

Article

Headspace-Selected Ion Flow Tube Mass Spectrometry Workflows for Rapid Screening and Quantitation of Hazardous Volatile Impurities in Personal Care Products

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Abstract: Personal care products (PCPs) are intended for regular application by consumers and therefore assuring the safety of these products is very important. Recently, benzene contamination has been highlighted in certain PCPs. The present study applies selected ion flow tube mass spectrometry (SIFT-MS) to a simultaneous headspace analysis of benzene, 1,4-dioxane, and formaldehyde—all known or suspected carcinogens—in nine haircare products with supporting qualitative analysis by gas chromatography–mass spectrometry (GC-MS). Headspace-SIFT-MS method development is compatible with the method of standard additions, which is necessary for the quantitation of volatile impurities in these complex emulsions. Benzene was quantified above the low-ng g⁻¹ limit of quantitation (LOQ) in three products, dioxane above the sub-μg g⁻¹ LOQ in all products, and formaldehyde above the low-μg g⁻¹ LOQ in two products, providing a quantitative analysis at concentrations relevant to consumer safety. This study facilitated the development of generic workflows for SIFT-MS method development and application in routine analysis of PCPs. The assessment of workflows for SIFT-MS compared to a conventional GC-MS analysis suggests that 8- to 30-fold throughput enhancements may be possible for quantitative and screening analysis using SIFT-MS.

Keywords: SIFT-MS; VOC; benzene; 1,4-dioxane; formaldehyde; headspace; standard additions; personal care product; volatile impurity



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1. Introduction

Personal care products (PCPs) are formulated for regular use on the body, and it is hence very important that the safety of such products is assured [1,2]. Several volatile organic compounds (VOCs) feature among impurities or ingredients of particular concern, including the known or suspected carcinogens benzene, 1,4-dioxane, and formaldehyde.

Benzene, although banned as an ingredient for more than a decade [1], has recently reemerged as an impurity in ingredients used to formulate various PCPs, raising significant safety concerns [3–5]. Its current pharmacopeial limit (as a residual solvent in pharmaceutical products) is 2 ppm [6,7], and its drinking water limits are significantly lower (in the very low ppb range in the European Union (EU) [8] and United States of America (USA) [9]).

1,4-Dioxane is similarly banned as an ingredient in cosmetics [1] but is an inevitable byproduct of the manufacture of various polymers and excipients, such as Polysorbate 80. Hence, pharmacopeial monographs provide test procedures and define limits for 1,4-dioxane in specific products. For example, 1,4-dioxane has limits in pharmaceutical products of 1 μg g⁻¹ in the EU [10] and 10 ppm in the USA [11].

Although otherwise banned as an ingredient, formaldehyde is present in products that use formaldehyde-donor preservatives [1] and can be present as a byproduct of ingredient manufacture. It can cause skin sensitization in some individuals [12], although recent work suggests that the dosage from PCPs may not constitute a cancer risk [13]. When

used in preservative applications, the EU limits free formaldehyde to 0.1% in oral products and 0.2% in nonoral products, with a declaration on labelling if the level is above 0.05% [1].

Screening finished product formulations (or individual ingredients) for all three impurities typically requires two analytical runs using conventional methods, since benzene and 1,4-dioxane are analyzed using gas chromatography (GC) [6,7,10,11] and formaldehyde using liquid chromatography (LC) [14]. Alternatively, by removing the chromatography step and applying soft chemical ionization (CI), selected ion flow tube mass spectrometry (SIFT-MS) can analyze these toxic compounds simultaneously from air and headspace in only tens of seconds [15–17]. The key parameters for successful application of SIFT-MS are that (1) sufficient partitioning of analyte to headspace occurs, and (2) matrix volatiles (such as carrier solvents or fragrance compounds) do not consume too much reagent ion signal [17,18]. Early phases of method development will reveal if these are a likely impediment to sample analysis [17].

The present study investigates, for the first time, the suitability of headspace-SIFT-MS as a potential all-in-one approach to the combined analysis of benzene, 1,4-dioxane, and formaldehyde in PCPs. SIFT-MS method development is conducted in parallel with a qualitative gas chromatography–mass spectrometry (GC-MS) analysis to confirm benzene and 1,4-dioxane identifications made using SIFT-MS. Nine hair and/or skin cleansing PCPs with varying formulations are analyzed using the newly developed procedure. Due to the use of surfactants in these PCPs and the impact that these ingredients have on the partitioning of the volatile impurities to headspace, the method of standard additions (with multiple additions) [19] was utilized for a quantitative sample analysis. To the best of our knowledge, this work represents the first extensive evaluation of the applicability of the standard addition approach to headspace-SIFT-MS because only proof-of-concept investigations have been described previously [20–23]. Furthermore, since SIFT-MS has only recently begun to be applied to the analysis of volatile impurities in PCPs, this article outlines the full workflow from method development through to routine sample analysis when utilizing the method of standard additions with SIFT-MS.

2. Materials and Methods

2.1. Instrumentation

2.1.1. SIFT-MS

A commercial SIFT-MS instrument (Voice200*ultra* model; Syft Technologies Limited, Christchurch, New Zealand) was equipped with a multipurpose (MPS) autosampler (Robotic Pro; GERSTEL, Mülheim, Germany). Samples were incubated in a virtual twelve-place agitator (composed of two physical six-place agitators; GERSTEL) prior to the sampling of the headspace and subsequent injection into the SIFT-MS instrument through a septumless sampling head (GERSTEL). Table 1 summarizes the reagent ion–product ion pairs used to target benzene, 1,4-dioxane, and formaldehyde in this study.

Table 1. Reagent ion–product ion pairs (product ions identified by mass-to-charge ratios) used to quantify target compounds, with branching ratio (as a percentage). For simplicity, other unused ion products of each compound are not shown. Formaldehyde also has its water adduct (m/z 49) included, as indicated in parentheses.

Compound, Molecular Formula	Reagent Ion	Product Ion Formula	Product Ion m/z	Branching Ratios	Reference
Benzene, C ₆ H ₆	H ₃ O ⁺	C ₆ H ₆ ·H ⁺	79	100%	[24]
	NO ⁺	C ₆ H ₆ ^{+•}	78	76%	
	NO ⁺	C ₆ H ₆ ·NO ⁺	108	24%	
	O ₂ ^{+•}	C ₆ H ₆ ^{+•}	78	100%	

Table 1. Cont.

Compound, Molecular Formula	Reagent Ion	Product Ion Formula	Product Ion m/z	Branching Ratios	Reference
1,4-Dioxane, C ₄ H ₈ O ₂	H ₃ O ⁺	C ₄ H ₈ O ₂ ·H ⁺	89	100%	[25]
	NO ⁺	C ₄ H ₇ O ₂ ⁺	87	55%	
	NO ⁺	C ₄ H ₈ O ₂ ^{+•}	88	45%	
	O ₂ ^{+•}	C ₃ H ₆ O ^{+•}	58	30%	
	O ₂ ^{+•}	C ₄ H ₈ O ₂ ^{+•}	88	65%	
Formaldehyde, CH ₂ O	H ₃ O ⁺	CH ₂ O·H ⁺	31 (49)	100%	[26]

2.1.2. GC-MS

In this study, GC-MS was utilized for the qualitative analysis of samples to provide confirmation of compounds tentatively identified using SIFT-MS.

A GC-MS analysis was conducted using an Agilent 7890 GC equipped with a 5977B mass selective detector (Agilent Technologies, Santa Clara, CA, USA) and coupled with a multipurpose autosampler (MPS Robotic Pro (dual head); GERSTEL, Mülheim, Germany). A 2 mL aliquot of the headspace was injected at 200 $\mu\text{L s}^{-1}$ into the split/splitless inlet (10:1 split ratio) of the GC device. Separation was achieved using a DB5-MS GC column 30 m \times 0.25 mm, 0.25 μm (Agilent Technologies). The oven was initially held at 40 $^{\circ}\text{C}$ for 1 min before ramping at 10 $^{\circ}\text{C min}^{-1}$ to 250 $^{\circ}\text{C}$ where it was held for the remainder of the 25 min run time. The MSD was operated in combined scan and selected ion monitoring mode with an electron impact source (70 eV) using m/z 78 and 51 for benzene, 91 and 92 for toluene, and 91 and 106 for xylenes and ethylbenzene. Signals for 1,4-dioxane were extracted from scan data using m/z 86. The source and quadrupole temperatures were 230 and 150 $^{\circ}\text{C}$, respectively.

2.2. Sample Preparation

For the headspace-SIFT-MS analysis, the headspace conditions for all analyses utilized 20 mL headspace vials incubated at 60 $^{\circ}\text{C}$ for 20 min. A 2.5 mL aliquot of headspace was removed using a heated gas-tight syringe (150 $^{\circ}\text{C}$) and injected into the SIFT-MS instrument's sample inlet at 50 $\mu\text{L s}^{-1}$, with a zero-air make-up gas flow through the heated inlet (120 $^{\circ}\text{C}$) to ensure that the total flow into the instrument was 25 mL min^{-1} . After sample injection, the syringe was flushed with zero air for 1 min at 200 mL min^{-1} .

In the method development phase, 1 g samples of product were utilized (neat or diluted with 9 mL of deionized water and vortexed for approximately 30 s). A full-scan automated headspace-SIFT-MS analysis was conducted, as described previously [27].

For the quantitative analysis (using the method of standard additions), 2 g of product was diluted in 2 mL of deionized water and vortexed for approx. 30 s. Sequence schedules for automated preparation and analysis of standard additions with SIFT-MS have been described previously [20].

For the headspace-GC-MS analysis, samples (1 g or 1 g diluted in 9 mL of deionized water) were incubated for 20 min at 60 $^{\circ}\text{C}$.

2.3. Samples and Standards

The hair and/or skin cleansing PCPs analyzed in this study (Table 2) were obtained from a local supermarket (Tesco, Cambridge, UK).

Standards for calibration (i.e., for the spikes in standard additions samples) of benzene, 1,4-dioxane, and formaldehyde were prepared in-house from chemicals supplied by Sigma-Aldrich (Gillingham, UK). Benzene, dimethylsulfoxide (DMSO), and 1,4-dioxane (anhydrous) had purities of $\geq 99\%$, $\geq 99.5\%$, and $\geq 99.8\%$, respectively, while formaldehyde was a 1000-ppm aqueous standard.

Table 2. Summary of the nine hair and skin cleansing PCPs analyzed in this study and ingredient list as stated on the product label.

Product Number	Product Type/Description	Ingredients
1	Micellar cleansing water	Hexylene glycol, glycerin, Poloxamer 184, disodium cocoamphodiacetate, sodium EDTA, myrtrimonium bromide
2	Shower gel	Sodium laureth sulfate, sodium chloride, cocamidopropyl betaine, glycerin, sodium benzoate, citric acid, sodium lactate, polyquarternium-7, panthenol, sodium EDTA, menthyl lactate, dipropylene glycol, propanediol, <i>Cucumis sativus</i> fruit extract
3	Anti-dandruff shampoo	Sodium laureth sulfate, cocamidopropyl betaine, salicylic acid, sodium coco-sulfate, glycerin, sodium chloride, sodium citrate, parfum, DMDM hydantoin, citric acid, sodium hydroxide, sodium benzoate, caramel, linalool, maltodextrin, hexylene glycol
4	Medicated shampoo	Macrogol lauryl ether, sodium lauryl ether sulfate, cocodiethanolamine, cocamidopropyl betaine, imidazolidinyl urea, sodium EDTA, citric acid, perfume, sodium chloride, solubilized coal tar extract (20 mg/mL)
5	Body wash (children)	Sodium laureth sulfate, cocamidopropyl betaine, sodium chloride, glycerin, parfum, disodium cocoamphodiacetate, citric acid, sodium benzoate, potassium sorbate, PEG-150 distearate, sodium glutamate diacetate, hexylene glycol, sodium hydroxide, ascorbyl palmitate
6	Shower cream	Sodium laureth sulfate, glycerin, sodium chloride, cocamidopropyl betaine, sodium benzoate, citric acid, glycol distearate, laureth-4, sodium lactate, panthenol, hydrolyzed wheat protein, sodium EDTA, bisabolol, dipropylene glycol, tocopherol acetate, geranium oil
7*	Shampoo (baby)	Cocamidopropyl betaine, decyl glucoside, sodium cocoyl isethionate, polyquarternium-10, coconut oil, glycerin, sodium methyl cocoyl taurate, PEG-80, sorbitan laurate, PEG-150 distearate, sodium chloride, sodium EDTA, citric acid, sodium benzoate, parfum
8	Charcoal facial scrub	Kaolin, glycerin, starch, decyl glucoside, iron oxides, sodium laureth sulfate, PEG-7 glyceryl cocoate, perlite, PEG-30 dipolyhydroxystearate, zinc gluconate, trideceth-6, sodium hydroxide, pumice, charcoal powder, sodium EDTA, citric acid, xanthan gum, polyglycerin-10, polyglyceryl-10 myristate, polyglyceryl-10 stearate, acrylates (various), sodium dehydroacetate, salicylic acid, phenoxyethanol, parfum
9	Shower gel	Sodium laureth sulfate, sodium chloride, cocamidopropyl betaine, citric acid, parfum, sodium benzoate, sodium EDTA, potassium sorbate, benzophenone-4, sodium hydroxide, hexylene glycol

* This sample was only analyzed quantitatively using standard additions; it was not used in method development.

Stock solutions were prepared as follows. The high-level benzene stock was made by adding 20 μ L to 10 mL of DMSO (stock A). The low-level benzene and dioxane stock solution was prepared by adding 1 mL of stock A and 200 μ L of dioxane and filled up to 10 mL with DMSO (stock B). The low-level spike solution was made by adding 50 μ L of stock B to 5 mL of formaldehyde standard (stock C). The high-level benzene spike solution was prepared by adding 0.5 mL of A to 4.5 mL of water (total volume = 5 mL; stock D).

Standard addition spikes were 40, 80, and 120 μ L of stock C added to 4 mL of sample (2 mL of shampoo, 2 mL of water). For product 4, an additional high-level spike for benzene was added using 20, 40, and 60 μ L of stock D.

3. Results

In principle, all analytes (benzene, 1,4-dioxane, and formaldehyde) are readily detected using SIFT-MS, but due to the complexity of the matrices, careful method development and data evaluation must be conducted. For a successful headspace-SIFT-MS analysis, it is important to understand the bulk composition (the emulsion) and volatile composition (variable and potentially interfering fragrance and other components). Hence, in this section, the specificity of the SIFT-MS analysis is first evaluated through internal and external tests—the former compares multiple reagent ion–product ion pairs for SIFT-MS,

and the second is provided by the GC-MS analysis. Second, the method of standard additions is utilized with SIFT-MS for a quantitation of impurities. Finally, the temporal stability of the standard additions' calibration is investigated.

3.1. Specificity of SIFT-MS Analysis

Figure 1 shows example headspace injections for targeted (i.e., selected ion monitoring) analysis of 1,4-dioxane in product 9 using the NO^+ reagent product ion and the electron transfer product at m/z 88 (Table 1). The sudden rise and fall in measured signal, flanked by the background response, is the result of the syringe injecting headspace slowly during the continuous SIFT-MS analysis. Instrument response to a target ion is determined by averaging data from 50 to 80 s. Care was taken to avoid averaging the initial spike in concentration into the results—this is an important quality assurance check for headspace-SIFT-MS analysis. Note also that data for all product ions of all analytes (Table 1) are acquired in the same run for a given sample. Headspace concentrations in parts per billion by volume (ppbV) were calculated by instrument software [17] but are here termed “relative headspace response” to avoid confusion with the concentrations reported in the condensed phase. In this work, concentrations were evaluated based on primary product ions, and the interference rejection approach ordinarily applied automatically by software [16,17] was applied manually at the end. Full product ion data are summarized in the Supplementary Materials.

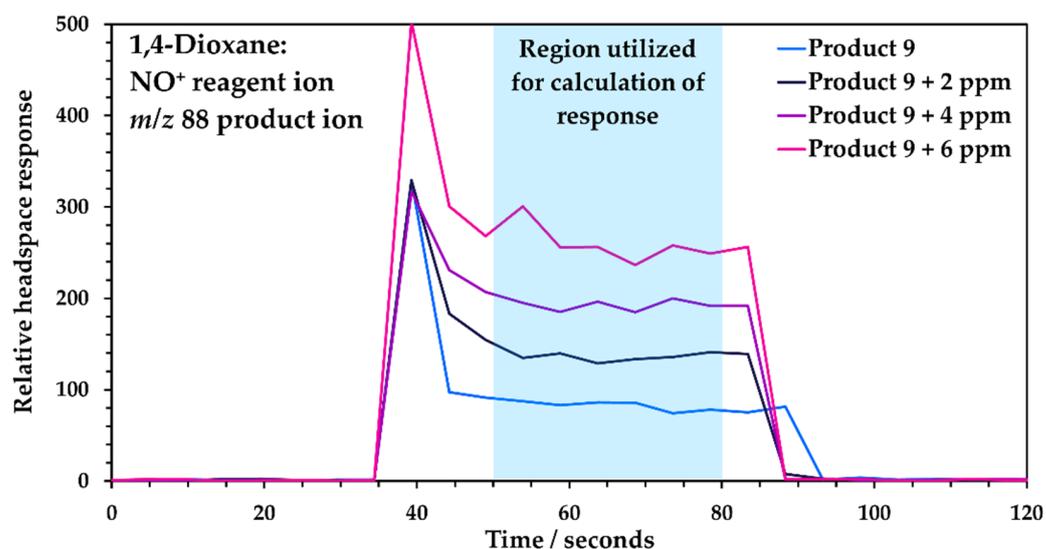


Figure 1. Real-time SIFT-MS analysis of 1,4-dioxane using the NO^+ reagent ion with the m/z 88 product ion. The headspace injections shown are for product 9 and three additions of calibration standard.

The initial static headspace-SIFT-MS analysis (using a selected ion monitoring (SIM) approach) suggested that some samples had significant benzene and/or dioxane present (Section 3.1.1). A verification of these results was conducted in two independent ways, as described in the subsections below (Sections 3.1.2 and 3.1.3).

3.1.1. Conventional Approach: Automated Interference Rejection in Static Headspace-SIFT-MS SIM Analysis

The conventional approach for evaluating SIFT-MS specificity is based on a comparison of concentration determinations obtained using the individual primary product ions (arising from different reagent ions and/or ionization mechanisms) [16,17]. Note that although there is an automated algorithm implemented in instrument software, this should not be relied upon during method development because it is designed for routine analysis, that is, once samples are properly characterized.

The use of simple static headspace analysis across the range of samples analyzed here (Table 2) showed that there was significant variability in performance of the reagent ion–primary product ion pairs (Table 1). This was likely due to the very different formulations of the haircare products (i.e., matrix effects). In some cases, this performance changed when the matrix was diluted ten-fold in water—due to an ion (or ions) being interfered with by a compound(s) with different headspace partitioning behavior. This variable behavior necessitates deeper examination by the method developer to ascertain the breadth of application of a generic method and, therefore, whether a custom method needs to be developed for some/many sample types.

Although static headspace analysis can be utilized for the evaluation of specificity, due to complicated interactions between surfactants and the target volatile impurities, it cannot be utilized with a simple aqueous calibration to quantify the compound in neat or even 10% dilution (nor can LOQs be evaluated). The analyst must matrix-match because the impact of a surfactant on quantitation for a given sample is very difficult to predict. Static headspace data can, however, be utilized for method development, enabling:

- The evaluation of the best dilution ratio for sensitivity across target compounds;
- Confirmation that interference is occurring or not (assuming different partitioning of isobars). For a given set of headspace conditions, noninterfered ions should yield very similar headspace concentration determinations.

3.1.2. Matrix Evaluation Using Full-Scan Static Headspace SIFT-MS Analysis

Full mass scans are a powerful tool for SIFT-MS method development, providing (1) an identification of major volatile components in the matrix and (2) the ability to evaluate these components for various types of interference. Interference can occur due to (1) a major primary product ion, (2) a minor product ion (generally more of an issue if the matrix volatile is at high concentration relative to the analyte), (3) isotopologues (most often ^{13}C —1% per carbon atom in the product ion and located one m/z higher), and (4) secondary product ions [17].

Figure 2 shows full-scan spectra for three of the test products across the three positively charged reagent ions. They demonstrate the variability of volatile composition of these matrices and locate target compounds and selected matrix volatiles by the m/z of their product ion(s). For all samples, the full-scan data indicate that headspace complexity can be accommodated by SIFT-MS, both in terms of the amount of reagent ion consumed [17,18] and in terms of the potential for analyte interference [17]. Assessing the latter is addressed further in Section 3.2.

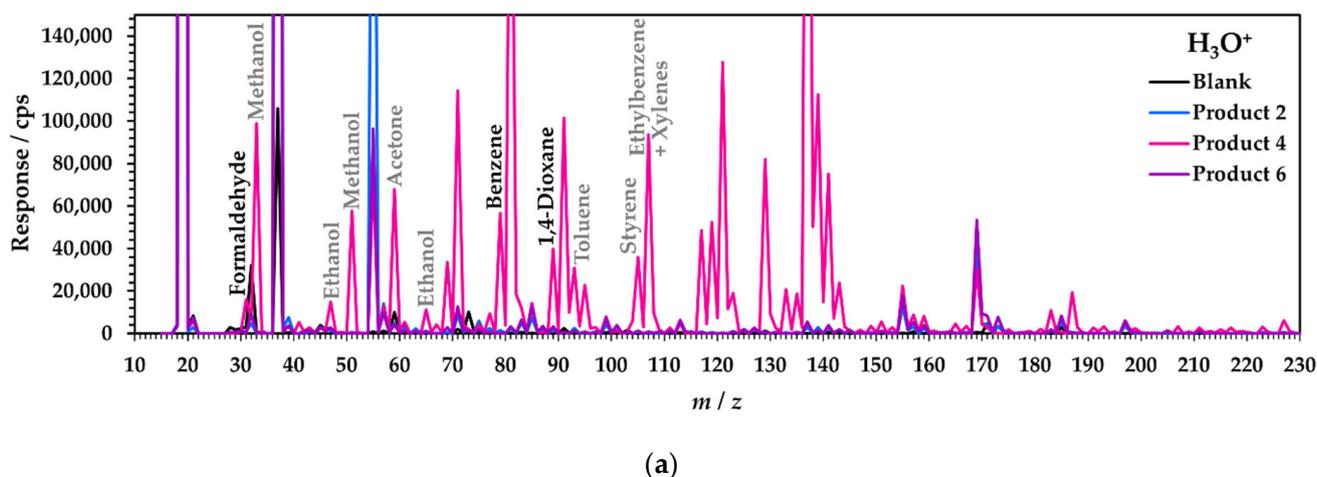


Figure 2. Cont.

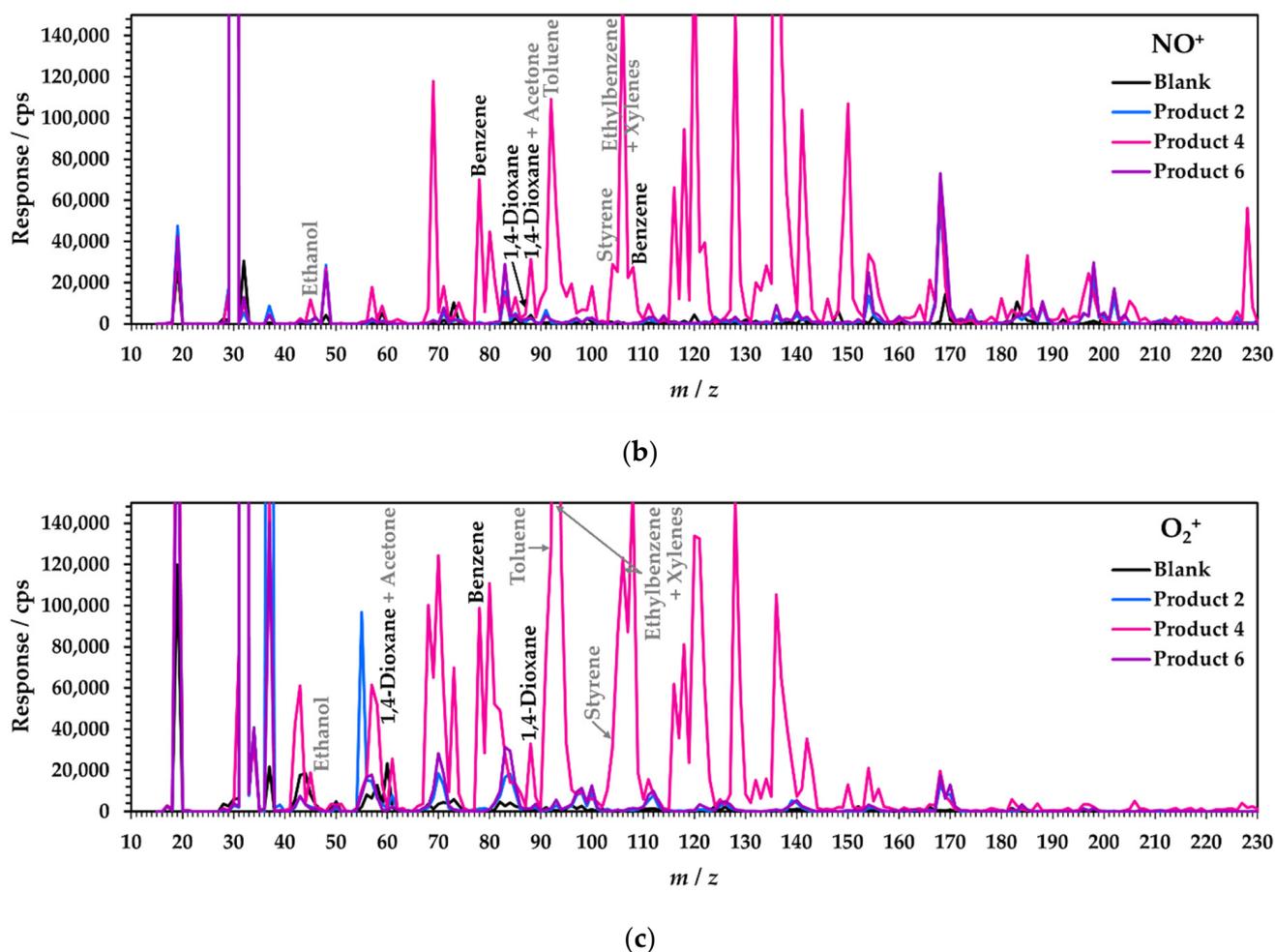


Figure 2. Full-scan headspace-SIFT-MS analysis of 1 g of neat products 2, 4, and 6 for the positively charged reagent ions (a) H_3O^+ , (b) NO^+ , and (c) O_2^+ . Target compounds (Table 1) are annotated in black text, while selected matrix species are annotated in gray text. The instrument response is shown in counts per second (cps), corrected for m/z -dependent transmission [17]. For clarity, data are plotted as curves although they are acquired with 1 m/z steps.

3.1.3. Matrix Evaluation Using Static Headspace-GC-MS Analysis

A qualitative static headspace-GC-MS analysis was used to confirm the presence of analytes tentatively identified in the initial headspace-SIFT-MS analysis. Example chromatograms are shown in Figure 3. As shown via annotations, the GC-MS data confirmed the presence of benzene and 1,4-dioxane identified in the headspace SIFT-MS spectra. However, formaldehyde could not be confirmed under the chromatographic conditions utilized in this study. It is noted, however, that reliable quantitation has been described previously in other applications including breath [26], and in air and polymers [28].

3.2. Quantitation Using the Method of Standard Additions with SIFT-MS

As mentioned in the previous section, the test products are complex matrices, and a quantitative analysis of volatile impurities cannot be conducted using static headspace analysis with an aqueous calibration curve. Hence, the method of standard additions using multiple additions [19] was employed. In this section, the determinations of benzene, 1,4-dioxane, and formaldehyde are reported both as full-run analyses (Section 3.2.1) and as a function of time with a view to optimizing the workflow (Section 3.2.2).

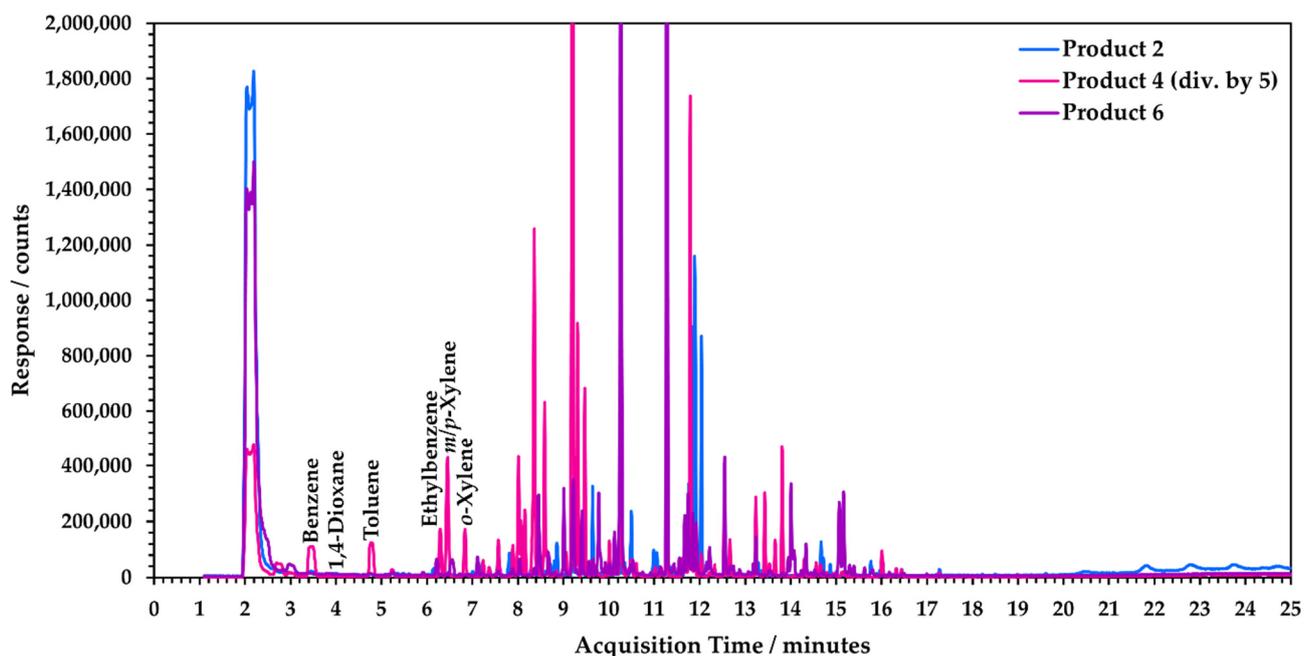


Figure 3. Total ion chromatograms for headspace of 1 g of products 2, 4, and 6.

3.2.1. Full Standard Additions for Each Sample

Figure 4 shows standard additions' curves for two test products across all analytes (displaying all primary product ions). Full data (corrected for a 50% dilution in water) are given in the Supplementary Materials Tables S1–S3 (for benzene, 1,4-dioxane, and formaldehyde, respectively). Since responses for all primary product ions for a target compound were calibrated in aqueous headspace, significant variations in product ion responses arose from interference by other volatiles in the PCP itself. In addition to elevating the concentration reading, the slope was frequently altered due to a different headspace partitioning between the analyte and interferent. The lowest concentration reading represented the upper limit to the compound concentration [17]. Where other primary product ions gave a concentration within 20% of the lowest reading, the mean of these and the lowest reading was calculated to give the reported result [16,17]. This demonstrated the advantage of having multiple product ions collected simultaneously for benzene and 1,4-dioxane. The results for all products tested are summarized in Table 3. The responses demonstrated good linearity in most cases (linear regression coefficient, R^2 , greater than 0.99).

The full data summarized in Tables S1–S3 (Supplementary Materials) show that for a given reagent ion–product ion pair, there are variations in slope between products. This is due to a differing headspace partitioning from the different formulations and demonstrates that matrix-matched calibration is essential. A different partitioning impacts the limits of quantitation (LOQs) because each product requires a unique determination. Here, LOQs were calculated using $10\times$ the peak-to-peak noise from the relevant blank product. Values obtained for each primary product ion are summarized in Tables S1–S3 of the Supplementary Materials for benzene, 1,4-dioxane, and formaldehyde, respectively. The LOQs were applied to the data summarized in Table 3.

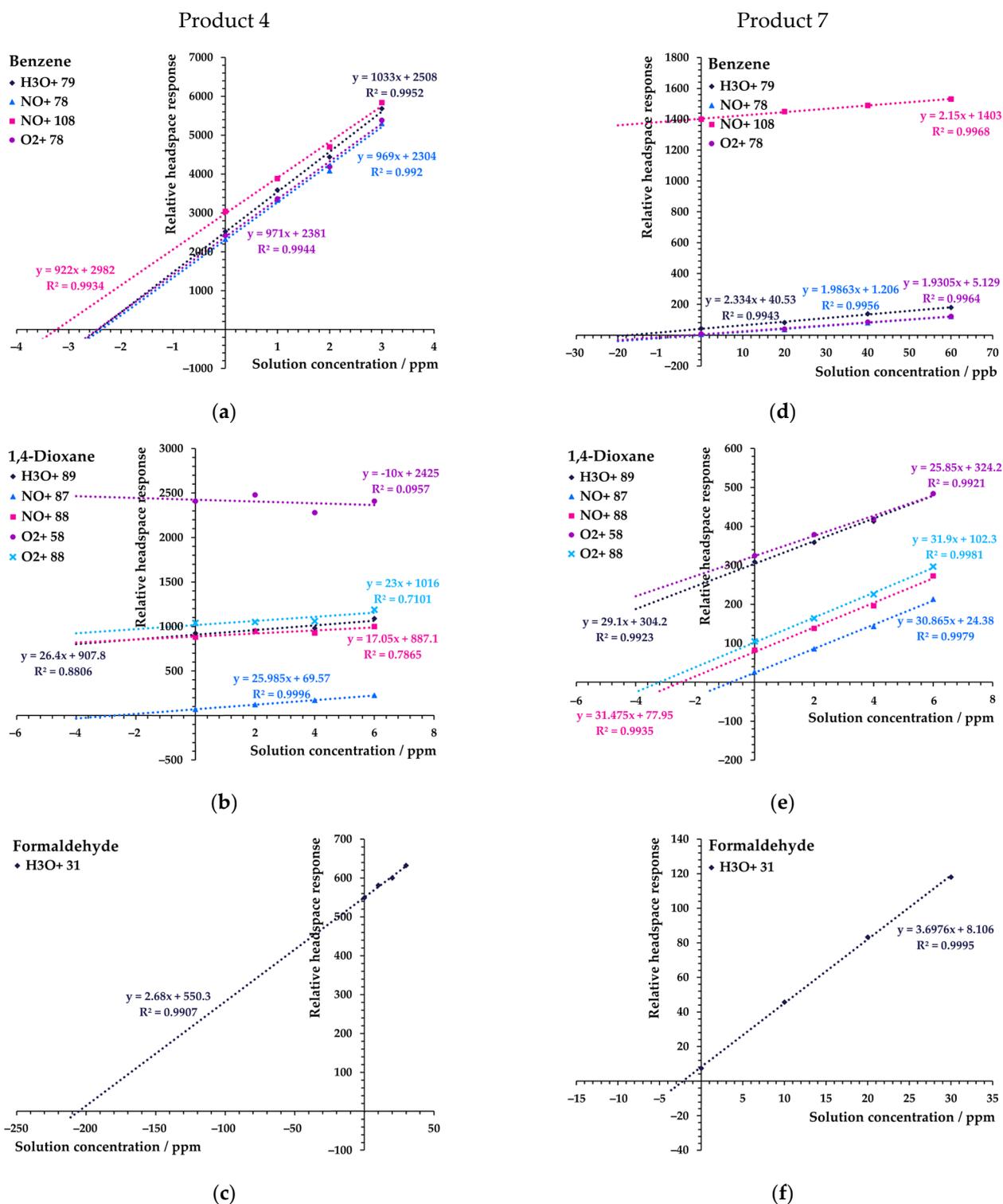


Figure 4. Results of headspace-SIFT-MS analysis of benzene (a,d), 1,4-dioxane (b,e), and formaldehyde (c,f) in products 4 (left) and 7 (right) using the method of standard additions. See the text for an explanation of why product ions for a given analyte can exhibit markedly different responses.

Table 3. Benzene, 1,4-dioxane, and formaldehyde content in nine haircare products obtained using the method of standard additions with headspace-SIFT-MS. Quantitation ions and the linearity of the standard additions curve (as measured using the linear regression coefficient, R^2) are shown.

Product Number or Calibration	Benzene			1,4-Dioxane			Formaldehyde	
	Concentration in Product/ $\mu\text{g g}^{-1}$	Quantitation Ion(s)	Linearity (R^2)	Concentration in Product/ $\mu\text{g g}^{-1}$	Quantitation Ion(s)	Linearity (R^2)	Concentration in Product/ $\mu\text{g g}^{-1}$	Linearity (R^2)
1	<LOQ	N78	>0.992 (4 ions)	0.40	N87	>0.998 (H89, N87, N88)	<LOQ	0.992
2	4.44	N78, O78	>0.995 (4 ions)	0.66	N87	>0.995 (5 ions)	<LOQ	1.000
3	<LOQ	N78	>0.991 (4 ions)	1.63	N87	>0.991 (5 ions)	31.8	0.995
4	1052	H79, N78, O78	>0.992 (4 ions)	1.34	N87	0.9996 (N87)	103	0.991
5	<LOQ	N78	>0.994 (4 ions)	0.57	N87	>0.996 (except O58)	<LOQ	0.999
6	<LOQ	O78	>0.990 (4 ions)	0.67	N87	>0.992 (5 ions)	<LOQ	0.997
7	<LOQ	N78	>0.994 (4 ions)	0.39	N87	>0.992 (5 ions)	<LOQ	0.999
8	3.39	N78	>0.992 (except N108)	0.56	N87	>0.990 (except O58)	<LOQ	0.996
9	<LOQ	N78	>0.996 (4 ions)	0.83	H89	>0.994 (except O58)	<LOQ	1.000
Water cal.			>0.993 (4 ions)			>0.992 (5 ions)		0.9939
Water cal.: High benzene			>0.997 (4 ions)					

3.2.2. Temporal Stability of the Standard Additions' Curve

Having demonstrated that the method of standard additions was readily applied to SIFT-MS analysis of haircare products, the temporal stability of the product's calibration stability was then assessed. The rationale for this investigation was that an analytical workflow can be significantly accelerated if the full method of standard addition calibration does not need to be conducted on every sample tested for a given product formulation because only a single headspace measurement needs to be made. A reduction in calibration demand increases sample throughput and reduces the time to report the first analytical result in a batch. Stability was investigated for up to 44 days for product-analyte combinations of quantitation ions that reported concentrations above the LOQ (Table 3). In short, this involved applying the "Day Zero" slope from the standard addition calibration to the nonspiked sample collected on subsequent days and comparing this result to the data obtained from the full standard additions' measurement made on those days. Products 3 and 8, together with the formaldehyde data in product 4, were excluded due to poor reproducibility. The results obtained are shown in Figure 5. The 1,4-dioxane concentrations almost all lay within $\pm 20\%$ of the "Day Zero" value for up to 44 days after calibration. Only two of the seven products had quantifiable benzene present. For these, the lower concentration sample (product 2) exhibited stability over the full 44 days, whereas the higher concentration sample (product 4) only exhibited six days' stability before a substantial shift occurred. The latter is postulated to be due to the instability of the 50% dilution in water (loss of benzene over time), so solution stability should be probed in future method development. Although results are considered preliminary, they suggest that there is scope for applying earlier standard addition calibrations if the matrix and analyte(s) demonstrate sufficiently stable behavior during method development.

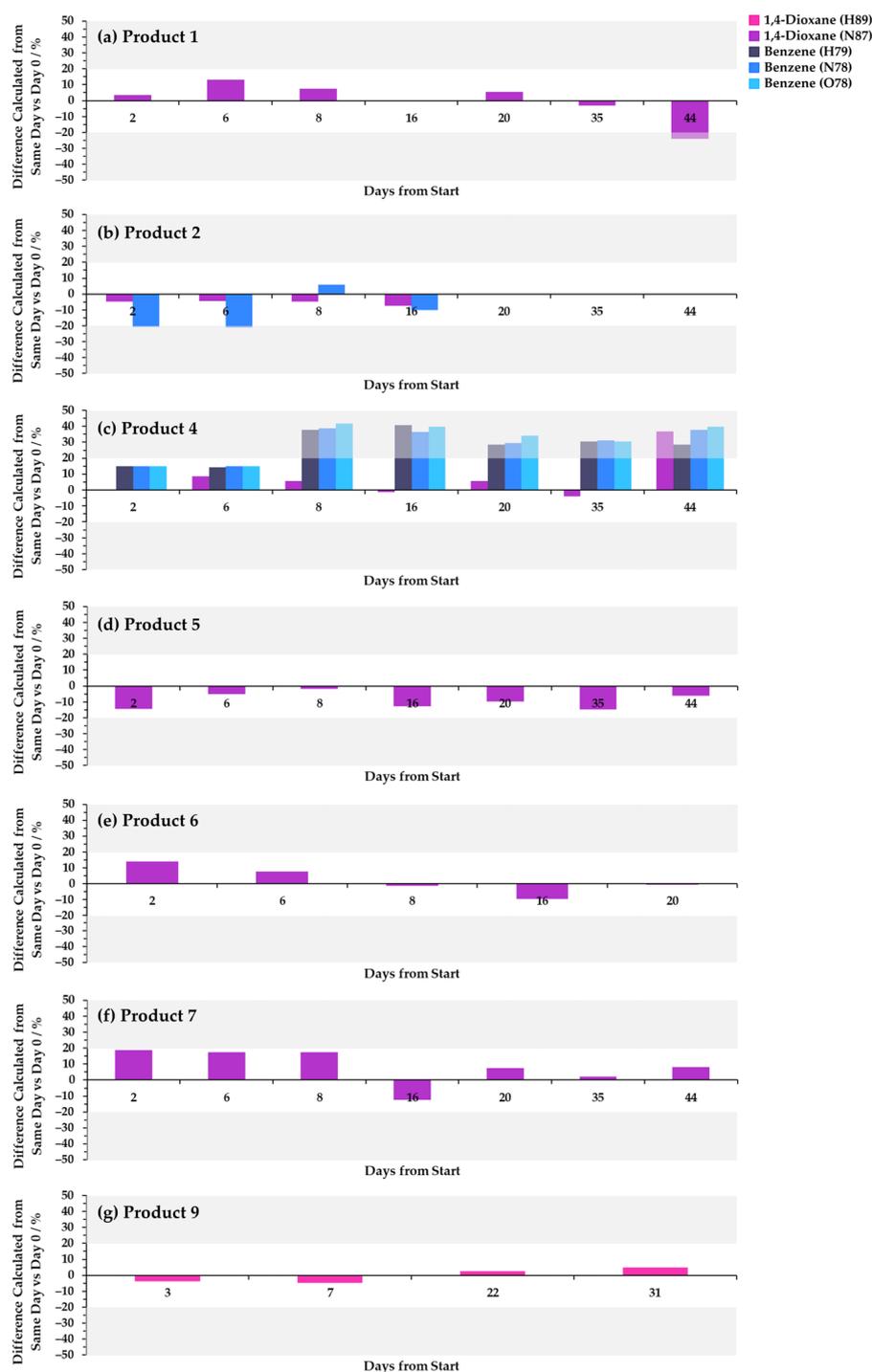


Figure 5. Difference (in %) in calculated concentration based on same-day standard additions' measurement versus those using a calibration conducted 2 to 44 days prior. Light gray bands indicate regions outside the typically accepted $\pm 20\%$ range. See the text for more details.

4. Discussion

The previous section demonstrated the ease with which standard additions can be applied in automated headspace-SIFT-MS analysis, even for multiple analytes across wide concentration ranges. In this section, implications of the results for (1) method development and (2) routine analysis workflow optimization are discussed. SIFT-MS method development and sample analysis are quite different from GC-MS, so SIFT-MS-specific workflows need to be followed. Recommended workflows are presented in detail for the first time.

4.1. Method Development Approach

A generic workflow for SIFT-MS application development and sample analysis was described recently [17]. However, specialized sample preparation techniques such as multiple headspace extraction [29] require customized workflows. This section recommends a workflow for effective method development when the method of standard additions is required for quantitative and screening analyses.

4.1.1. Preparation: Analyte Library Entry Optimization for the SIFT-MS Instrument

Prior to any method creation in software (and hence before sample analysis), it is recommended that the library entries on the specific SIFT-MS instrument be checked—primarily in terms of giving a quantitative agreement across the reagent ion–product ion pairs for each analyte. The reason for doing this is that for some analytes, there can be minor variations from instrument to instrument, or from one instrument model to another, or between helium and nitrogen carrier gases [30]. Agreement between concentrations calculated from the primary product ions (the potential quantitation ions) in a clean matrix ensures that the results obtained on the product matrix during method development are of maximum value (e.g., related to decisions on specificity).

The recommended procedure for optimizing the library entry for a specific instrument is as follows:

1. Prepare a sample of the analyte at a concentration in the low parts-per-million range (by volume in the gas phase; ppmV).
2. Run a full-scan analysis to confirm that product ions are present as stated in the library.
3. Create and run a targeted method (this improves the signal-to-noise ratio (S/N)), adding new m/z if necessary.
4. Calculate updated reaction rate coefficients, k , and product ion branching ratios, R_b , as necessary to align the concentration data generated from each primary product ion. Note that the k for the H_3O^+ reaction will normally be left unchanged—for most VOCs, the rate coefficients are calculated relative to the H_3O^+ rate [31].
5. Create an updated library entry that will be used in the workflows summarized below.

Note that for best results, this procedure should be carried out in the closest clean/blank match to the sample matrix. The most important factor is the humidity: it should be equivalent to, or slightly higher than, the most humid samples, not dry.

4.1.2. Workflow 1: Method Development for a Product Class (e.g., Haircare Products)

Table 4 summarizes the recommended workflow for the development of a standard additions–SIFT-MS method that will accommodate a broad range of formulations within a product class. It assumes that the underlying principles of ion–molecule reaction chemistry and quantitation are understood, since these principles underpin a reliable, quantitative SIFT-MS analysis [17]. Note, however, that for relatively complex matrices such as haircare products, the use of parallel, qualitative GC-MS analysis is strongly recommended, because it can be used to support claims that the SIFT-MS analysis is specific (or demonstrate that it is not—especially through nondetection). Calibration stability should be investigated during method development and validation because it can provide significant benefits for routine analysis (Section 4.2).

Table 4. The recommended headspace-SIFT-MS method development workflow for products that likely require quantitative analysis using standard additions.

Step	Sub-Step	Commentary
1. Identify products for method development	A. Select a variety of formulations from different manufacturers.	Evaluation of a variety of product formulations helps ensure broad applicability.
	B. Prepare samples for static headspace analysis. ¹	Initial analysis is qualitative.

Table 4. Cont.

Step	Sub-Step	Commentary
2. Untargeted analysis of products	A. Acquire full-scan data using SIFT-MS and GC-MS.	From these data, identify the most significant matrix volatiles.
	B. Additional data checks for SIFT-MS.	Check matrix volatiles for (1) total load on the instrument (i.e., how much reagent ion signal do they consume?), and (2) the extent of secondary chemistry.
3. SIFT-MS method development, part I	A. Create your “draft” targeted (SIM) SIFT-MS method in software tool.	Be sure to include major matrix volatiles in the method (including relevant secondary chemistry). Most often, this will be solvent, but volatiles could also be important.
	B. Reprocess the full-scan SIFT-MS data in software tool.	This extracts indicative concentration data for each volatile from the full-scan spectra acquired in Step 2.
4. SIFT-MS data evaluation ² [17]	A. Is this product ion in good agreement with one or more other ions at the lower end of the range?	This often indicates that the SIFT-MS technique is specific for the compound. However, this can sometimes be fortuitous, e.g., a compound with product ions lies at one <i>m/z</i> less and agreement is due to isotopologue interference (subtraction is usually straightforward in this case).
	B. Does the concentration appear significantly lower than expected?	If it does, then: (1) Are relevant secondary product ions included in the method? (2) Did this ion appear reliable when you updated the library parameters for the instrument? (Consider especially the different conditions between samples used for library and matrix.)
	C. For higher-reading ions, is there any indication of interference arising from the matrix or other high-concentration volatiles in the sample?	Some of these may not be flagged by software tools: (1) Isotopologues (most commonly ¹³ C). (2) Minor primary product ions, including those of very little or no significance at trace concentrations. (3) Secondary product ions. These may differ from the library if concentrations are sufficiently elevated. Watch for their isotopologues, too.
5. Confirm SIFT-MS specificity for product	A. Does the GC-MS analysis confirm that the analyte is present?	If GC-MS does not confirm the presence of analyte, then the SIFT-MS analysis may not be specific. Can SIFT-MS be applied as a rapid screening tool?
	B. Does the GC-MS analysis confirm the identity of suspected interfering species or reveal unsuspected interference in SIFT-MS?	If GC-MS confirms the interferent’s identity, can this be used to facilitate a quantitative analysis using SIFT-MS (e.g., through a subtraction approach)?
6. SIFT-MS method development, part II	A. Refine the SIFT-MS method using findings from Steps 4 and 5.	This primarily involves adjusting product ion selections.
	B. Re-extract data from scans or reanalyze samples with the SIM method.	At this point, decide on data quality required for decision making. SIM data acquisition will give better insights for quantitation (especially for Step 7).
	C. Reevaluate the data.	See step 4 above. If acceptable, move to Step 7, otherwise repeat Steps 4 and 6.
7. Determine quantitation approach	A. Reassess suitability of the headspace approach for the matrix.	Confirm that the analysis is best served by the method of standard additions. Or is the matrix suited to static headspace analysis (simple calibration) or multiple headspace extraction (MHFE), for example?
	B. Evaluate calibration stability.	For each product, assess the calibration stability over days to weeks to determine the frequency of recalibration.
8. Validation	A. Method should be validated using standard protocols for each product.	Validate on individual product ahead of routine sample analysis because performance is likely to vary by formulation. ³ See [32] for general guidance for headspace methods. Additionally, for standard additions, these should be optimized to the specific product. ⁴

¹ The inclusion of neat products and, for example, dilutions in water early in method development can aid in the confirmation of interference since often, the interferent(s) will exhibit different headspace partitioning, affecting reagent ion–product ion pairs differently. In the method of standard additions (with multiple additions) [19], different slopes and intercepts provide parallel insights to the developer/analyst. ² This step should be followed for each analyte in each product. Efficiencies can be gained by tabulating concentration data calculated by each product ion [16,17]. ³ Variations arise due to fundamental differences in headspace partitioning between matrices and the fact that changes in the headspace composition can change the SIFT-MS quantitation ion(s). See, for example, the change in quantitation ion for 1,4-dioxane in product 9 (Table 3). ⁴ Standard additions’ spikes were not optimized in this study, except for benzene with product 4 (Section 2.3 and Figure 4a).

4.1.3. Workflow 2: Method Customization for a Previously Untested Product

The approach described in Section 4.1.2 results in a generic method, although at Step 8 (Table 4) it emphasizes the need to validate the method on the specific product/formulation. When applying the method developed in Step 7 of the previous workflow to a product not included in the generic method development, the degree of redevelopment will depend on the similarity, or lack thereof, to previously tested products. In particular, the need for a complementary analysis by GC will depend on the complexity of the new product's matrix.

The recommended workflow for a new product/formulation is as follows:

1. Acquire SIFT-MS full-scan and SIM data—the latter use the generic method as in Step 7 in Table 4.
2. Identify major matrix volatiles and ensure that the product matrix does not overload the instrument (Step 2, Table 4).
3. Evaluate the specificity of the individual SIFT-MS product ions (Step 4, Table 4).
4. If there are concerns regarding specificity, then use full-scan GC-MS to confirm the presence of interfering compounds or not (Step 5, Table 4). Decide the appropriateness of a screening procedure versus a quantitative method for this formulation.
5. Customize the method to the product by eliminating product ions that report high (Step 6, Table 4).
6. Validate the method for the product (Step 8, Table 4).

4.2. Proposed Workflow for Routine Analysis

A validated procedure for a specific product/formulation enables the analyst to conduct routine analysis. This section summarizes workflows for quantitative and rapid screening analyses using SIFT-MS. It is anticipated that a quantitative analysis will be suited to a subset of products, because matrix complexity and (potential) variability will impact the ability of the SIFT-MS technique to provide a specific analysis (see Table 4, Step 5). Hence, two workflows are outlined in the subsections below: one for screening and one for quantitative analysis. In either case, if calibration is stable for days to weeks as observed in this study for benzene and 1,4-dioxane (assessed in Step 7B, Table 4), then workflows can be made more efficient, reducing the time taken to report results and increasing sample throughput. This is illustrated in Figure 6 using sequence schedules for (a) GC-MS and (b) SIFT-MS methods that utilize full standard additions on each sample, plus (c) a temporal separation of standard additions' calibration for SIFT-MS. With the rapid analysis provided by SIFT-MS, there is potential to increase throughput 8- to 30-fold compared to a conventional GC-MS analysis, while cutting by at least two-thirds the time to report the first result. In addition to the economic advantages of delivering faster results to customers and generating more revenue through higher throughput, reduced calibration demand provides environmental advantages through reduced solvent usage.

4.2.1. Workflow 3: Routine, Rapid Screening Analysis

Based on the principle that SIFT-MS will give an upper limit to the true concentration [17] due to its lower inherent specificity compared to chromatographic methods, the recommended routine workflow is:

1. Calibrate for standard additions. The required frequency of calibration was determined in method development (Step 7 of Table 4) and confirmed for the product during method validation (Step 8).
2. Prepare and analyze samples according to the standard operating procedure.
3. Apply calibrations to individual product ions and subtract blanks.
4. Is the reported concentration above the threshold for the lowest-reading ions?
 - Yes: test using the standard GC-MS or LC method.
 - No: product passes.

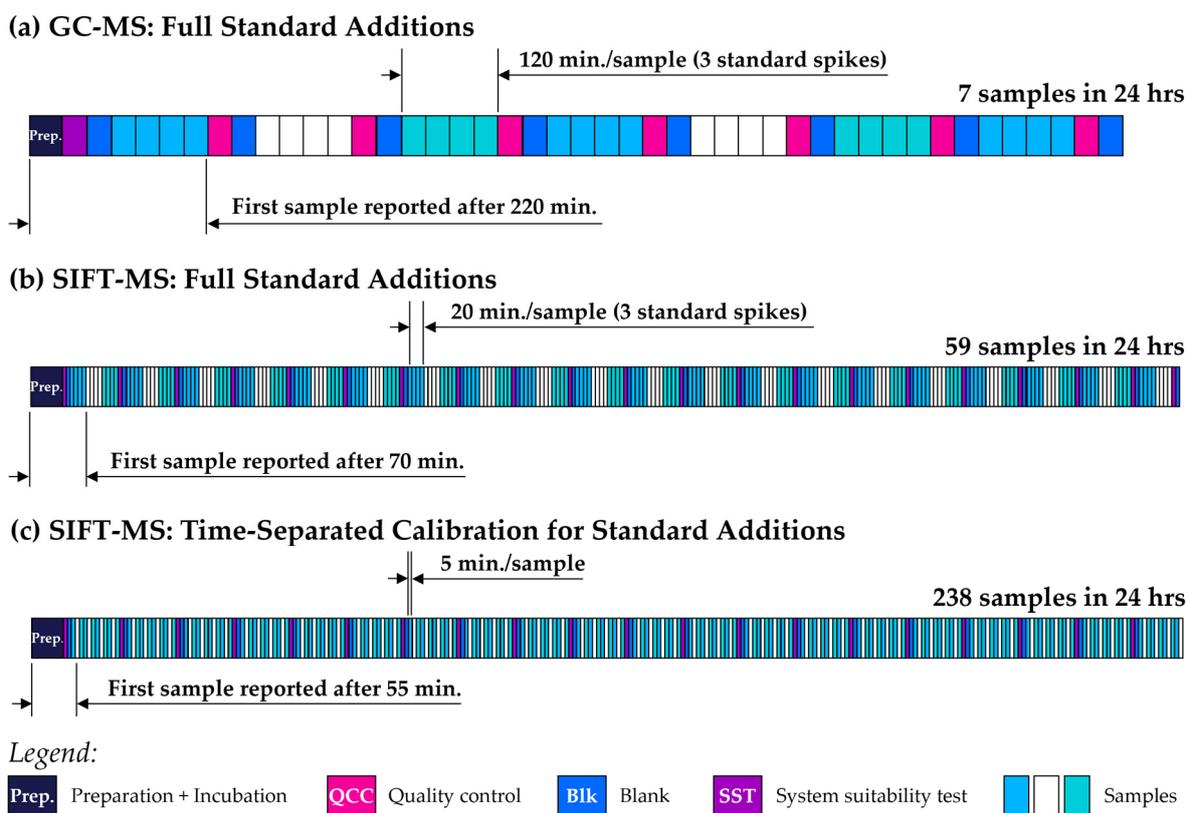


Figure 6. Sequence schedules for efficient standard additions analysis of benzene and 1,4-dioxane using GC-MS and SIFT-MS over a 24 h period. Full standard additions (with three calibration spikes—indicated back-to-back using the same fill color) for (a) GC-MS and (b) SIFT-MS. With calibration offset in time, SIFT-MS can achieve a throughput equivalent to a static headspace analysis (c).

4.2.2. Workflow 4: Routine Quantitative Analysis

When SIFT-MS quantifies the analyte with high specificity, the workflow for quantitative analysis can be utilized.

1. Calibrate for standard additions. Calibration frequency was determined in method development (Step 7, Table 4) and validation (Step 8).
2. Prepare and analyze samples according to the standard operating procedure.
3. Apply calibrations to individual product ions and subtract blanks.
4. Inspect data for product ion agreement observed in method development. Is behavior similar?
 - Yes: process data and report results.
 - No: (i) Retest and report using the standard GC-MS or LC method. (ii) Further investigate the product using SIFT-MS to understand why there was a problem and gauge whether it is an outlier or a change (e.g., to the formulation) that could cause issues for routine testing in future. If the latter, then return to Workflow 2.

5. Conclusions

The compatibility of automated headspace-SIFT-MS with the method of standard additions (with multiple additions) [19] was demonstrated in this study. Using this sample preparation approach, SIFT-MS simultaneously analyzed benzene, 1,4-dioxane, and formaldehyde in hair and skin cleansing PCPs with LOQs in the 1.0–15 ng g⁻¹, 0.19–4.5 µg g⁻¹, and 2.8–3.7 µg g⁻¹ ranges, respectively (product- and quantifying ion-independent). Higher LOQ ranges for 1,4-dioxane and formaldehyde arose from poorer headspace partitioning compared to benzene. For a given product, LOQs across SIFT-MS reagent ion–product ion pairs varied due to (i) different sensitivities and (ii) some ions

suffering from matrix interference. Nevertheless, all LOQs evaluated here easily met the needs of current regulations to the best of the authors' knowledge. The ability to analyze chromatographically challenging formaldehyde in the same analytical procedure as benzene and 1,4-dioxane means that it is unnecessary to conduct a duplicate analysis using LC and GC-MS.

Method development and routine analysis protocols were proposed based on this study and prior work by the authors and their collaborators. By conducting SIFT-MS method development on complex systems in parallel with GC-MS, and by carefully examining the SIFT-MS results across the reagent ion–product ion pairs, developers can have greater confidence in the ability of SIFT-MS to reliably quantify volatile impurities in condensed-phase PCPs. By using multiple pairs per compound, where possible, modest variations in the matrix can usually be readily accommodated. A more rigorous approach optimizes and validates the method for each product to be tested.

Future work applying the method of standard additions with SIFT-MS should look to compare quantitation across measurement platforms, especially for formaldehyde. Broader application within, and beyond, this product category should also be considered. Further investigations should be conducted to confirm the feasibility of separating the standard additions' calibration curve from routine single static headspace analysis of a given formulation.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/analytica5020010/s1>, Tables S1–S3: full concentration data for benzene, 1,4-dioxane, and formaldehyde, respectively.

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