report the first quantitative result is four-fold faster (less than 90 min).

### Syft Tracer™: Next-Generation Platform for Real-Time Volatiles Analysis

Selected ion flow tube mass spectrometry (SIFT-MS) was commercialized by Syft Technologies in the early 2000s and has made significant inroads in industrial and laboratory applications (Smith *et al.* (2023)). These applications include workplace protection, fenceline monitoring, semiconductor cleanroom monitoring, and analysis of volatile impurities in consumer goods and pharmaceuticals. Key benefits of SIFT-MS in these applications are:

- Excellent multi-analyte detection sensitivity (without pre-concentration),
- High specificity,
- Immediate, quantitative results, and
- Direct, chromatography-free analysis with minimal or no sample preparation.

Syft Tracer™, the new generation SIFT-MS platform, builds on this legacy through significant improvements focused on delivering reliable long-term performance in the most demanding applications. Enhancements include:

- Increased sensitivity (typically 50% higher than the legacy platform),

- *Fine Auto Retune* for optimal signal levels,
- *Performance Authenticator* for superior analytical stability,
- Hardware advancements to maximize system lifetime,
- System optimization for 24/7 data collection, and
- Even easier operation and data interpretation.

Improved stability enables even smaller process changes to be detected reliably, plus it further enhances calibration stability. Moreover, in multi-use implementations, the ability to conduct a very wide range of analyses on one stable hardware configuration increases efficiency compared to chromatographic systems with frequent inlet liner and column changes.

## A Revolutionary Workflow for Condensed-Phase Volatile Impurities Analysis: Formaldehyde in Gelucire

The benefits of Syft Tracer™ to laboratory workflows are demonstrated by considering the analysis of a chromatographically challenging volatile – formaldehyde – in a challenging matrix (Gelucire 44/14). It should also be noted that formaldehyde is released very slowly from Gelucire at the incubation temperature used here (50 °C), but higher temperatures cannot be utilized because they promote sample degradation. This means that the MHE analysis is more challenging than the prototypical styrene system (Perkins and Langford (2022a)), so provides a stringent test of Syft Tracer™. Since an autosampler was used for sample incubation and delivery, the presented results reflect variability in samples themselves and the Syft Tracer™ instrument.

### 1. Method

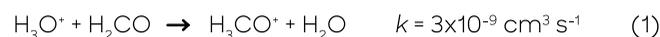
This work utilized a Syft Tracer™ SIFT-MS instrument operating on helium carrier gas coupled with a multipurpose autosampler (MPS Robotic Pro, GERSTEL; Mülheim, Germany). Each sample was incubated in a GERSTEL agitator throughout its six-cycle MHE sequence (see Perkins and Langford (2022a)). Headspace was sampled using a 2.5-mL headspace syringe (heated to 150 °C) and subsequently injected at a flow rate of 50  $\mu\text{L s}^{-1}$  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  $\mu\text{L s}^{-1}$ , a make-up gas flow (ultra-high purity nitrogen) was also introduced through the sampling head and dilution was accounted for in concentration calculations. The analysis time for each sample was 120 s.

Commercially available Gelucire 44/14 excipient was supplied by a third-party. For SIFT-MS headspace analysis, approximately 200 mg was placed in each 20-mL headspace vial.

Measurements were made in two runs of 13 and 27 days each over an 86-day period. During this period no instrument changes were made, but numerous other analytical procedures utilized the same instrument hardware configuration.

## 2. Selective, direct, and real-time analysis of formaldehyde

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

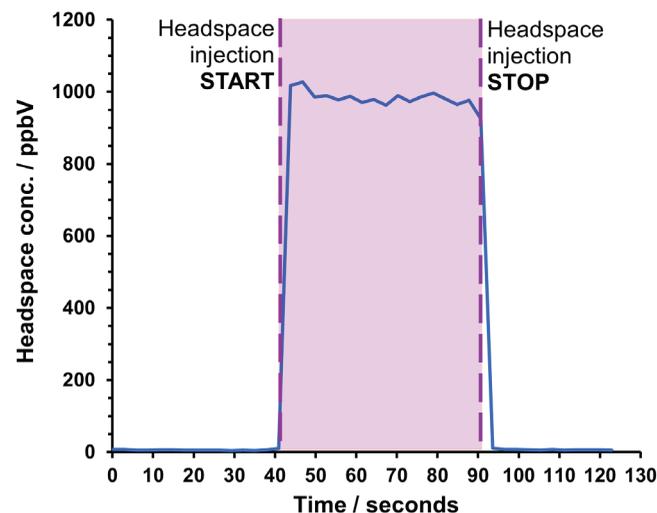


The  $\text{H}_3\text{CO}^+$  product ion is detected at a mass-to-charge ratio ( $m/z$ ) of 31. This product ion  $m/z$  is specific to detection of formaldehyde due to the ultra-soft ionization in SIFT-MS and its infrequent occurrence for other volatiles. See Langford (2023) for an overview of SIFT-MS specificity.

Formaldehyde quantitation was conducted throughout the 86-day study using the literature reaction rate coefficient ( $k$ ) above. That is, no formaldehyde calibration was conducted; data are as reported by the instrument and hence demonstrate instrument stability over an extended period. For similar reasons, no internal standard was utilized. Data were only corrected for the mass of sample in the vial.

Figure 1 shows real-time analysis of formaldehyde using Syft Tracer™, with background measurements before and after the formaldehyde measurement that occurs synchronous with sample injection. Reported concentrations are the mean of the values obtained during sample injection (i.e., between approximately 50 and 80 s in Figure 1). The direct SIFT-MS analysis contrasts starkly with the requirements of high-performance liquid chromatography (HPLC) and gas chromatography (GC) analyses, which include derivatization prior to sample injection and subsequent chromatographic separation. SIFT-MS provides truly online and real-time analysis.

*Figure 1. Real-time SIFT-MS analysis of formaldehyde: the first headspace injection from six cycles of headspace generation in MHE measurements on Gelucire 44/14 incubated at 50 °C (Day 0, replicate 1).*



### 3. Repeatable and reproducible analysis

Figure 2 summarizes the formaldehyde headspace concentrations obtained using a Syft Tracer™ SIFT-MS instrument over two runs within an 86-day period. No calibration was applied, and no internal standard was utilized. The six data points (in different colors) for a given data set represent the measurement made for the six injections in a full MHE analysis (Perkins and Langford (2022a)). These data illustrate:

1. The **repeatability** of Syft Tracer™, even for a challenging analyte and matrix. Across the study duration, the repeatability (as measured by percentage relative standard deviation, %RSD) for a given injection number on a given day is in the range 0.31 to 3.4%. For the full MHE calculation on a given day (Figure 3) – which is subject to slightly more variability than individual injections due to the integration procedure – the range of RSDs is 0.9 to 6.6%.
2. The **reproducibility** of Syft Tracer™, with two runs (of 13 days and 27 days) giving very similar concentrations and RSDs of less than 5%, which is well within the acceptable range ( $\pm 20\%$ ).

Figure 2. Headspace-SIFT-MS analysis of formaldehyde content in Gelucire 44/14 (incubated at 50 °C) over two runs of (a) 13 and (b) 27 days. Triplicate, full six-injection MHE was conducted on each of the 13 days that measurements were made. The %RSD for each MHE injection was calculated across all measurements during each period.

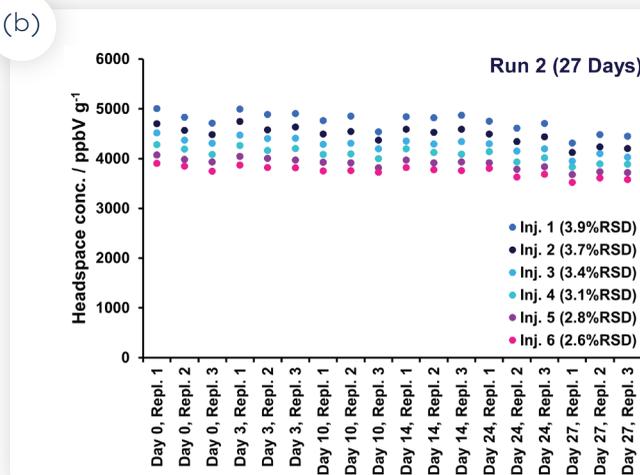
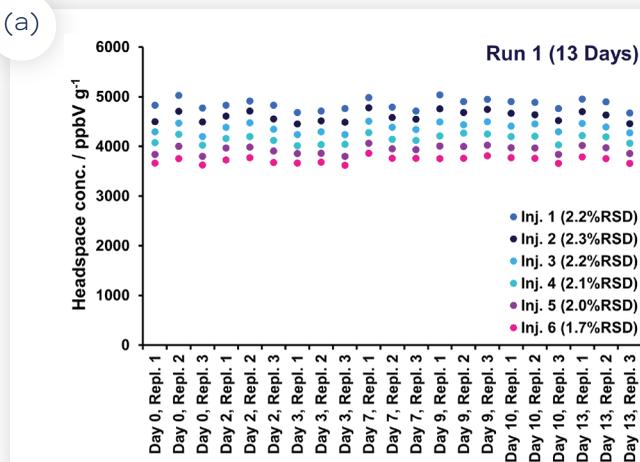
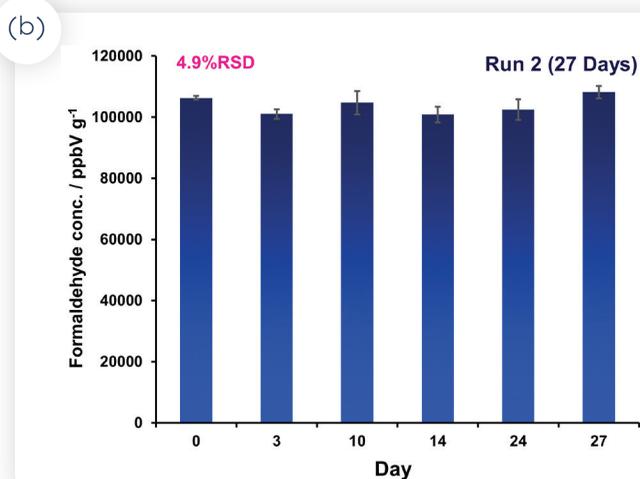
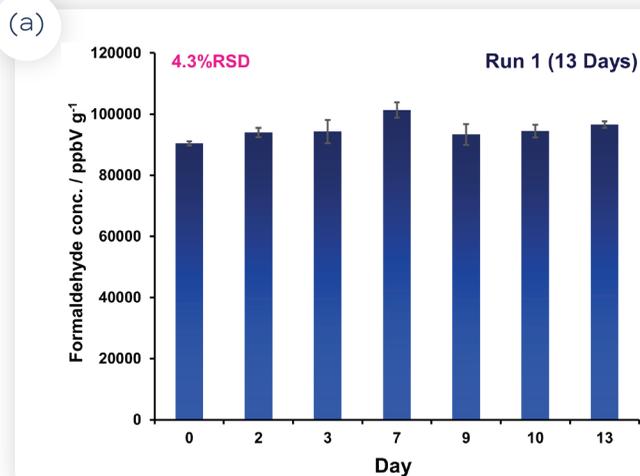


Figure 3. Concentrations of formaldehyde in Gelucire 44/14 over two runs of (a) 13 and (b) 27 days. The mean of the three daily replicates is shown and error bars are one standard deviation. The RSDs were calculated from the individual replicates in the measurement period.



Syft Tracer™ provides extremely stable quantitation, even without calibration, because:

1. The soft chemical ionization is highly repeatable in its interaction with analytes,
2. Ionization is very clean (it occurs in the flow tube, which is physically separated from the ion source and detection system),
3. The instrument components are optimized for stability, and
4. One instrument configuration is used for very diverse analytical procedures (chromatography-free analysis means that there are no inlet liners, column, or detector changes to make, plus sample prep is minimal and simple).

This unparalleled quantitative stability and analytical flexibility supports enhanced workflows through the ability to separate calibration from routine analysis (and calibrate infrequently), as discussed below.

#### 4. Syft Tracer™ enhances workflows

The data in Figure 3 were derived from full MHE measurements on each replicate sample. It has been demonstrated previously for polystyrene (Perkins and Langford (2022a)) and ranitidine formulations (Perkins and Langford (2022c)) that the first injection of MHE correlates repeatably with the results of full MHE. Given the stability of the formaldehyde measurements over each of the runs (Figures 2 and 3), these data provide an ideal test case for assessing the temporal separation of a full MHE run (so-called “MHE calibration”) from quantitative measurements on the same sample type using a single headspace injection. The correlation factor to be applied across the full data set for each run was calculated from the mean of the values for the run’s Day 0. This correlation factor was then applied to all replicates, including those of the Day 0 samples.

Figure 4. Difference in calculated formaldehyde concentrations for (a) run 1 and (b) run 2 when using the ‘Day 0’ calibration factor for the 1<sup>st</sup> MHE injection compared with the full six-injection MHE calculation for the individual samples. The individual ‘Day 0’ measurements are recalculated from their mean values and shown in purple/pink. All data in the two runs meet acceptance criteria.

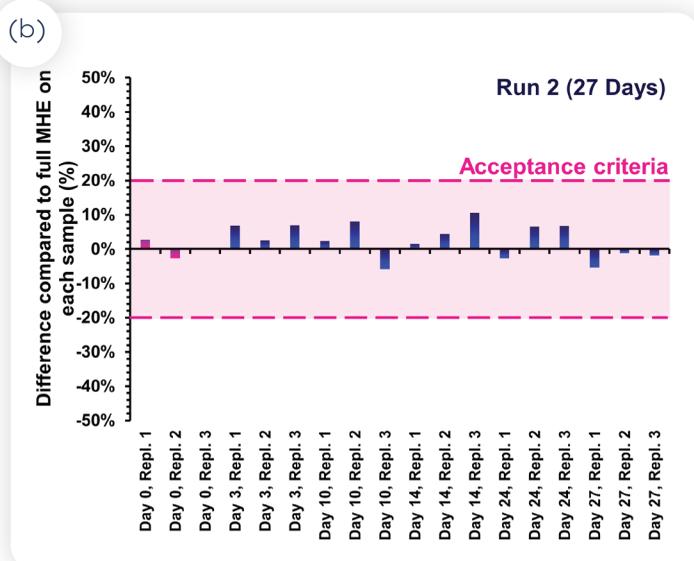
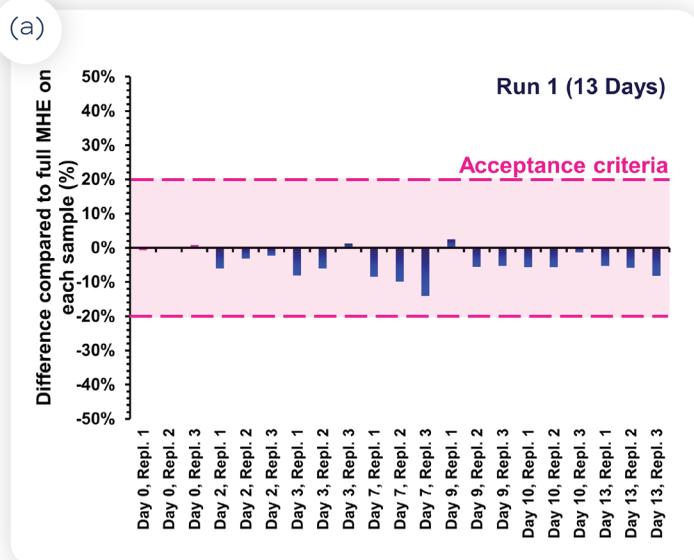
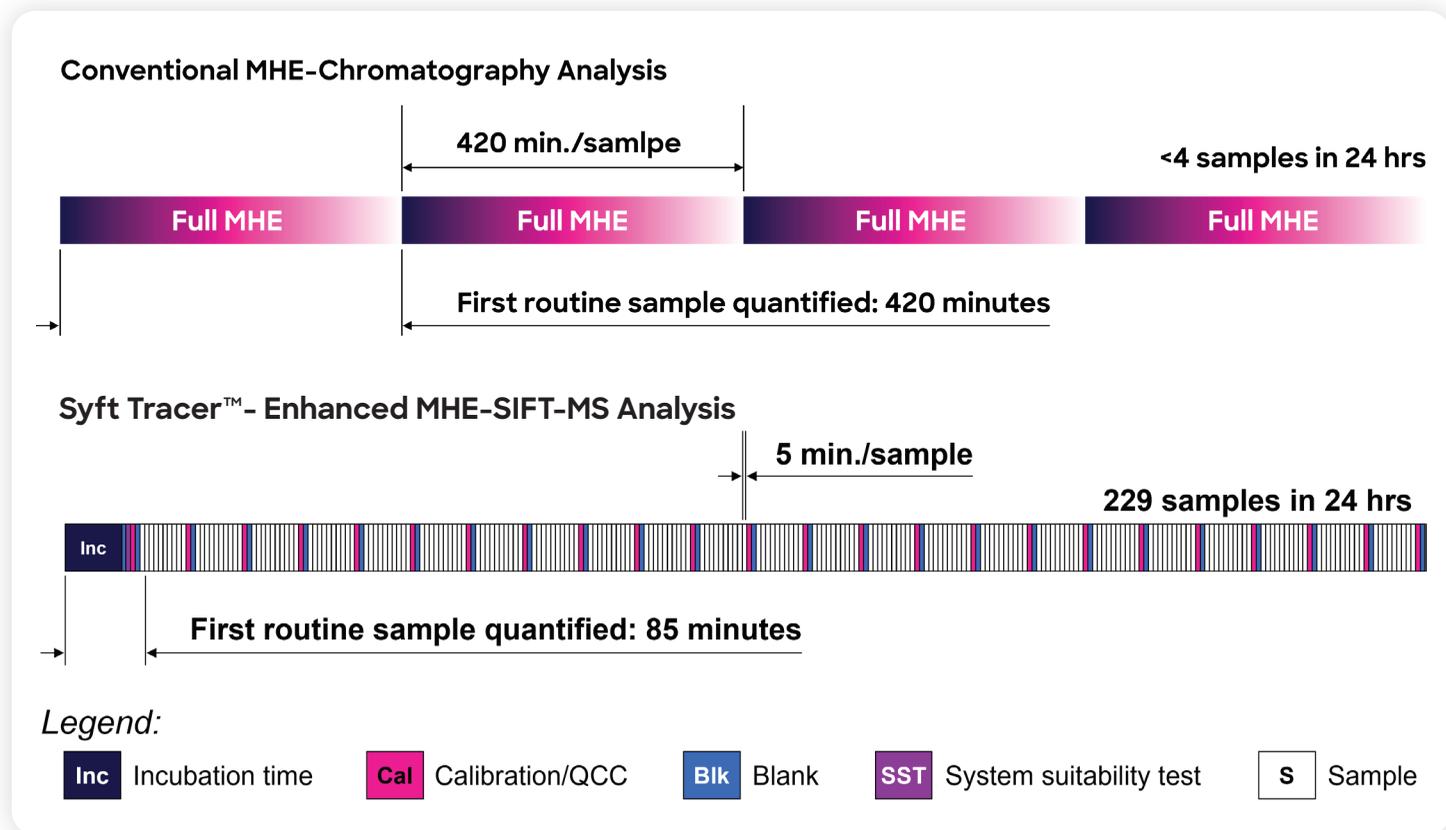


Figure 4 shows the percentage difference in the value calculated from the average Day 0 calibration factor compared with the value calculated from the full MHE analysis. **All data lie well within 20% of the full MHE measurement, indicating that for samples of consistent particle size and morphology quantitative analysis – even of a chromatographically challenging species, such as formaldehyde – can be achieved in the condensed phase from a single injection using an MHE calibration made nearly one month in advance.**

The impact of these results on workflow is considerable. No longer does full MHE need to be conducted on each sample – or daily on a small batch. Quantitative analysis of volatile impurities in condensed-phase samples can be achieved at any time on “walk-up” samples without the need to undertake conventional calibration or MHE calibration. With typical incubation times and SIFT-MS run-times of 5 min, a result is obtained for formaldehyde in Gelucire in under 90 min (including system suitability, quality control checks and blanks; Figure 5). Samples with shorter headspace equilibration times obviously yield results faster. This contrasts with chromatographic approaches, which – even when ignoring sample preparation and potential configuration changes – require MHE calibration at least daily (Figure 5).

The stability of Syft Tracer™, coupled with the ease with which methods targeting analytes of diverse functionalities can be run without change to the hardware configuration, means that one instrument can serve the needs of multiple teams. Regular calibrations can be scheduled such that they do not interfere with day-to-day operation (e.g., schedule calibrations during the weekend), providing rapid quantitative test results for diverse volatile impurities in multiple condensed-phase systems.

Figure 5. The enhanced MHE-SIFT-MS workflow revolutionizes quantitative VOC analysis in condensed-phase samples. It reduces the time to first result four-fold compared to daily calibration, while enabling over 220 additional routine samples to be analyzed in a 24-hour period.



## Conclusions

- Syft Tracer™ has demonstrated long-term stability, yielding reproducible quantitative data without the need for daily calibration.
- Chromatography-free analysis enables maximum flexibility on one platform.
- Simple, direct, and derivatization-free analysis of formaldehyde at high sensitivity.
- Reducing the calibration frequency in routine analysis enables significant workflow benefits to be realized, including four-fold faster time to first result for quantitative analysis of condensed-phase samples.
- Over 220 samples per day can be analyzed quantitatively for formaldehyde and other impurities using the enhanced workflow.

## References

- Hastie C, Thompson A, Perkins MJ, Langford VS, Eddleston M, Homer, N (2021). Selected ion flow tube-mass spectrometry (SIFT-MS) as an alternative to gas chromatography/mass spectrometry (GC/MS) for the analysis of cyclohexanone and cyclohexanol in plasma. *ACS Omega* 6, 48, 32818–32822. <https://doi.org/10.1021/acsomega.1c03827>.
- Langford VS (2023). SIFT-MS: Quantifying the volatiles you smell... and the toxics you don't. *Chemosensors* 11, 111. <https://doi.org/10.3390/chemosensors11020111>.
- Perkins MJ, Hastie C, Whitlock SE, Langford VS (2023). Head-to-head comparison of Class 2A and 2B residual solvents analysis using SIFT-MS and GC-FID. Syft Technologies application note.
- Perkins MJ, Langford VS (2021a). Application of routine analysis procedures to a direct mass spectrometry technique: Selected ion flow tube mass spectrometry. *Rev. Sep. Sci.* 3(2), e21003. <https://doi.org/10.17145/rss.21.003>.
- Perkins MJ, Langford VS (2021b). Standard validation protocol for selected ion flow tube mass spectrometry methods applied to direct headspace analysis of aqueous volatile organic compounds. *Anal. Chem.* 93, 8386–8392. <https://doi.org/10.1021/acs.analchem.1c01310>.
- Perkins MJ, Langford VS (2022a). Multiple Headspace Extraction-[SIFT-MS]. Part 1: A Protocol for Method Development and Transfer to Routine Analysis. *Rev Sep Sci.* 4(1), e22001. <https://doi.org/10.17145/rss.22.001>.
- Perkins MJ, Langford VS (2022b). Simple, Rapid Analysis of Formaldehyde Impurities in Gelucire Excipient using SIFT-MS. Syft Technologies application note.
- Perkins MJ, Langford VS (2022c). Simple, rapid analysis of N-Nitrosodimethylamine (NDMA) impurity in ranitidine products using SIFT-MS. Syft Technologies application note.
- Smith D, Španěl P, Demarais N, Langford VS, McEwan MJ (2023). Recent developments and applications of selected ion flow tube mass spectrometry (SIFT-MS). *Mass Spec. Rev.* e21835. <https://doi.org/10.1002/mas.21835>.
- Španěl P, Smith D (2008). Quantification of trace levels of the potential cancer biomarkers formaldehyde, acetaldehyde and propanol in breath by SIFT-MS. *J. Breath Res.* 2, 046003. <https://doi.org/10.1088/1752-7155/2/4/046003>.



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