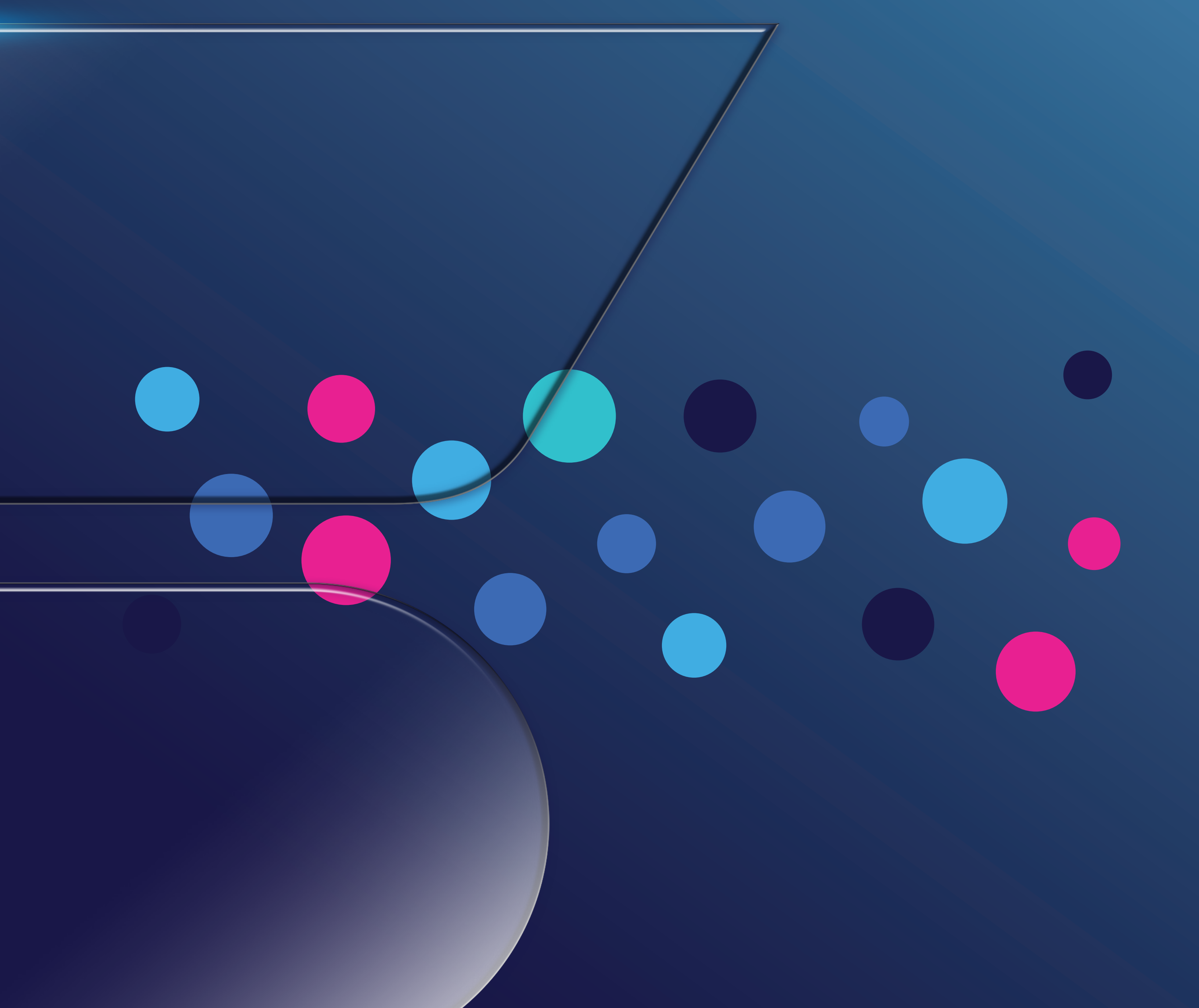
HEADSPACE-SIFT-MS:

FLEXIBILITY THAT REVOLUTIONIZES WORKFLOWS FOR DIVERSE SAMPLES

Vaughan S. Langford[1], Mark J. Perkins[2], and Leslie P. Silva[3]
[1] Syft Technologies Limited, Christchurch, New Zealand
[2] Element Materials Technology, Cambridge, United Kingdom
[3] Syft Technologies Inc., Los Angeles, CA, USA



Abstract

The characteristic flexibility, stability, high throughput, and fast time to report analytical results of the Syft Tracer™ next-generation SIFT-MS instrument apply across multiple headspace approaches for diverse matrices. This application note briefly summarizes the use of (1) dissolution, (2) multiple headspace extraction (MHE), and (3) the method of standard additions, then provides a guide for identifying the appropriate headspace approach for various matrices. For contract drug manufacturing organizations (CDMOs) and contract research organizations (CROs) with short or long sample runs on diverse volatiles and matrices, Syft Tracer™ provides a uniquely productive and cost-effective analytical solution.

INTRODUCTION

Syft Tracer™ exploits the latest advancements in selected ion flow tube mass spectrometry (SIFT-MS) technology to revolutionize workflows and maximize productivity for diverse volatile impurities (Langford and Perkins (2023), Langford, Silva, and Perkins (2023)). The ultra-soft chemical ionization in SIFT-MS provides the foundation on which flexible, stable analysis with high throughput and fast time to report results are delivered from one instrument configuration (Langford and Perkins (2023), Perkins and Langford (2023a)) – in stark contrast to conventional chromatographic techniques.

This application note demonstrates the breadth of headspace approaches – across diverse matrices – that are compatible with automated Syft Tracer™ instruments:

- Dissolution, for water soluble articles and those soluble in at least six organic solvents,
- Multiple headspace extraction (MHE) across diverse matrices, and
- The method of standard additions, for emulsions and samples that exceed the SIFT-MS instrument's dynamic range for static headspace or MHE analysis.

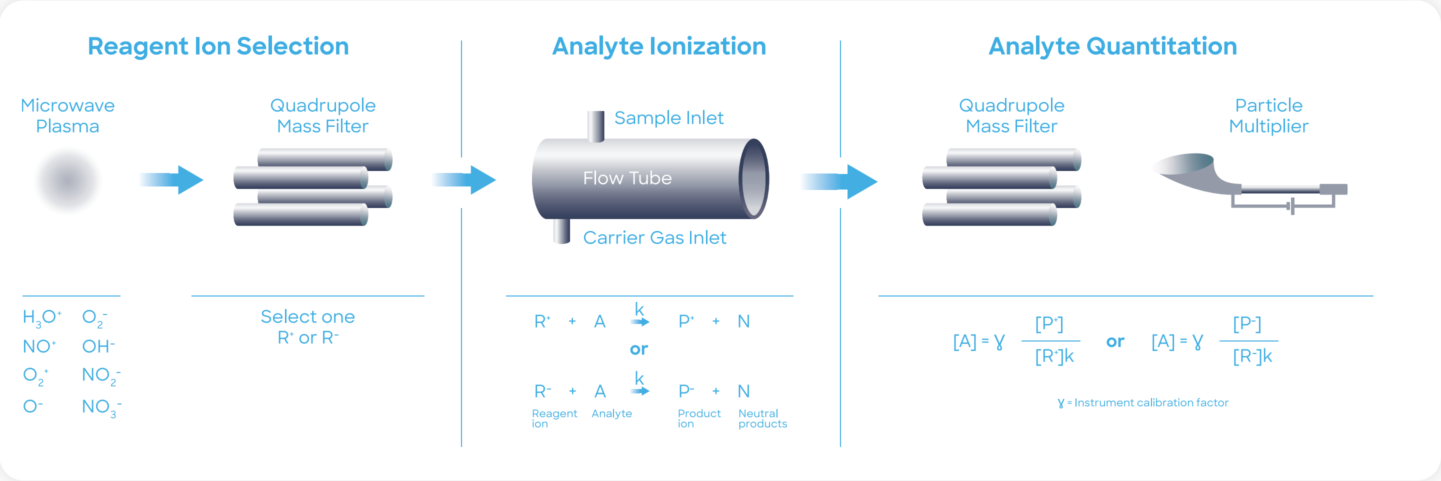
Relevant application notes and peer-reviewed publications are cited in support of these methodologies, demonstrating the practical application. Combined, a comprehensive toolkit for volatile impurity analysis is provided for analysts in contract drug manufacturing organizations (CDMOs) and contract research organizations (CROs) who need to address productivity challenges arising from multiple short or long sample runs on diverse volatiles and matrices.

SYFT TRACER™: REVOLUTIONARY AUTOMATED VOLATILES ANALYSIS

SIFT-MS (Figure 1) uses ultra-soft chemical ionization (CI) to generate mass-selected reagent ions (Smith et al. (2023)) that rapidly 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 new-generation Syft Tracer™ instruments. These reagent ions react with diverse 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 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.

Syft Tracer™ is readily automated through coupling it with a multipurpose autosampler based on syringe-

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



injection technology (e.g., MPS Robotic Pro, GERSTEL; Mülheim, Germany controlled using GERSTEL's Maestro software). Typical automated incubation conditions use a GERSTEL agitator (two are recommended, which the Maestro software controls as a virtual 12-place system) with samples prepared in 10- or 20-mL headspace vials capped with pierceable septa. Headspace is usually sampled with a 2.5-mL headspace syringe (heated to 150 °C) and subsequently injected at a flow rate of 50 or 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 total nominal sample flow into the SIFT-MS instrument is 420 μL s^{-1}, a make-up gas flow (ultra-high purity nitrogen or zero air) is also introduced through the sampling head. Most automated SIFT-MS instruments are operated on helium carrier gas. The analysis time is typically 120 s for any single-polarity analysis with a total runtime of 5 min due to sample analysis, vial transportation, syringe flush, etc.

THE HEADSPACE ANALYSIS "TOOLKIT" FOR AUTOMATED SIFT-MS

Dissolution, MHE, and the method of standard additions are longstanding sample preparation approaches used with conventional chromatographic techniques to tackle volatiles analysis in diverse matrices. These complementary approaches are also compatible with automated-SIFT-MS – albeit with some adaptations. Together these approaches comprise a toolkit that enables a wide variety of matrices to be analyzed using the same stable Syft Tracer™ configuration.

1. Direct analysis vs chromatographic analysis

The modifications to dissolution, MHE, and standard additions approaches in transferring them to SIFT-MS primarily arise from the elimination of chromatographic separation in SIFT-MS (Figure 1). In chromatographic procedures, high concentrations of solvent can usually

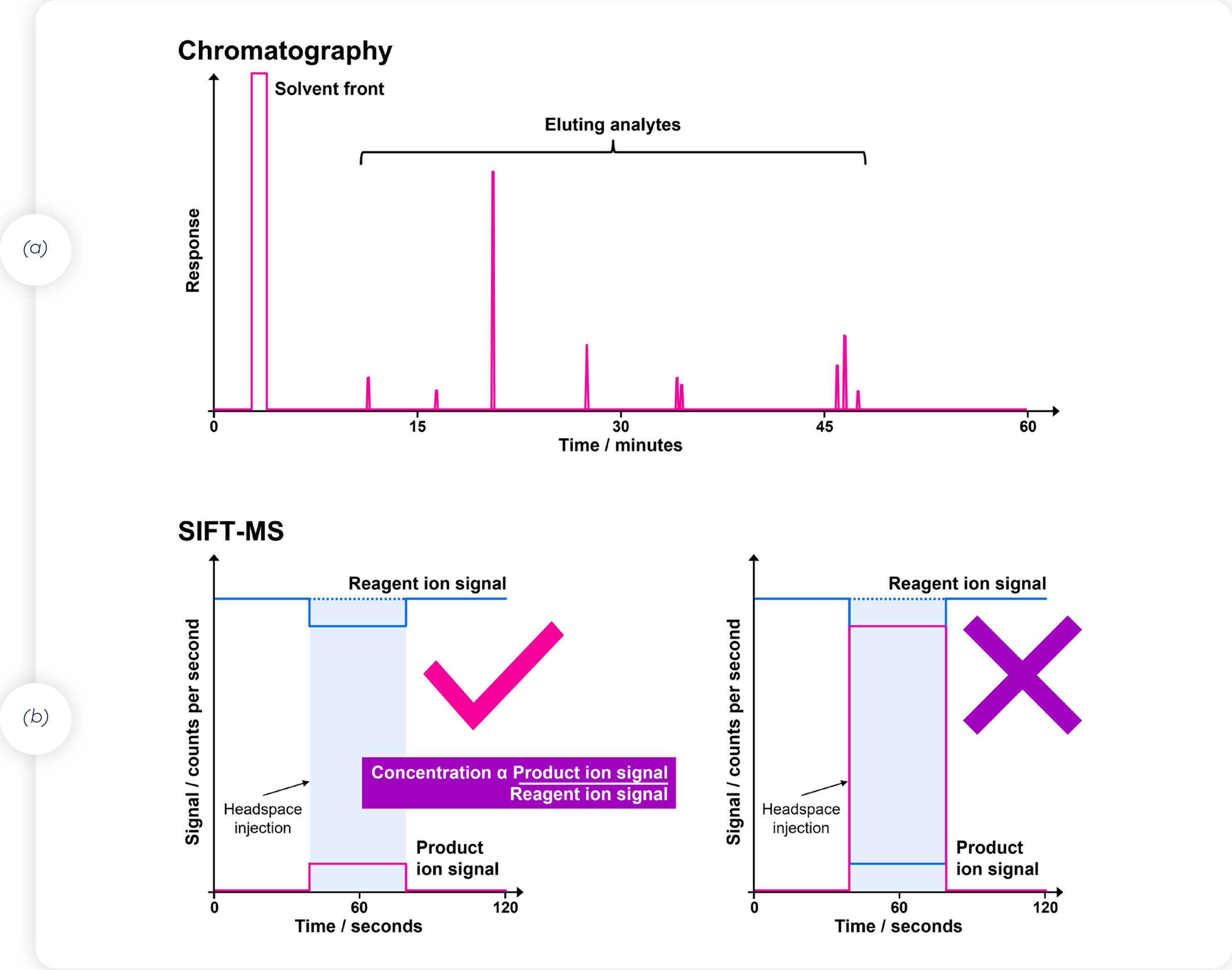


Figure 2. Schematic diagram emphasizing the difference between chromatographic and direct sample analysis. (a) Chromatography techniques separate components in time, readily accommodating high concentrations of solvent. (b) SIFT-MS has no temporal separation and analyzes the sample in real-time, so care must be taken to ensure that compatible solvents are used and that the instrument is not overloaded.

be accommodated because of the temporal separation of the solvent and analytes (Figure 2(a)). Since SIFT-MS is chromatography-free, sample flows continuously through the SIFT-MS ionization chamber (flow tube) without any temporal separation of analytes. This means that the total concentration of reactive compounds in the sample (solvent, matrix volatiles, and analytes) must be understood, and mitigated if necessary (e.g., through slower sample injection or dilution). To avoid saturation of the instrument, it is therefore important to understand solvent compatibility (see Perkins, Silva, and Langford (2023) for guidance). Figure 2(b) shows schematic examples of headspace sample injections that lie within and outside the instrument's linear range. The conventional first principles SIFT-MS concentration calculation (Smith *et al.* (2023), Langford (2023)) applies when over 80% of reagent ion signal remains. Hence the left-hand example of a headspace injection is acceptable, whereas the right-hand one is not. Note, however, that use of a calibration approach (e.g., in dissolution below) or the method of standard additions can enable quantitation to be conducted outside the conventional linear range.

2. Dissolution

Static headspace analysis has been widely used with SIFT-MS for many years – in both manual and automated forms – especially for food and biomedical applications (Smith *et al.* (2023), Langford (2023)). Its benefits include high sensitivity and selectivity, breadth of analysis (due to soft chemical ionization), high sample throughput, and simplicity (through elimination of derivatization, drying, and preconcentration steps). Figure 3 provides a high-level summary of the dissolution workflow and illustrates a typical approach to calibration and analysis of test samples.

SIFT-MS is, therefore, readily applied to analysis of dissolved drug products and other soluble materials assuming solvent compatibility (see preceding section and Perkins, Silva, and Langford (2023)). Table 1 summarizes important static headspace-SIFT-MS analysis literature related to the dissolution approach. It should be noted, however, that more generic publications exist, broadly describing the application of SIFT-MS to routine headspace analysis (Perkins and Langford (2021a)) and proposing a generic method validation approach (Perkins and Langford (2021b)). Compared to chromatographic techniques, automated headspace-SIFT-MS provides significant advantages in terms of time to report results, sample throughput, and workflow efficiency.

3. Multiple headspace extraction (MHE)

MHE provides a convenient alternative to exhaustive extraction methods – such as dynamic headspace analysis – for matrix-independent quantitation of volatiles from systems for which it is difficult to prepare calibration standards. Polymer matrices and other insoluble products are prototypical systems for MHE, but it can be applied broadly (e.g., to solutions).

For a given sample, MHE involves repeatedly generating equilibrium headspace concentrations, analyzing it, and flushing it (Figure 4; see Perkins and Langford (2022f)). Headspace is not usually depleted after six regeneration cycles, so (i) the natural logarithm of each concentration measurement is calculated, (ii) a linear fit made and extrapolated, and (iii) the area under the curve evaluated to give the total volatile concentration in the product.

Figure 3. Typical analytical workflow for the dissolution approach and a schematic calibration curve illustrating determination of analyte concentration in a test sample.

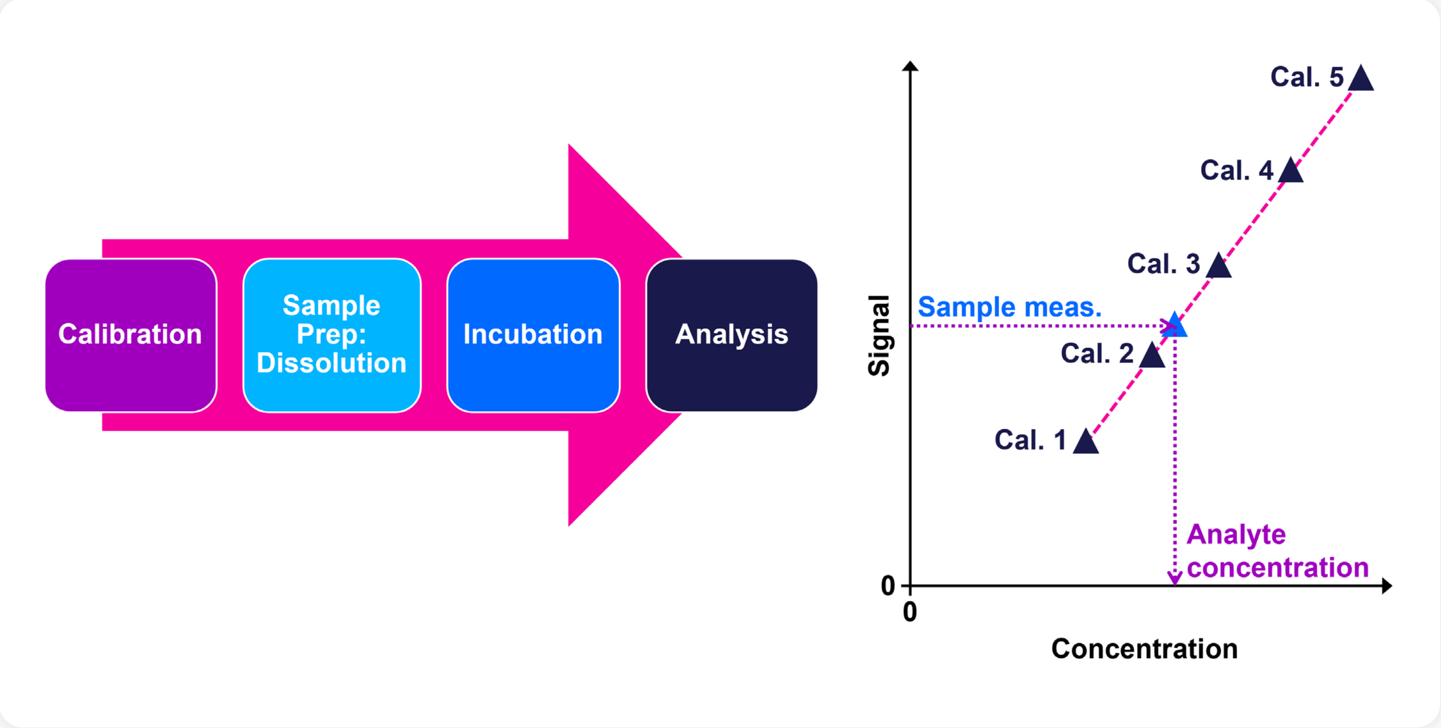
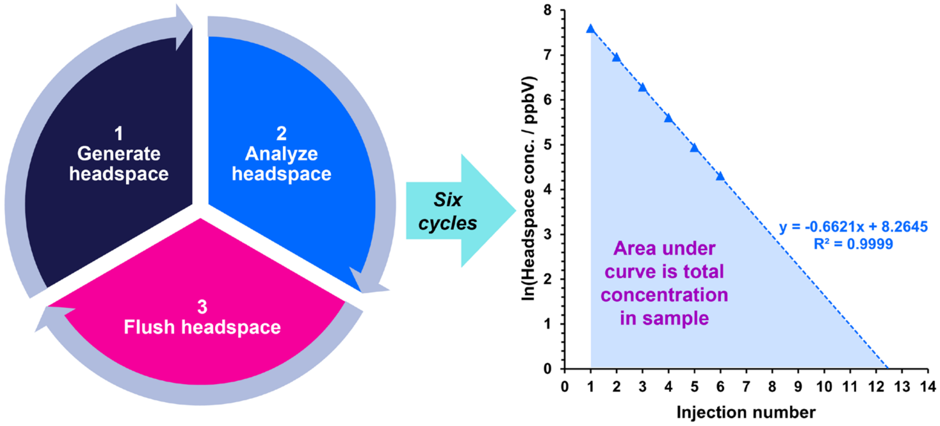


Table 1. The most significant studies for the three procedures in the headspace-SIFT-MS tool kit.

Approach	Case Studies	Significance	Reference(s)
Dissolution	Residual solvents alternative procedure (USP<1467>) Comparison of USP<1467> procedure with standard <467>	Meets performance criteria for water-soluble products (Classes 2A and 2B). Successful comparison of SIFT-MS procedure with standard one.	Biba et al. (2021) Perkins and Langford (2022a) Perkins et al. (2023)
	Compatibility with six non-aqueous solvents	Extends SIFT-MS from conventional aqueous systems.	Perkins, Silva, and Langford (2023)
	Ethylene oxide in PEG excipient	High sensitivity eliminates slow matrix purification step.	Silva et al. (2022)
	Benzene and trihalomethanes in aqueous headspace	High-sensitivity benzene analysis; ability to analyze using both polarities from one sample.	Perkins and Langford (2022b)
MHE	Styrene in polystyrene	Method development benefits; repeatable 'MHE calibration'.	Perkins and Langford (2022c)
	Nitrosamine in ranitidine and valsartan drug products	Quantitative headspace analysis direct from powders.	Perkins and Langford (2022d,2022e)
	Formaldehyde in Gelucire excipient	Reproducible 'MHE calibration' over weeks: enhanced workflow.	Perkins and Langford (2022f,2023a)
	Aldehyde solutions	'MHE calibration' applies with different analyte concentrations.	Perkins and Langford (2023c)
Standard additions	Benzene in consumer products	Analysis of emulsions of various types (syrup, crushed tablet, lotions).	Silva and Langford (2022)
	Formaldehyde in fragrance matrix	Quantifying formaldehyde with total VOC levels significantly above linear range.	Perkins and Langford (2023b)

Figure 4. The MHE workflow and the results of a six-cycle analysis illustrating determination of the analyte concentration from the area under the curve.



MHE is a slow and expensive analytical procedure for chromatographic techniques, but recent work has demonstrated that revolutionary productivity advancements are achieved with MHE-SIFT-MS (Perkins and Langford (2023a), Langford and Perkins (2023)). See Table 1 for a summary of the key MHE-SIFT-MS literature.

4. The method of standard additions

Challenging matrices, such as emulsions, typically require use of the method of standard additions because headspace partitioning varies significantly with small changes in matrix composition. The method of standard additions accounts for this because calibration is conducted in the specific sample matrix.

For SIFT-MS, standard additions are also useful where the linear range is significantly exceeded (e.g., due to significant solvent presence). Calibration usually addresses minor to moderate exceedances.

Figure 5 schematically illustrates the multiple-step procedure for standard additions, which involves analyzing the sample itself followed by the sample spiked with sequential doses of standard. Extrapolation to blank instrument signal yields the concentration of analyte in the matrix. Examples are cited in Table 1.

SIFT-MS delivers more rapid analysis of samples than GC-based approaches (Perkins and Langford (2023b)), making it more economic. Moreover, standard addition analyses utilize the same instrument configuration as dissolution and MHE, so are readily accommodated in parallel with them. They likewise benefit from calibration stability, maximizing analyst and instrument productivity (Langford, Silva, and Perkins (2023).

SELECTING THE APPROPRIATE ANALYTICAL APPROACH

The previous section sketched the analytical approaches that comprise the headspace-SIFT-MS toolkit for analysis of volatile impurities. This section provides guidance for procedure selection based on the sample matrix. It is noteworthy that selection of a procedure is not usually dependent on the analyte in SIFT-MS (except if it suffers from poor headspace partitioning) because the soft chemical ionization approach selectively and sensitively quantifies a very wide variety of volatile impurities in its standard configuration.

Table 2 summarizes the approaches for SIFT-MS-compatible quantitative headspace analysis of various matrices. Several questions that may assist selection of an appropriate experimental approach, and preparation of samples to best satisfy its requirements, are:

- Does the sample dissolve in a SIFT-MS-compatible solvent that is miscible with water?
- Do all target compounds partition sufficiently to headspace from the final solution which is to be analyzed by headspace?
- What are the approximate concentrations of residual solvents/matrix volatiles in the solid matrix? Are these such that they might prevent effective MHE analysis?
- For MHE of solids, is the sample homogenous and is at least one dimension less than 300 microns to facilitate migration of volatiles to the headspace? If not, can the sample be prepared with a dimension in this range?

Figure 6 provides a tool that supports selection of the most appropriate analytical procedure. It emphasizes the need to consider the total volatile compound load in the sample's headspace due to the chromatography-free, direct sample analysis applied in SIFT-MS.

Figure 5. Typical analytical workflow for the method of standard additions and schematic results plot illustrating in-sample calibration and determination of analyte concentration in the original sample.

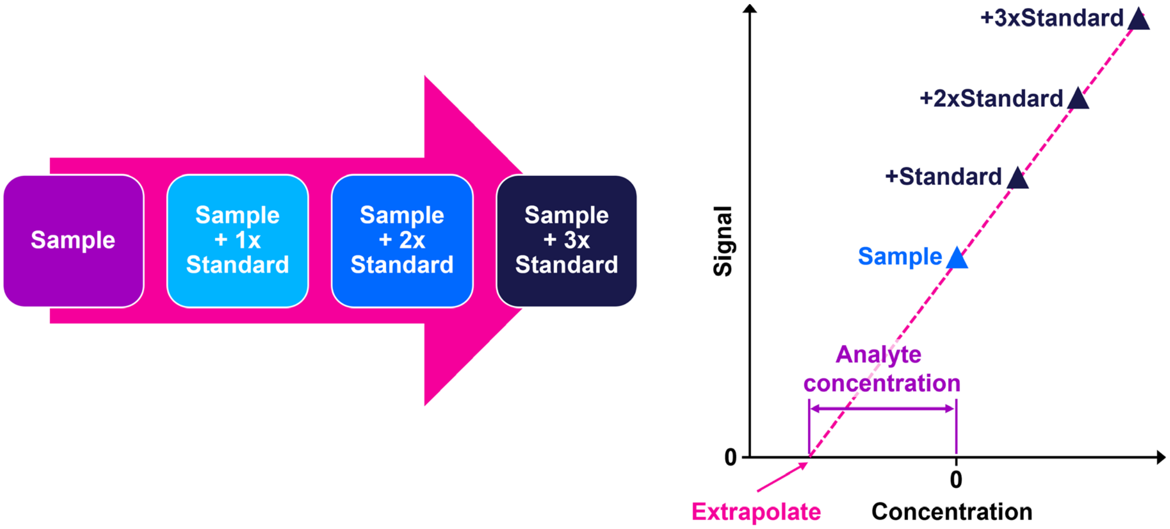


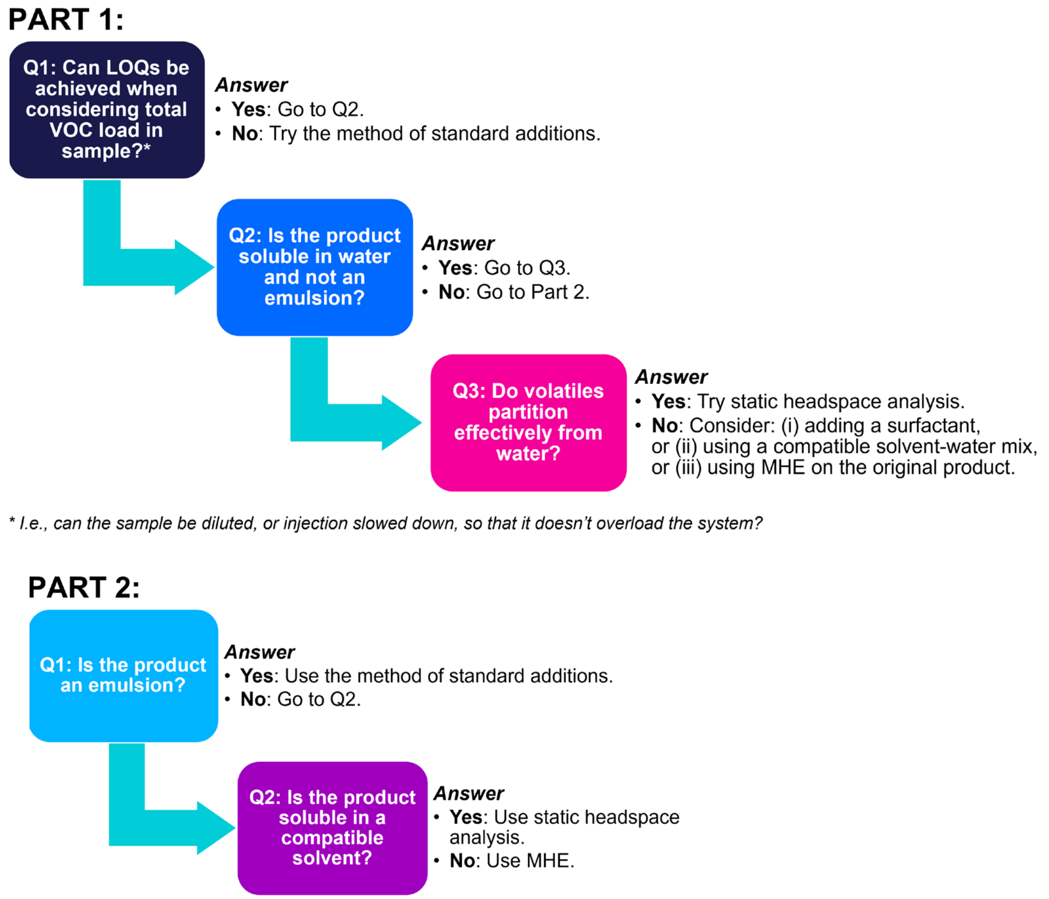
Table 2. Selection of "toolkit" approach based on sample matrix.

Sample Matrix	Dissolution	MHE	Standard Additions	Constraints on Preferred Approach
Aqueous solution (i.e., article dissolves in water)	Yes	Option	Option	Analyte must partition adequately
Dissolves in SIFT-MS-compatible solvent*	Yes	No	Option	Must not saturate reagent ion or interfere with analyte
Aqueous emulsion or (low volatility) oil-based product	No	Option	Yes	Care must be taken to ensure standard additions are properly homogenized
Solid – polymer, etc., or insoluble in compatible solvent	No	Yes	No	Residual solvents in the matrix can be problematic for MHE
Solid – soluble, but analyte partitions poorly from solution	No**	Yes	No	Residual solvents in the matrix can be problematic for MHE

* Usually requires subsequent dilution in water. See Perkins, Silva, and Langford (2023).

** Surfactants can be used to enhance solubility. For example, see Perkins and Langford (2023c).

Figure 6. A tool to aid selection of the most appropriate headspace-SIFT-MS approach for the sample matrix.



PART 1:

Q1: Can LOQs be achieved when considering total VOC load in sample?*

Answer
- **Yes**: Go to Q2.
- **No**: Try the method of standard additions.

Q2: Is the product soluble in water and not an emulsion?

Answer
- **Yes**: Go to Q3.
- **No**: Go to Part 2.

Q3: Do volatiles partition effectively from water?

Answer
- **Yes**: Try static headspace analysis.
- **No**: Consider: (i) adding a surfactant, or (ii) using a compatible solvent-water mix, or (iii) using MHE on the original product.

** I.e., can the sample be diluted, or injection slowed down, so that it doesn't overload the system?*

PART 2:

Q1: Is the product an emulsion?

Answer
- **Yes**: Use the method of standard additions.
- **No**: Go to Q2.

Q2: Is the product soluble in a compatible solvent?

Answer
- **Yes**: Use static headspace analysis.
- **No**: Use MHE.

In summary, Syft Tracer™ simplifies and speeds up headspace analysis across broad sample matrices using one flexible, stable configuration (Langford *et al.* (2023)). The headspace-SIFT-MS toolkit outlined here enables volatile impurities to be quantitatively analyzed in:

- water-soluble articles,
- articles soluble in a variety of organic solvents,
- emulsion-type products, and
- insoluble products (such as polymeric packaging).

CONCLUSIONS

- Syft Tracer™ analyzes volatiles in a broad range of matrices through multiple compatible headspace approaches.
- Chromatography-free analysis using ultra-soft chemical ionization enables maximum analytical flexibility in one stable instrument configuration.
- Syft Tracer™ provides faster times to first quantitative results and higher sample throughputs than chromatographic techniques.
- Syft Tracer™ has demonstrated long-term stability, delivering large gains in efficiency (analyst and instrument).
- Simplified, high-sensitivity analysis of toxic impurities such as benzene, ethylene oxide, formaldehyde, and volatile nitrosamines.
- Syft Tracer™ is easy to use – operators do not need to be an expert to prep and analyze samples, in contrast with chromatography systems.

REFERENCES

Biba E, Perkins MJ, Langford VS (2021). Stimuli to the Revision Process: High-throughput residual solvent analysis using selected ion flow tube mass spectrometry (SIFT-MS). United States Pharmacopeia. *Pharm. Forum* 47(6). https://online.usppf.com/usppf/document/GUID-2EE1BF6B-C82B-4F11-8E0B-C5520A4E8C3D_10101_en-US.

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.

Langford VS, Perkins MJ (2023). Syft Tracer™: Next-generation volatile impurity analysis for enhanced workflows. Syft Technologies application note. Available online: http://bit.ly/3LYH2IP.

Langford VS, Silva LP, Perkins MJ (2023). Syft Tracer™: Revolutionary productivity for volatile residue and impurity analysis. Syft Technologies application note. Available online: https://bit.ly/3ZU3SEJ.

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. Available online: https://bit.ly/3zfDM3Y.

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 [SIFT-MS] 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). Rapid residual solvent analysis: Validation of an alternative procedure for USP method <467> using SIFT-MS. Syft Technologies Application Note. Available online: http://bit.ly/3Eq7Qx4.

Perkins MJ, Langford VS (2022b). Application of headspace-SIFT-MS to direct analysis of hazardous volatiles in drinking water. *Environments* 9, 124. https://doi.org/10.3390/environments9100124.

Perkins MJ, Langford VS (2022c). [MHE-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 (2022d). Simple, rapid analysis of N-nitrosodimethylamine (NDMA) impurity in ranitidine products using SIFT-MS. Syft Technologies application note. Available online: https://bit.ly/3GB8wzW.

Perkins MJ, Langford VS (2022e). Simple, rapid analysis of NDMA in a recalled valsartan product using SIFT-MS. Syft Technologies application note. Available online: https://bit.ly/3QFclbR.

Perkins MJ, Langford VS (2022f). Simple, rapid analysis of formaldehyde impurities in Gelucire excipient using SIFT-MS. Syft Technologies application note. Available online: https://bit.ly/3Xca3nd.

Perkins MJ, Langford VS (2023a). Improved MHE-SIFT-MS workflow: Even faster quantitation of formaldehyde in Gelucire excipient. Syft Technologies application note. Available online: http://bit.ly/431xTp2.

Perkins MJ, Langford VS (2023b). High-throughput SIFT-MS analysis of formaldehyde in fragrances using the method of standard additions. Syft Technologies application note.

Perkins MJ, Langford VS (2023c). Improved MHE-SIFT-MS workflows: 2. Concentration-independent "MHE calibration". Syft Technologies application note.

Perkins MJ, Silva LP, Langford VS (2023). Extending SIFT-MS residual solvent and volatile impurity analysis to water-insoluble articles. Syft Technologies application note.

Silva L, Connor A, Bastian C, Williams C, Morseth Z, Franco E (2022). Simple, rapid analysis of ethylene oxide in a Polysorbate 80 Excipient using SIFT-MS. Syft Technologies application note. Available online: https://bit.ly/3QLWRmC.

Silva L, Langford V (2022). High-throughput, quantitative analysis of benzene in personal care products using headspace-SIFT-MS. Syft Technologies application note. Available online: http://bit.ly/3Xv3Cew.

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.

Syft™

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

AN01_No.42_May2023_Rev1