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TECHNICAL NOTE

PROGRESS WITH ALTERNATIVE SOLVENTS FOR SIFT-MS: 2024 UPDATE

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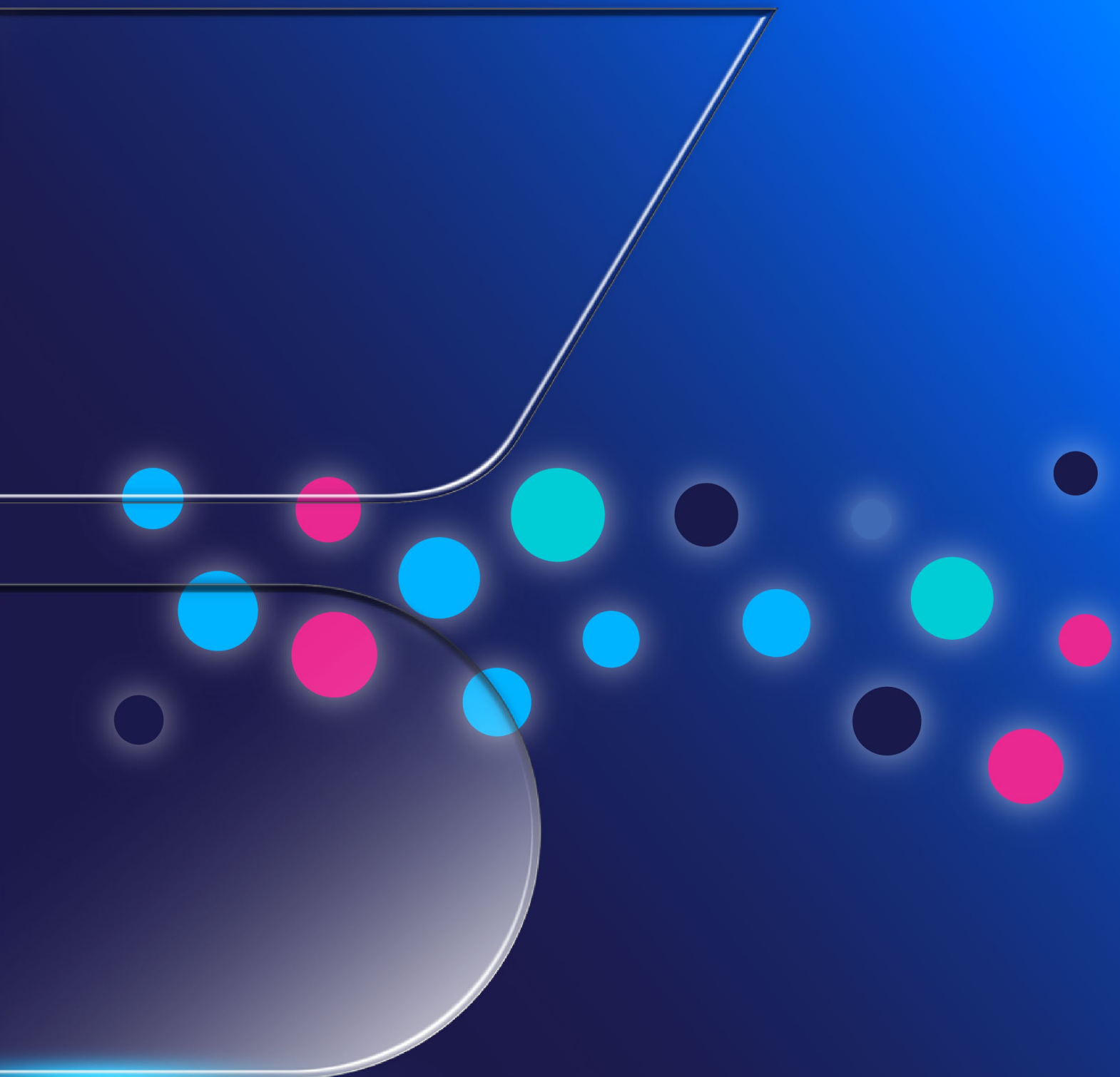


ABSTRACT

Automated headspace-SIFT-MS can utilize certain non-aqueous solvents. This technical note updates progress made in 2024 with the addition of three new solvents and results for selected, diverse analytes.

INTRODUCTION

Although aqueous solutions are the preferred matrix for high-throughput, quantitative headspace-SIFT-MS analyses, it has been demonstrated previously that there are non-aqueous solvent options for SIFT-MS (Perkins, Silva, and Langford (2023)). Furthermore, that study provided criteria by which additional "alternative solvents" could be evaluated.

This technical note gives a brief and eclectic update on recent progress with alternative solvents for SIFT-MS, summarizing results obtained for additional analytes and introducing more solvents. Occasionally the results obtained with alternative solvents are surprising – especially the sensitivity enhancement observed for formaldehyde in neat triacetin. Data presented illustrate various interesting effects – both beneficial and problematic – that method developers should be attentive to.

METHODS

The results presented below utilize a standard SIFT-MS instrument configuration for automated analysis (Langford and Perkins (2024)):

- A Syft Technologies SIFT-MS instrument (Voice200*ultra* or Syft Tracer™) configured with an autosampler inlet and mounting hardware.
- An 'xyz' robotic autosampler configured for headspace analysis (including a 2.5-mL headspace syringe).

The approach used to evaluate alternative (i.e., non-aqueous) solvents is described in Perkins, Silva, and Langford (2023). Where 'levels' rather than concentrations are stated below, these refer to the 'levels' used in Perkins, Silva, and Langford (2023), which were designed to give headspace concentrations of similar magnitude in water, despite disparate partitioning from the aqueous phase.

Unless otherwise stated, standard headspace-SIFT-MS conditions are utilized (10 mL of solution in a 20-mL headspace vial, with 20-min incubation at 60 °C; Perkins and Langford (2021a, 2021b)).

UPDATES ON SOLVENTS EVALUATED PREVIOUSLY

1. Triacetin

Perkins, Silva, and Langford (2023) evaluated triacetin at high dilution (<6%) because the solvent becomes immiscible in water at approximately 6%. However, triacetin is also compatible with SIFT-MS at 100% due to its low vapor pressure. For practical application, however, two constraints should be noted:

1. Only very polar analytes partition to headspace better than they do in pure water; for example, methanol (Figure 1). That is, triacetin is not a broadly applicable solvent for headspace analysis at 100%.
2. Triacetin can accumulate in the automated instrument at ppmV concentrations when multiple need samples are run back-to-back due to its high boiling point (Figure 2). Method developers and routine analysts alike should be alert to this behavior because in some samples it could be problematic. For example, it could lead to deterioration of method repeatability and linearity.

Nevertheless, triacetin may be very well suited to use as a stock solvent for calibration mixes, since it retains low- to mid-polarity components very effectively – their partitioning to headspace is significantly poorer in triacetin (Figure 1).

Figure 1. Headspace partitioning of triacetin at 60 and 100 °C relative to water (60 °C) for the analyte suite in Perkins, Silva, and Langford (2023) at level '20'. Note the logarithmic axis for the relative responses.

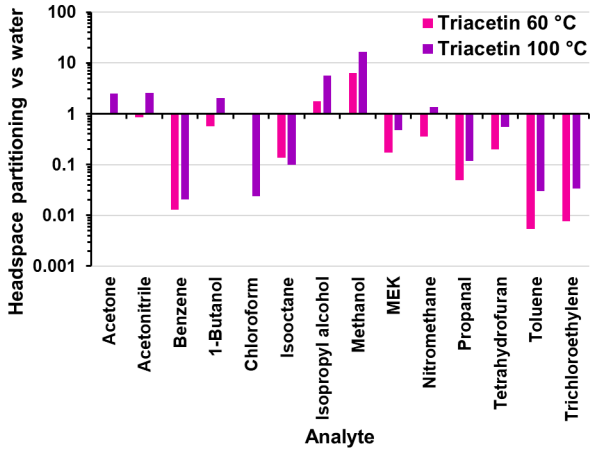
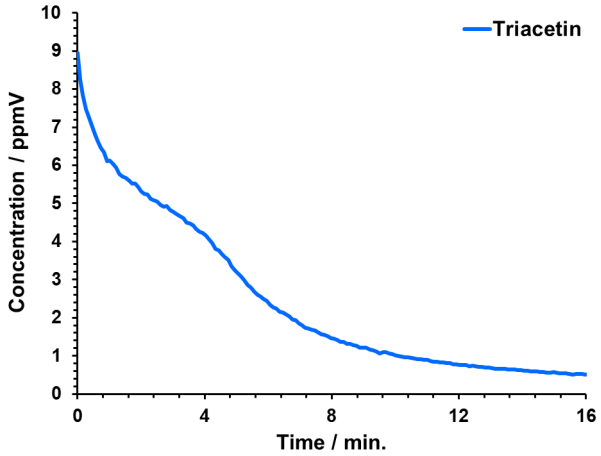


Figure 2. Real-time SIFT-MS monitoring of the decay of triacetin residue in the inlet after several samples were analyzed for formaldehyde from neat triacetin.



In addition to the VOC suite used previously (Perkins, Silva, and Langford (2023)), feasibility has been assessed for use of triacetin as a solvent for two high-polarity, mutagenic VOCs: formaldehyde and *N*-nitrosodimethylamine (NDMA). Measured SIFT-MS injection profiles for these compounds are shown in Figures 3(a) and 3(b), respectively, for water and triacetin incubated at 60 °C. The spike concentration units for formaldehyde in triacetin are surprising (annotated on Figure 3(a)) – this is not a typographical error, but rather demonstrates the approx. 300-fold sensitivity increase obtained compared to water. Hence, triacetin is an ideal solvent for analysis of trace formaldehyde impurities. Unfortunately, only a modest sensitivity gain is achieved for NDMA (less than two-fold). In both cases, repeatability is enhanced through more consistent injection profiles. Real-time analysis during headspace injection enables SIFT-MS to provide insights into dynamics of sample delivery. Note that triacetin can be used at higher incubation temperatures than water (e.g., 100 °C), further enhancing partitioning and therefore sensitivity (Figure 1). While injection peak shapes suffer at higher temperatures, they are still better than water at 60 °C. This is also evident in analysis of formic and acetic acids (Figure 4), where analogous to NDMA only modest sensitivity enhancements over water are achieved.

Figure 3. Injection profiles for headspace-SIFT-MS analysis of (a) formaldehyde and (b) NDMA in water and triacetin at 60 °C.

(a) (b)

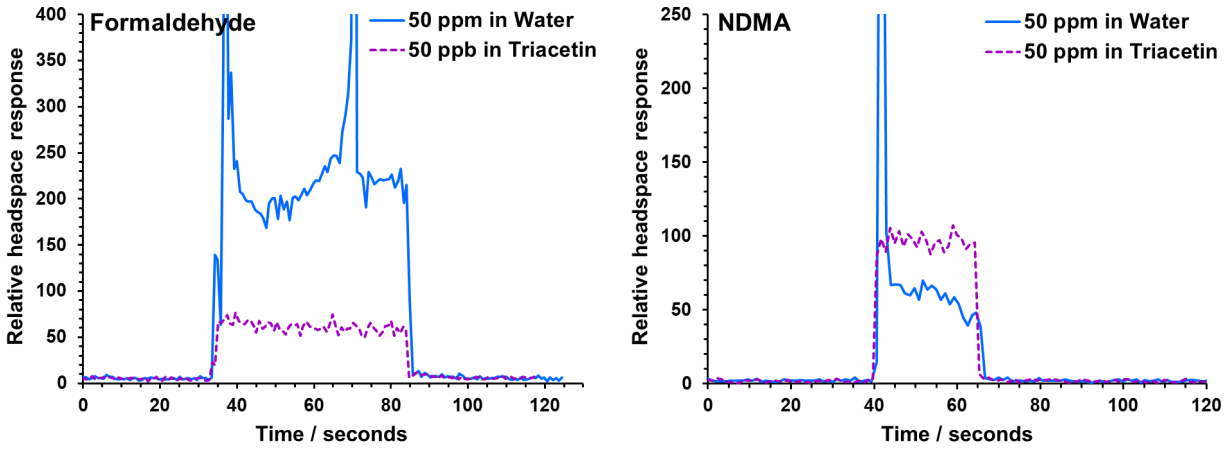
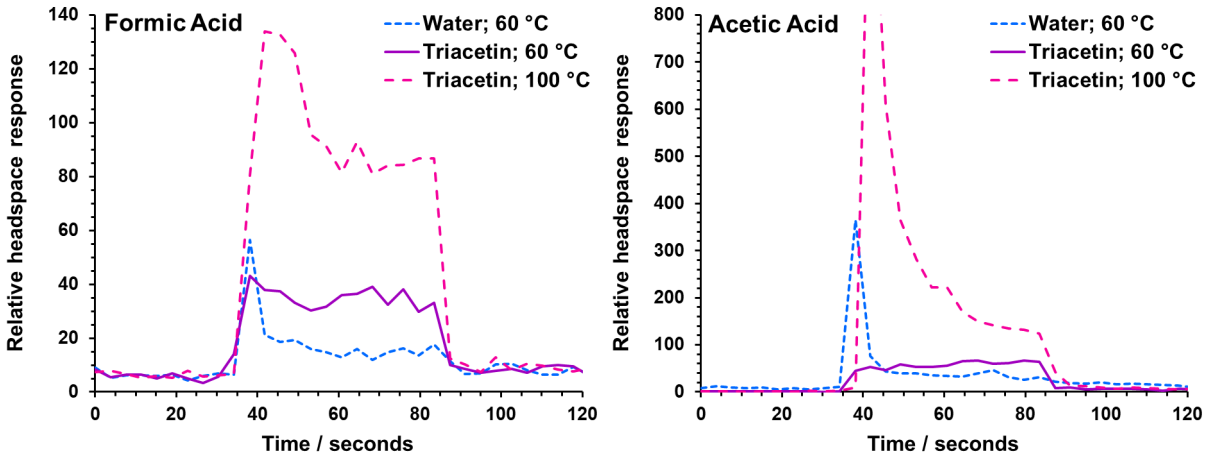


Figure 4. Injection profiles for headspace-SIFT-MS analysis of 10-ppm solutions of (a) formic acid and (b) acetic acid in water at 60 °C and triacetin at 60 and 100 °C.

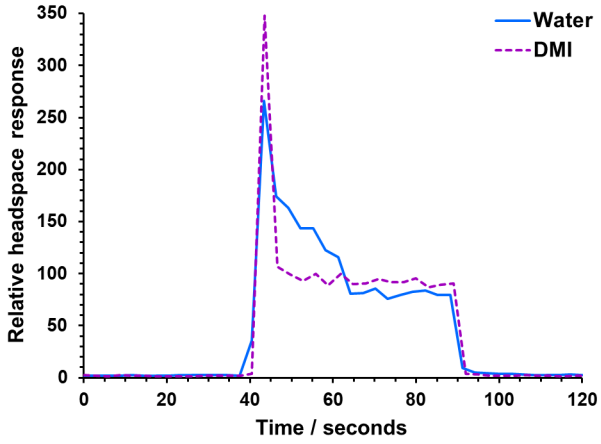
(a) (b)



2. 1,3-Dimethyl-2-imidazolidinone (DMI)

With the ability to utilize DMI at any dilution level up to 100%, it appears a flexible alternative solvent for SIFT-MS (Perkins, Silva, and Langford (2023); Perkins and Langford (2023)). Unfortunately, the modest sensitivity improvements observed for various polar solvents in previous work (Perkins and Langford (2023)) do not translate to NDMA: the headspace injections in Figure 5 show very similar sensitivities for water and DMI. However, the improved injection profile for DMI may provide improved repeatability.

Figure 5. Injection profiles for headspace-SIFT-MS analysis of NDMA at 50 ppm in water and DMI (60 °C incubation).

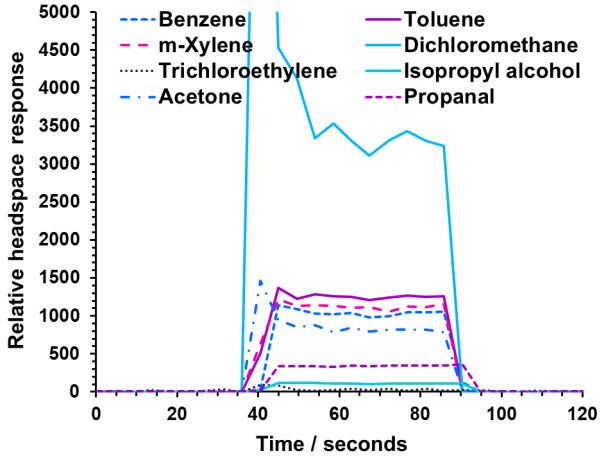


ADDITIONAL SOLVENTS FOR HEADSPACE-SIFT-MS

1. Acetonitrile

Although acetonitrile reacts very rapidly with the H_3O^+, its reactions with NO^+ and $O_2^{+\cdot}$ are significantly slower (Španěl and Smith (1998)) enabling these ions to be applied to trace analysis of VOCs in aqueous headspace at 5% and 2.5%, respectively. Acetonitrile is therefore more practical than methanol, for which only NO^+ can be utilized due to fast H_3O^+ and $O_2^{+\cdot}$ reactions (Perkins, Silva, and Langford (2023)). In particular, several chlorinated VOCs can be analyzed in this matrix that could not be analyzed using SIFT-MS in the analogous methanol:water matrix because these VOCs only react significantly with $O_2^{+\cdot}$. Figure 6 demonstrates simultaneous analysis of diverse VOCs in 2.5% acetonitrile solution (in water), including dichloromethane and trichloroethylene. For analytes in the test mix at both 2.5 and 5%, the linear regression coefficient (R^2) for levels 0 to 500 is >0.992, except for dichloromethane ($O_2^{+\cdot}$ only) and the low-sensitivity NO^+ reaction of trichloroethylene.

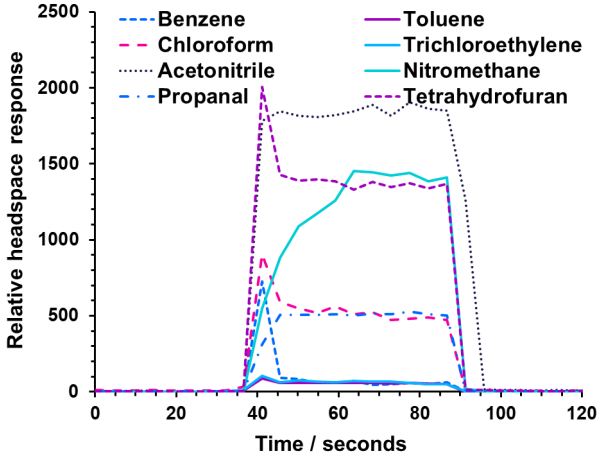
Figure 6. Injection profiles for headspace-SIFT-MS analysis of selected, diverse VOCs in 2.5% acetonitrile (balance water) solution at the "50" level (see Perkins, Silva, and Langford (2023)) with 60 °C incubation.



2. *N,N'*-Dimethylpropyleneurea (DMPU)

DMPU is related to DMI (see above and Perkins, Silva, and Langford (2023)) and therefore its suitability has been evaluated up to 100% at 60 °C. Injection profiles for several VOCs are shown in Figure 7. Note that the slow rise in nitromethane concentration requires a narrower data extraction window for that compound (approx. 65 – 85 s versus 50 – 85 s for the other analytes). At 50% dilution in water, across all product ions in the mix repeatability of the 250-level standard had relative standard deviations (RSDs) from 1.2 to 8.1%, and linearity (R^2) >0.991.

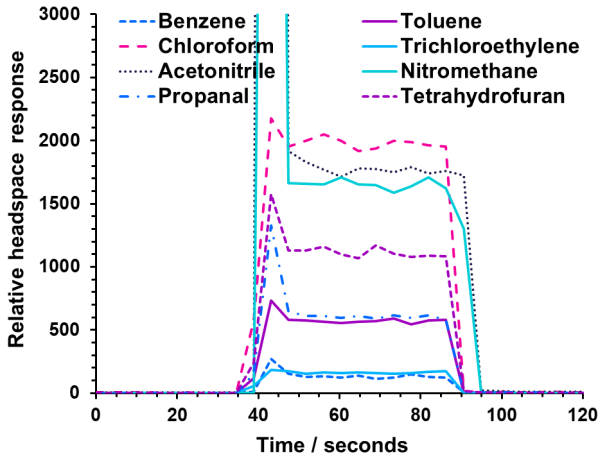
Figure 7. Injection profiles for headspace-SIFT-MS analysis of selected, diverse VOCs in 50% DMPU at the "250" level (see Perkins, Silva, and Langford (2023)) with 60 °C incubation.



3. Propylene Glycol (PG)

PG is a widely used carrier solvent for flavors and fragrances – among other consumer and industrial applications. Like DMPU and DMI, PG can be utilized as a neat alternative solvent at 60 °C. All analytes shown yield ideal injection profiles once the initial spike has recovered (Figure 8). Repeatability at 50% dilution in water has RSDs from 1.7 to 8.6% at the 250 level for all product ions targeted in the standard mix (Perkins, Silva, and Langford (2023)), while linearity from level 0 to 500 has $R^2 > 0.998$ (except one isooctane ion, for which $R^2 = 0.99$). Note that analogous to water (see the technical note "Enhanced Headspace-SIFT-MS Analysis of Aqueous Solutions Using Salts and Surfactants"), potassium carbonate (K_2CO_3) can be utilized in PG to enhance headspace partitioning of certain analytes, so should be considered in method development.

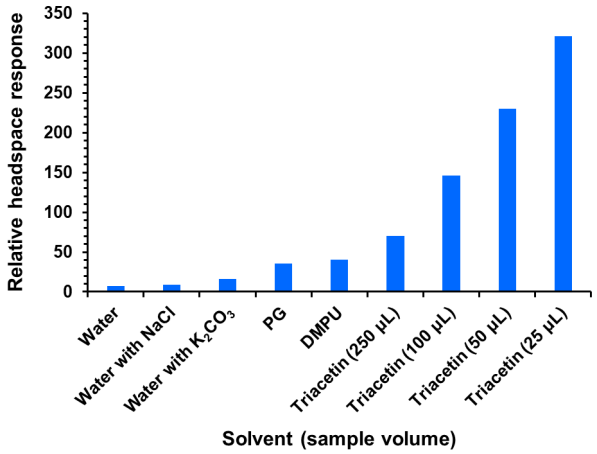
Figure 8. Injection profiles for headspace-SIFT-MS analysis of selected, diverse VOCs in 50% PG at the "250" level (see Perkins, Silva, and Langford (2023)) with 60 °C incubation.



FORMALDEHYDE ANALYSIS: A MULTI-APPROACH COMPARISON

The high polarity of formaldehyde means that it partitions poorly to the headspace of pure water. Figure 9 compares performance of headspace analysis for a variety of matrices, including the use of salts (sodium chloride and potassium carbonate; see the technical note "Enhanced Headspace-SIFT-MS Analysis of Aqueous Solutions Using Salts and Surfactants"), and neat organic solvents (PG, DMPU, and triacetin). Several spiking volumes are shown for formaldehyde in triacetin (i.e., aqueous spikes are more concentrated towards the right side of Figure 9) to illustrate the sensitivity is strongly dependent on water content in this solvent. Maximizing sensitivity requires minimizing water content.

Figure 9. Relative headspace responses for SIFT-MS analysis of formaldehyde (250 ppb; 60 °C incubation) in various matrices. See the text for more details.



CONCLUSIONS

- Acetonitrile, DMPU, and PG are new alternative solvents for SIFT-MS, and triacetin has now been demonstrated at 100%. See Table 1.
- Non-aqueous solvents open more headspace applications for high-throughput, static headspace-SIFT-MS, including dissolution of water insoluble articles for residual solvents analysis.
- Surprisingly large sensitivity enhancements compared to water are sometimes observed for non-aqueous solvents – e.g., formaldehyde in triacetin.
- SIFT-MS can analyze diverse compounds in a single run, so careful evaluation of the benefits and potential drawbacks of the alternative solvent should be made during method development (e.g., like DMI, neat DMPU and triacetin negatively impact headspace analysis of non-polar analytes).
- SIFT-MS straightforwardly monitors carryover in real-time and can give insight into the quality of sample introduction.

Table 1. Solvents with demonstrated headspace-SIFT-MS compatibility to date, including usable reagent ions, upper limit recommended in water, and some practical comments. Updated from ref. Perkins, Silva, and Langford (2023) under the terms and conditions of the Creative Commons Attribution (CC-BY 4.0) license (https://creativecommons.org/licenses/by/4.0/))

Solvent [1]	Practical Reagent Ions	Limit [2]	Comments
Acetonitrile	NO^+, $O_2^{+\cdot}$	≤5%	For $O_2^{+\cdot}$: ≤2.5%
DMAC	H_3O^+, NO^+, $O_2^{+\cdot}$	≤50%	Impacts analysis of acetone
DMF	H_3O^+, NO^+, $O_2^{+\cdot}$	≤10%	Impacts analysis of 1-butanol, butylamines, etc.
DMI	H_3O^+, NO^+, $O_2^{+\cdot}$	≤100%	Watch for impurities in solvent, including adsorption from air
DMPU	H_3O^+, NO^+, $O_2^{+\cdot}$	>50%	Watch for carryover at high percentages.
DMSO	H_3O^+, NO^+, $O_2^{+\cdot}$	≤25%	Impacts analysis of benzene and isooctane
Methanol	NO^+	≤20%	Useful if analyte(s) selectively analyzed using NO^+
Propylene glycol	H_3O^+, NO^+, $O_2^{+\cdot}$	>50%	Watch for carryover at high percentages.
Triacetin	H_3O^+, NO^+, $O_2^{+\cdot}$	<6%, 100%	Limited by miscibility in water, but neat solvent is also suitable. Watch for carryover at high proportions.

[1] DMAC = dimethylacetamide, DMF = *N*,*N*-dimethyl formamide, DMI = 1,3-dimethyl-2-imidazolidinone, DMPU = *N*,*N*'-dimethylpropyleneurea, DMSO = dimethyl sulfoxide.

[2] Maximum percentage recommended (diluted in water).

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