

Article

Pharmaceutical Residual Solvent Analysis: A Comparison of GC-FID and SIFT-MS Performance

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Abstract: Residual solvents in pharmaceutical excipients, active pharmaceutical ingredients (APIs), and finished products are usually analyzed using gas chromatography (GC)-based techniques according to a pharmacopeial monograph, such as the United States Pharmacopeia's (USP) chapter <467>. GC analyses are often slow, which limits sample throughput. Selected ion flow tube mass spectrometry (SIFT-MS) removes the rate-limiting chromatographic separation step, potentially offering faster sample analyses. This approach was demonstrated recently with the publication of an alternative SIFT-MS procedure which was successfully validated against the performance criteria in USP chapter <1467>. The present study expands upon the previous work by conducting a head-to-head comparison of GC-flame ionization detection (GC-FID) and SIFT-MS procedures. The results obtained in this cross-platform study demonstrated similar performance for the GC-FID and SIFT-MS procedures for linearity ($R^2 > 0.94$ and 0.97 , respectively) and repeatability (<17%RSD and <10%RSD). For accuracy and recovery, acceptance criteria (within 20%) were achieved for most compounds across the two drug products (SIFT-MS suffered fewer failures, possibly due to shorter wait times prior to analysis). Additionally, SIFT-MS analyzed samples over 11-fold faster than GC-FID, increasing daily sample throughput and reducing the time taken to determine the result. This study therefore suggests that residual solvent analysis using SIFT-MS may support workflow improvements for pharmaceutical manufacturers.



Citation: Perkins, M.J.; Hastie, C.; Whitlock, S.E.; Langford, V.S. Pharmaceutical Residual Solvent Analysis: A Comparison of GC-FID and SIFT-MS Performance.

AppliedChem **2023**, *3*, 290–302.<https://doi.org/10.3390/appliedchem3020018>

appliedchem3020018

Academic Editor: Dag Ekeberg

Received: 3 April 2023

Revised: 11 May 2023

Accepted: 15 May 2023

Published: 1 June 2023



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Keywords: SIFT-MS; selected ion flow tube mass spectrometry; DIMS; residual solvents; headspace analysis; high-throughput analysis

1. Introduction

Residual solvents in pharmaceutical products are defined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) as “organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques” [1] (p. 1). Residual solvents are grouped into three classes based on toxicity. Class 1 solvents are known to have unacceptable toxicities and should be avoided (the exception is 1,1,1-trichloroethane, which is an environmental hazard). Solvents in Class 2 are associated with less severe toxicity but should be limited to protect patients. Finally, Class 3 solvents are those with low toxic potential and should be used where practical to do so. Note that Class 2 solvents are further divided into subclasses 2A, 2B, and 2C. This is based largely on the combination of the permitted daily exposure (PDE) determined from toxicological considerations (concentration in solution) and the degree to which they partition to headspace. From Class 2A to 2C, there is generally significant diminution in headspace partitioning, to the extent that the United States Pharmacopeia (USP) General Chapter <467> Residual Solvents [2] states that acceptance criteria are not met for several compounds in Class 2C, and an alternative procedure must be used.

Analytical procedures for determination of residual solvents are not prescribed by the ICH Q3C guideline [1]. It states (p. 4), “Any harmonized procedure for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible.” Several analytical procedures are described in USP <467> [2] (two sets of GC operating conditions and three sets of headspace conditions) to accommodate the broad range of drug products and residual solvents within the scope of this method. These procedures enable the levels of all Class 1 and most Class 2 residual solvents to be evaluated using gas chromatography with flame ionization detection (GC-FID) in water-soluble and -insoluble articles. Alternative procedures to USP chapter <467> [2] are permitted if acceptance criteria are met [3]. For example, a generic GC-FID procedure that utilizes less sample, lower-reactivity solvent (dimethyl acetamide, DMAC), and has a faster run time was developed for use with new chemical entities (NCEs) [4]. This method has a run time of 20 min, compared to 60+ min for the compendium method [2].

Development of alternative procedures for residual solvent analysis is not restricted to chromatographic techniques. A viable commercially available alternative approach could be based on direct-injection mass spectrometry (DIMS), which analyzes volatile organic compounds (VOCs) directly from air and headspace [5,6]. DIMS techniques eliminate the rate-limiting chromatographic separation step because they utilize soft chemical ionization, which provides high specificity in real time while not reacting to any significant extent with major components of air (e.g., nitrogen, oxygen, carbon dioxide, argon, and water). Direct analysis, coupled with high sensitivity, means that samples can be analyzed at higher throughputs than can be achieved using chromatographic methods, potentially providing rapid sample screening that complements conventional methods. For example, four-fold higher sample throughputs have been reported for static headspace analysis of VOCs in porcine plasma [7] and drinking water [8], while multiple headspace extraction (MHE) of styrene residue in polystyrene gave an eight-fold throughput enhancement [9].

Selected ion flow tube mass spectrometry (SIFT-MS) is a DIMS technique that has emerging applications for analysis of volatile impurities—including residual solvents—in pharmaceutical products [10,11]. Figure 1 provides a schematic overview of the key differences between SIFT-MS and GC-FID instrumentation. Recently, SIFT-MS has been demonstrated as an acceptable alternative procedure for analysis of water-soluble Class 2A and Class 2B residual solvents based on performance criteria being met [12,13]. That study demonstrated that SIFT-MS can analyze up to 17-fold more samples per day than GC-FID based on daily calibration of each technique and 24 h operation [13]. Biba et al. [12] did not, however, directly compare the new SIFT-MS-based alternative procedure to the standard GC-FID method—a requirement for adoption of the SIFT-MS alternative procedure by the pharmaceutical industry.

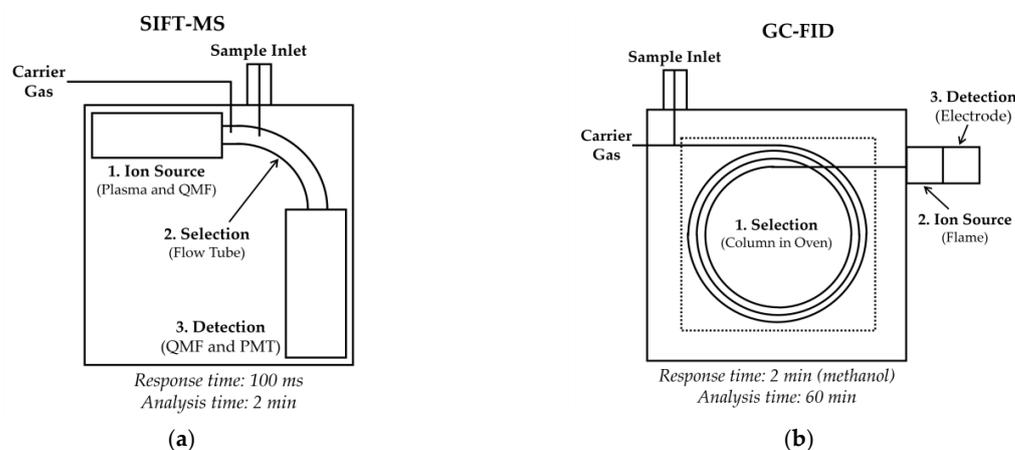


Figure 1. Schematic overview of the (a) SIFT-MS and (b) GC-FID techniques illustrating the different approach to analysis in DIMS compared to conventional chromatography. QMF = quadrupole mass filter; PMT = particle multiplier tube.

The present study addresses the need to compare the performance of the SIFT-MS alternative procedure [12] to the standard USP <467> procedure using GC-FID [2]. It does this by analyzing identically prepared samples on side-by-side SIFT-MS and GC-FID instruments. Specifically, comparison is made of the repeatability and linearity of the standard solutions, and the accuracy and recovery for spiked solutions prepared from two finished acetaminophen (paracetamol) products—a tablet and an oral suspension. Results obtained for these formulations also enable several recommendations to be made when applying the SIFT-MS procedure to new products.

2. Materials and Methods

2.1. Automated SIFT-MS Analysis

The SIFT-MS analytical technique has been described in detail previously [10,14]. Briefly, SIFT-MS is a DIMS technique that analyzes air and headspace continuously by using ultra-soft chemical ionization that efficiently ionizes a very broad range of VOCs, but does not ionize the bulk constituents of air. A microwave discharge in air is used to generate the reagent ions, with eight available (H_3O^+ , NO^+ , $\text{O}_2^+\bullet$, $\text{O}^-\bullet$, OH^- , $\text{O}_2^-\bullet$, NO_2^- and NO_3^-) on the SIFT-MS instrument used in this study (Voice200*ultra*; Syft Technologies Limited, Christchurch, New Zealand) [15]. Rapid switching of reagent ions provides high specificity because the multiple reaction mechanisms give independent measurements of each analyte, while the absence of chromatographic separation means that it is straightforward to analyze VOCs of diverse chemical functionalities. Instrument detection limits in the part-per-trillion by volume (pptV) range are typically achieved for 1 s ion dwell times for direct analysis of air, with no preconcentration or drying required [16,17].

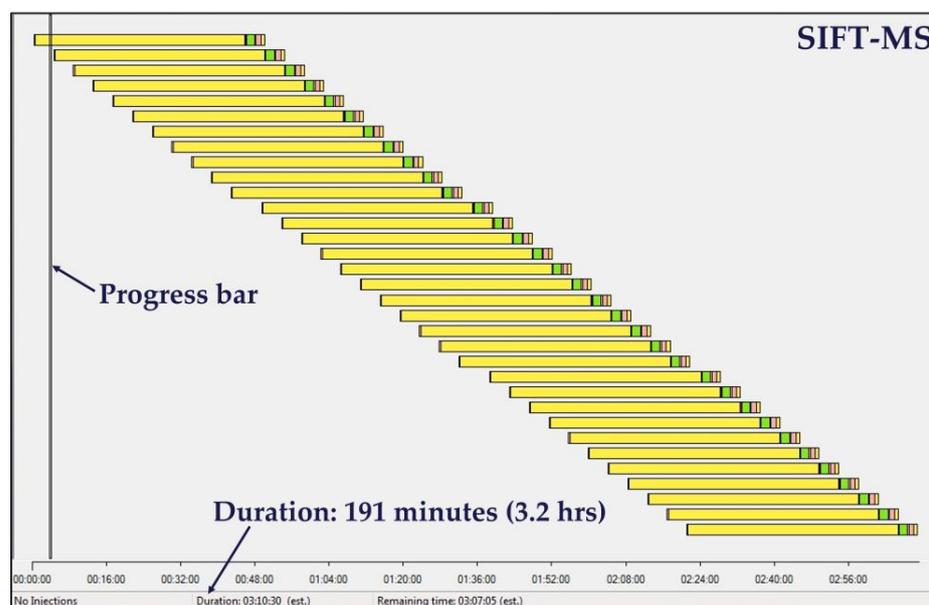
The SIFT-MS instrument was equipped with a GERSTEL multipurpose (MPS) autosampler (Robotic Pro; Mülheim, Germany). Samples were incubated in a virtual twelve-place GERSTEL agitator (composed of two physical six-place agitators) prior to sampling of the headspace and subsequent injection into the SIFT-MS instrument through a GERSTEL septumless sampling head. The GERSTEL Maestro software's "PrepAhead" sequence schedule is shown in Figure 2a.

The headspace conditions for all analyses used 6 mL of solution in a 20 mL headspace vial incubated at 60 °C for 45 min. A 2.5 mL aliquot of headspace was removed via a heated syringe (150 °C) and injected into the SIFT-MS instrument's sample inlet at 25 $\mu\text{L}\cdot\text{s}^{-1}$, with a zero-air make-up gas flow through the heated inlet (150 °C) to ensure that the total flow into the instrument was 25 $\text{mL}\cdot\text{min}^{-1}$. After the injection, the syringe was flushed with zero air for 1 min at 200 $\text{mL}\cdot\text{min}^{-1}$. Figure 3 shows an example headspace injection for Class 2A solvents, where data for all reagent ions were collected in the same analytical run and concentrations are calculated by averaging data from 50 to 120 s. For residual solvents analysis, some compound-dependent signal drift is observed during sample injection, but this is consistent as demonstrated by the good repeatability (Table 1).

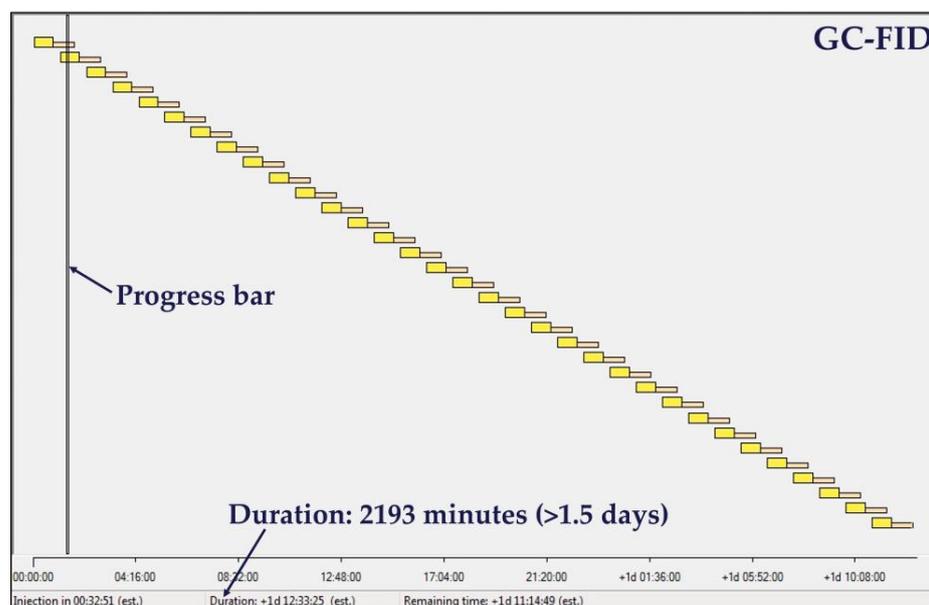
Residual solvents reported in this article were analyzed using the quantitation ions summarized in Table S1 [18–31]. The naming convention follows USP <467> [2]. The SIFT-MS reagent ions are rapidly switchable, so all positively charged ions were used in the method to provide the best combination of specificity and sensitivity. When multiple quantitation ions are used for an analyte, software cross-compares these, rejecting high-reading ions that suffer interference [11].

2.2. Automated GC-FID Analysis

GC-FID analysis was conducted using headspace operating parameter set 3 and procedure A of USP General Chapter <467> Residual Solvents [2]. The Agilent 7890 GC-FID (Agilent Technologies, Santa Clara, CA, USA) was coupled with a multipurpose autosampler (MPS Robotic Pro (dual head); GERSTEL, Mülheim, Germany). Samples were incubated for 45 min at 80 °C. The optimized schedule using the GERSTEL Maestro PrepAhead software is shown in Figure 2b.



(a)



(b)

Figure 2. Sequence schedules for automated (a) SIFT-MS and (b) GC-FID instruments running their <1467> and <467> methods, respectively. Rapid sample analysis with SIFT-MS enables 36 samples to be analyzed in just over 3 h rather than 36 h for GC-FID. These schedules were captured while sequences were running, as indicated by the vertical progress bar. Key to colors: yellow bars represent incubation/wait time, green sample injection (slow for SIFT-MS), pink syringe flush, and orange sample analysis (slow for GC-FID; synchronous with injection for SIFT-MS).

A 1 mL aliquot of headspace was injected at $200 \mu\text{L}\cdot\text{s}^{-1}$ into the split/splitless inlet (5:1 split ratio) of the GC. Separation was achieved using a VF-624ms column (30 m \times 0.32 mm \times 1.8 μm ; Agilent Technologies, Santa Clara, CA, USA) with a helium flow rate of $2.15 \text{ mL}\cdot\text{min}^{-1}$. The oven was initially held at $40 \text{ }^\circ\text{C}$ for 20 min before a ramp of $10 \text{ }^\circ\text{C}\cdot\text{min}^{-1}$ to $240 \text{ }^\circ\text{C}$, where it was held for 20 min. Eluting components were detected using a flame ionization detector (FID) operating at $250 \text{ }^\circ\text{C}$ with nitrogen makeup gas, hydrogen, and air flows of 25, 30, and $400 \text{ mL}\cdot\text{min}^{-1}$, respectively. A representative chromatogram is shown in Figure 4.

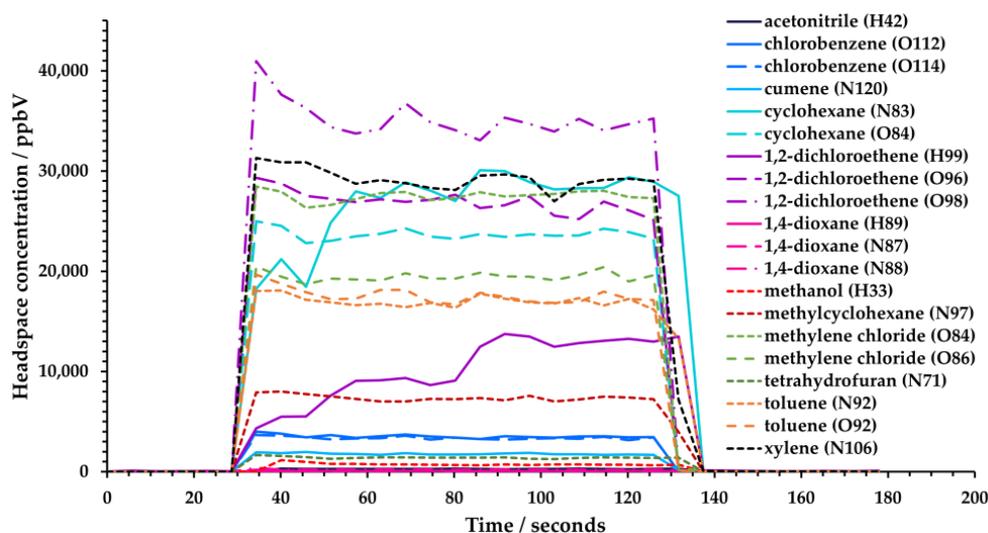


Figure 3. Example headspace-SIFT-MS analysis of a standard showing product ions for Class 2A compounds. See the text for further details.

Table 1. Comparative performance of SIFT-MS and GC-FID (versus USP <467> acceptance criteria [2]) for linearity, repeatability, accuracy, and recovery on identically prepared and scheduled samples. These results are derived from the mean of valid replicates.

Parameters	Acceptance Criteria	Results: SIFT-MS	Results: GC-FID
Linearity	$R^2 > 0.90$	$R^2 \geq 0.97$	$R^2 \geq 0.94$
Precision: Repeatability	RSD is <20% ¹	1.4–9.5%RSD	2.0–16.9%RSD
Accuracy	<20%		
1. Tablet			
a. 0.5 (50%) level	0.4–0.6	0.404–0.511	0.424–0.519 Exceptions: methylcyclohexane 0.387, pyridine 0.624, 1,2-dimethoxyethane 0.723
b. 1.0 (100%) level	0.8–1.2	0.844–1.126	0.819–1.079 Exceptions: 1,4-dioxane 0.719, methanol 0.744, acetonitrile 0.799
2. Oral suspension			
a. 0.5 (50%) level	0.4–0.6	0.429–0.564 Exceptions: 1,4-dioxane 1.002 (1 ion), hexane 0.627	0.420–0.570 Exceptions: 1,2-dimethoxyethane 0.386
b. 1.0 (100%) level	0.8–1.2	0.883–1.134 Exception: 1,4-dioxane 1.361 (1 ion)	0.893–1.079 Exceptions: 1,2-dimethoxyethane 0.769, methanol 0.771, 1,4-dioxane 0.772, MBK 0.792, acetonitrile 0.793, chloroform 0.796
Recovery	80–120% ²		
1. Tablet			
a. 0.5 (50%) level		81.3–102.3%	84.9–103.8% Exceptions: methylcyclohexane 77.5%, pyridine 124.8%, 1,2-dimethoxymethane 144.6%
b. 1.0 (100%) level		84.4–112.6%	89.4–107.9% Exceptions: 1,4-dioxane 71.9%, methanol 74.4%, acetonitrile 79.9%
2. Oral suspension			
a. 0.5 (50%) level		85.8–112.8% Exceptions: hexane 125.4%, 1,4-dioxane 200.3% (1 ion)	84.0–114.1% Exceptions: 1,2-dimethoxyethane 77.2%
b. 1.0 (100%) level		88.3–113.4% Exception: 1,4-dioxane 136.1% (1 ion)	88.2–107.9% Exceptions: 1,2-dimethoxymethane 76.9%, methanol 77.1%, 1,4-dioxane 77.2%, MBK 79.2%, chloroform 79.6%, acetonitrile 79.3%

¹ For “at least six independent *Spiked sample solution* preparations from the same lot” for each solvent present [2]. Here, six replicates were used. ² “The mean recovery for each *Spiked sample solution* should be 80–120%” [2].

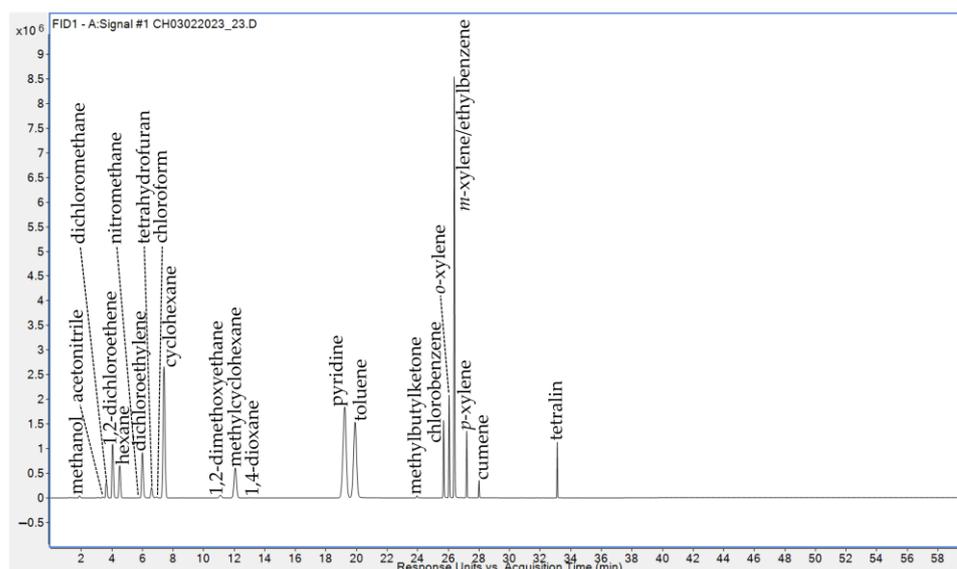


Figure 4. A representative, annotated GC-FID chromatogram for the combined Class 2A and 2B mixture.

2.3. Sample Preparation and Analysis

The study was conducted in two separate runs (Table S2) and different commercial standards were utilized for each. For Run 1, USP Class 2A and 2B standards were used (part numbers 1601281 and 1601292, respectively; USP, Rockville, MD, USA), while for Run 2, Sigma-Aldrich Class 2A and 2B standards were employed (part numbers PHR1064 and PHR1065, respectively; Sigma-Aldrich, Gillingham, UK).

Two acetaminophen (paracetamol) formulations were selected for the accuracy and recovery exercise: tablets (500 mg per tablet; Co-op private label, UK) and an oral suspension (250 mg per 5 mL dose; Calpol Six-plus sugar-free, Johnson & Johnson, High Wycombe, UK).

Preparation of samples (combining Classes 2A and 2B) was conducted batch-wise, as outlined in Table S2. Review of data from Run 1 indicated that drift was occurring based on sample preparation order due to evaporation of solvents with high partitioning to headspace. This also meant that spikes for the accuracy and recovery exercise did not retain integrity compared to the calibration set. To mitigate this effect, an important change was made for Run 2: the same container of standard stock solution was not sampled for all calibrations and spikes (although it had been capped at each step for Run 1). In Run 2, the stock solution was decanted into smaller capped containers and a new container was used for each step in the preparation process. An exception was made for the calibrations, where the same container was used to enable any evaporative losses to be monitored. In addition to differential preparation of calibration standards, they were run in triplicate at the beginning and end of the sequence to gauge possible instrument/sample drift in the method itself. These changes significantly improved performance in Run 2.

For both GC-FID and SIFT-MS measurements, the samples were analyzed in the same sequence for each run, as summarized in Table S2. Different sequences were used for Runs 1 and 2 to reduce drift and better characterize what remained.

3. Results

This section summarizes linearity, repeatability, accuracy, and recovery results obtained from side-by-side analysis of Class 2A and 2B solvents in water-soluble articles using GC-FID and SIFT-MS. This differs from the previous study [12], in which the specificity, range, and limit of quantitation (LOQ) were also evaluated for SIFT-MS analysis of Class 2 residual solvents. Full data for the present study are provided in the Supplementary Materials.

3.1. Linearity

Selected linearity data (acquired in Run 1) for SIFT-MS and GC-FID over the range 0.2 to 1.0 of the normalized concentration relative to the solvent limit defined in USP<467> [2] are shown in Figure 5. This is referred to as the “standard level”. Full data are given in Tables S3–S6 and Figures S1–S4 for both techniques. Class 2A and 2B results are tabulated separately. SIFT-MS responses are plotted in part-per-million by volume (ppmV) because volume:volume units are readily calculated by software based on instrument, library, and sample measurement parameters [11]. This unit also has the benefit of internally normalizing reagent ion drift (should it occur), since it is proportional to the ratio of product ion to reagent ion during sample measurement [11]. GC-FID responses are shown as peak area. Note that for most analytes with low response (Tables S5 and S6), the upper standard concentration (1.0) in GC-FID data was eliminated for calculation of linear regression coefficients (R^2) because a dip in signal was evident. SIFT-MS linear regression coefficients were calculated across the full range (0.2 to 1.0). The results are summarized in Table 1, showing that both techniques easily meet acceptance criteria. SIFT-MS, however, usually performed slightly better.

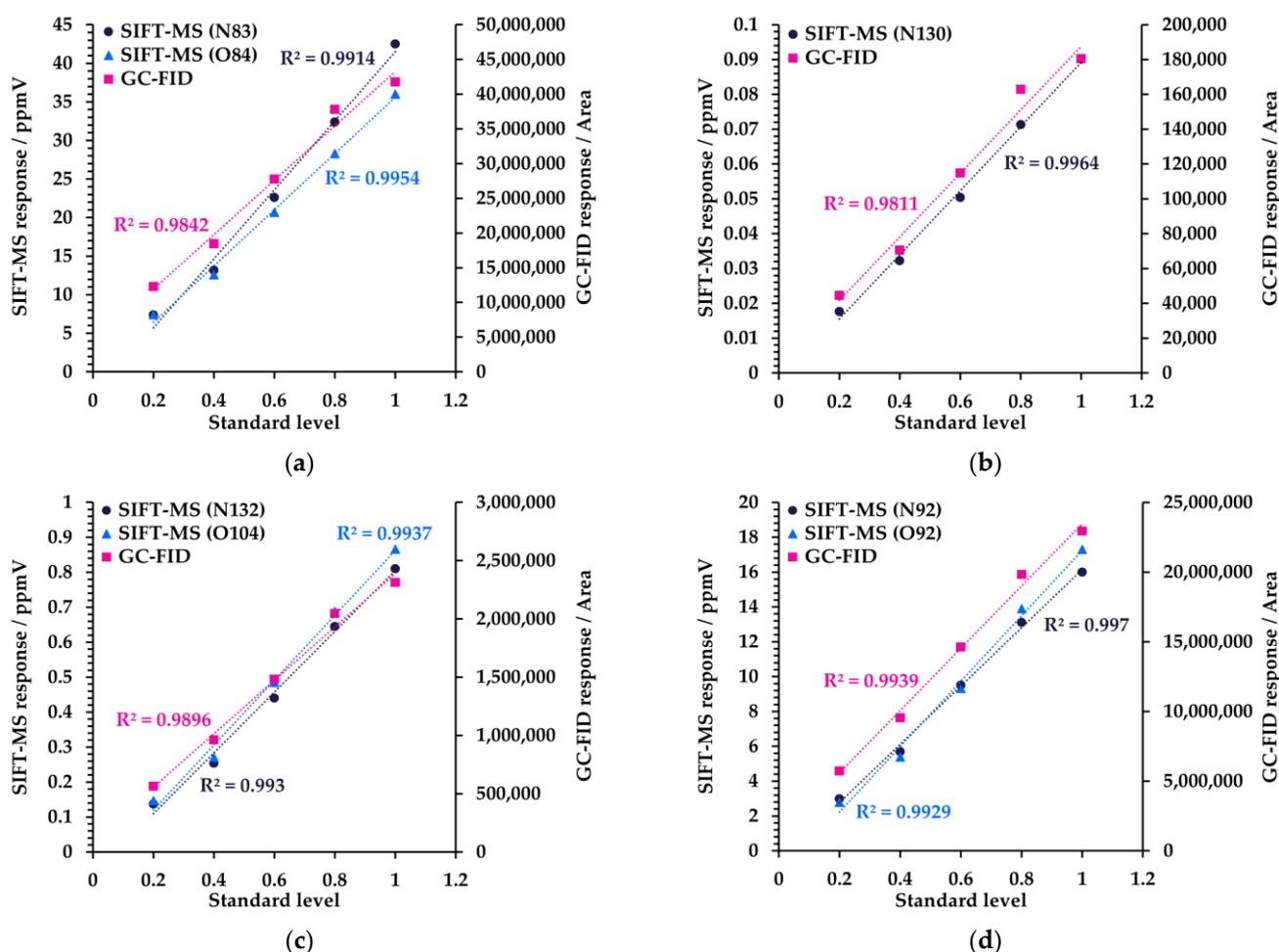


Figure 5. Linearity of SIFT-MS and GC-FID measurements for selected compounds: (a) cyclohexanone, (b) methylbutylketone (MBK), (c) tetralin, and (d) toluene. Linear regression coefficients (R^2) are shown. Full data are given in Tables S3–S6 and Figures S1–S4.

3.2. Precision

Table 1 summarizes the results obtained for repeatability across six replicates in Run 1. Full data are provided in Tables S7a and S8a for SIFT-MS and Tables S9a and S10a for

GC-FID for Class 2A and 2B, respectively. For both SIFT-MS and GC-FID, acceptance criteria are met for all compounds. It must, however, be noted that the largest relative standard deviation (RSD) for GC-FID arises only because individual xylene isomers have been summed to enable direct comparison with SIFT-MS. The individual isomers perform better, with *m*-, *o*-, and *p*-xylene having RSDs of 6.9, 4.1, and 6.9%, respectively. Taking this into account, 1,2-dimethoxymethane has the highest RSD (10.5%) for an individual analyte.

Repeatability data for Run 2 are shown in Tables S7b–S10b of the Supplementary Materials because they emphasize one of the largest challenges of residual solvents analysis: loss of volatile solvents from aqueous standards. In these tables, triplicate standards were analyzed before and after collection of accuracy and recovery data (Table S2). Drift is generally greater for more hydrophobic compounds. Calculation of repeatability from the two sets of triplicate measurements results in larger RSDs than the dedicated repeatability study during Run 1 (Table 1), but the results are useful for demonstrating that great care needs to be taken with experimental design.

Intermediate precision (SIFT-MS) was not re-investigated here, since it was described previously for different analysts using different standards and samples [12]. The reproducibility of SIFT-MS data across multiple geographically separated instruments and analysts will be described in a future publication.

3.3. Accuracy

Accuracy was calculated from the value measured for the spiked sample (0.5 (50%) or 1.0 (100%)) divided by the mean measurement of the 1.0 (100%) level calibrations analyzed in triplicate before and after the run, as shown in Equation (1).

$$\text{Accuracy} = \frac{\text{Response for Replicate}}{\text{Mean Response of Calibration (1.0)}} \quad (1)$$

These calibrations are summarized in Tables S7b–S10b for Run 2. During data analysis, it was discovered that several replicates for GC-FID analysis appeared to be compromised because the responses for all analytes were significantly lower than the other two replicates. These are indicated in gray text in Tables S13b, S14b, S17b and S18b, and are not included in calculation of accuracy. Several replicates appear slightly lower in the SIFT-MS data, but not to the same extent as for GC-FID, so these have been retained in all calculations.

Accuracy data from Run 2 (i.e., after improvement of the experimental procedure) are summarized in Table 1 and are calculated from the mean of replicate samples. Figure 6 visualizes the results across individual valid replicates. Full data across both tablet and oral suspension formulations are provided in the Supplementary Materials (Tables S11–S18) for both runs (Runs 1 and 2 have “a” and “b” identifiers, respectively, added to the above numbers).

Overall, the SIFT-MS results display higher accuracy than the GC-FID results, as measured in terms of the number of compounds that meet the acceptance criteria. For the tablet samples, SIFT-MS meets the acceptance criteria for all analytes (within 20% of standard) when means are used (Table 1), although for the occasional replicate, failure is evident (Figure 6). For GC-FID analysis, several failures per spike level occurred. The oral suspension was more challenging for both techniques. The SIFT-MS results will be discussed in more detail below. Just hexane failed at the 0.5 level and one quantitation ion of 1,4-dioxane failed at the 1.0 level.

In summary, GC-FID fails to achieve acceptance criteria more frequently than SIFT-MS. 1,2-Dimethoxyethane is problematic at both spike levels for GC-FID, while various compounds fall just short of the accuracy criteria at one level (Table 1).

3.4. Recovery

Analogous to accuracy (Section 3.3), recovery data are summarized here from Run 2, while full data for both runs are given in Tables S19–S26 of the Supplementary Materials.

Recoveries (as a percentage) were calculated against the 1.0-level calibration data (mean across the pre- and post-run calibration samples; Tables S7b–S10b) scaled by the spike level of the sample (0.5 or 1.0; see Equation (2)). The results obtained for SIFT-MS and GC-FID are given in Table 1 and Figure 7. Failures to meet acceptance criteria largely parallel those described above for accuracy.

$$\text{Recovery (\%)} = \frac{\text{Response for Replicate}}{\text{Mean Response of Calibration (1.0)} \times \text{Spike level}} \times 100 \quad (2)$$

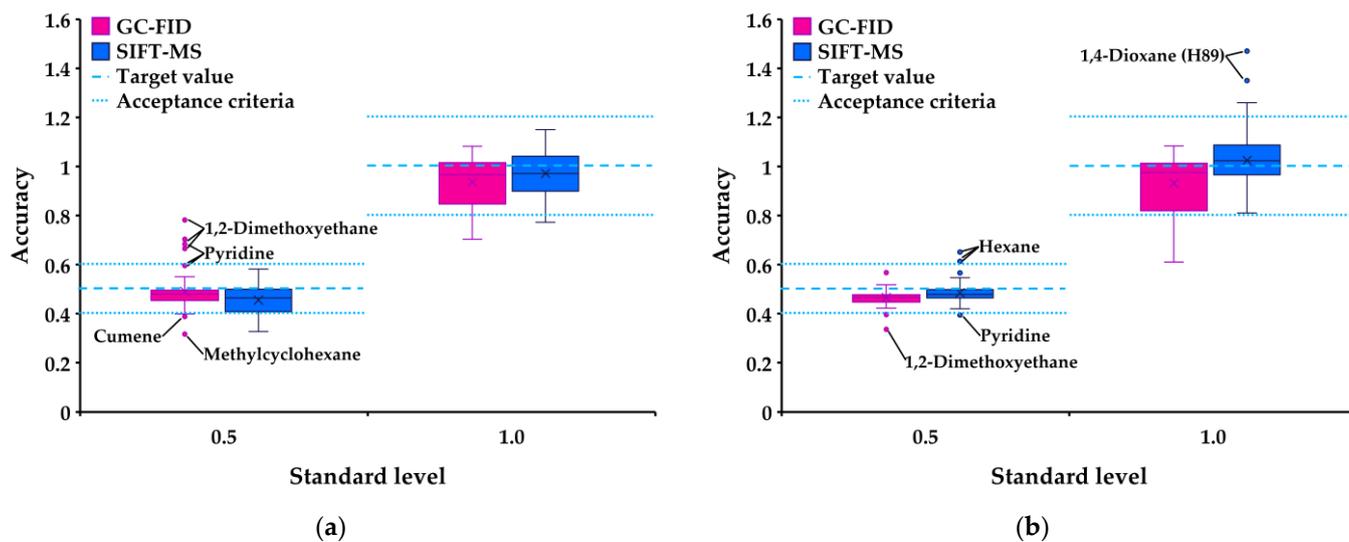


Figure 6. Box and whisker plots summarizing GC-FID and SIFT-MS accuracy for all valid Run 2 replicates for spiked solutions prepared from (a) tableted and (b) oral suspension formulations of acetaminophen (paracetamol). Standard levels were 0.5 (50%) and 1.0 (100%).

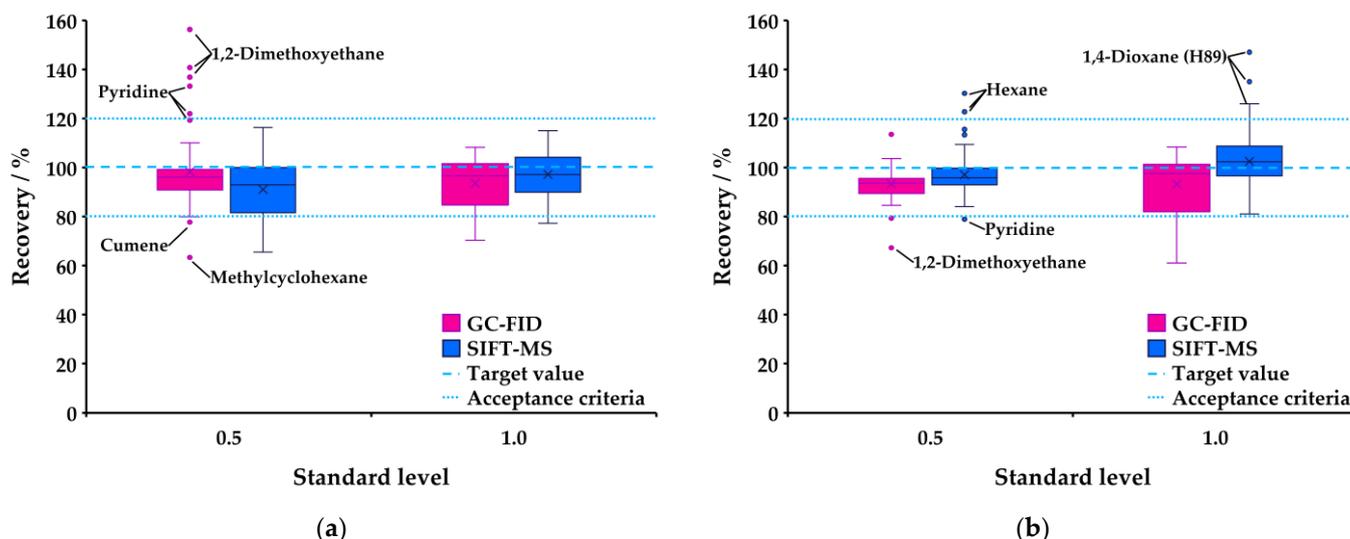


Figure 7. Box and whisker plots summarizing GC-FID and SIFT-MS recovery for all valid Run 2 replicates for spiked solutions prepared from (a) tableted and (b) oral suspension formulations of acetaminophen (paracetamol). Standard levels were 0.5 (50%) and 1.0 (100%).

4. Discussion

Analysis of Class 2 residual solvents in the headspace of water according to the USP General Chapter <467> [2] is challenging for several reasons. In physicochemical terms,

the solvents vary significantly in volatility and headspace partitioning. They also vary in terms of toxicity, which translates to widely differing permitted daily exposures (PDEs) from 0.5 to 38.8 mg per day [1,2]. For SIFT-MS, with its wide dynamic range and consistent high sensitivity to a broad range of solvents (VOCs) [11,14], the primary challenge is ensuring that integrity is maintained during sample preparation (ensuring that volatile and hydrophobic solvents are not lost). By modifying our sample preparation approach in a way that minimized the open–close cycles for the 100 mL stock solutions (by creating sub-samples), accuracy and recovery results were significantly improved in Run 2 compared to Run 1, resulting in most analytes meeting acceptance criteria. Accurate, precise, and rapid liquid transfers are clearly essential to the reliable performance of this method (*c.f.*, Ref. [4]).

For GC-FID, the lower sensitivity to compounds such as 1,2-dimethoxyethane, 1,4-dioxane, and pyridine may contribute to poorer accuracy and recovery performance than SIFT-MS. Another potential contributing factor that should be explored in a future study is whether the extended run time of the GC-FID batch contributes to analyte losses due to prepared samples sitting for extended periods in the autosampler tray while awaiting analysis (up to 36 h for GC vs. 3.2 h for SIFT-MS; see Figure 2). Losses due to very small leaks in septa, for example, would result in poorer accuracy and recovery. Finally, it should be noted that this study is actually broader than routine USP <467> analysis, so increased failures may be due to operating outside the optimized range of the GC-FID method.

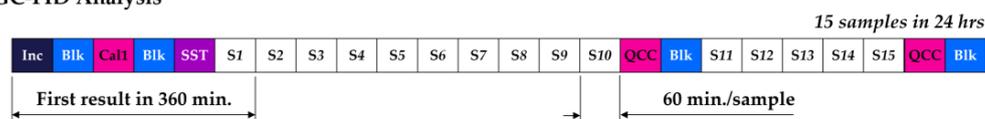
The accuracy and recovery data in Table 1 and Figures 6 and 7 show that SIFT-MS is struggling with analysis of 1,4-dioxane and hexane in the oral suspension. For 1,4-dioxane, the H_3O^+ quantitation ion (m/z 89; Table S1) suffers an unidentified interference giving poor accuracy and recovery, whereas the NO^+ quantitation ions (m/z 87 and 88) do not (Table S15b). Interestingly, in Run 1 the NO^+ 88 ion also suffered interference for this formulation (perhaps due to trace levels of acetone [27]), but NO^+ 87 still performed acceptably (Table S15a). This illustrates the utility of multiple, rapidly switchable reagent ions—with orthogonal ionization chemistry—that are applied in SIFT-MS instruments. When one quantitation ion suffers interference, another quantitation ion(s) can often be utilized. In fact, an instrument software feature for interference rejection is ordinarily applied automatically in data processing, giving a single concentration reading (or pass/fail) for each analyte [11]. However, multiple ions are not always an option: hexane is quantified via a single quantitation ion (m/z 85 with NO^+ ; Table S1). In the oral suspension data, hexane suffers matrix interference at the 0.5 level, causing it to fail in terms of accuracy and recovery. The level of the interference is modest, since acceptance criteria are met at level 1.0. Hence, trace quantitation of hexane may be challenging in this matrix using the standard approach, though the method of standard additions might provide an alternative [32]. When applying the SIFT-MS procedure to new products, use of full-scan analysis across all available reagent ions to identify potential matrix effects is recommended. In routine use, a test failure can be investigated using full-scan SIFT-MS analysis. If this does not confirm the identity of the solvent or identify an interferent, then further investigation should be conducted using conventional chromatographic methods with MS detection.

A more subtle interference issue is evident in some of the SIFT-MS linearity data presented in full in Figures S1 and S2, where there is a lack of agreement between different quantitation ions. This issue is most evident for some isotopologue peaks of ^{35}Cl and ^{37}Cl ; for example, chloroform ($\text{O}_2^{+\bullet}$ 84 and 86), 1,2-dichloroethene ($\text{O}_2^{+\bullet}$ 96 and 98), methylene chloride ($\text{O}_2^{+\bullet}$ 84 and 86), and trichloroethylene ($\text{O}_2^{+\bullet}$ 132 and 132). The use of multiple product ions reduces the impact of these interferences in the present results, for the reason given in the preceding paragraph. Furthermore, the practical application of the analytical method will ordinarily focus on solvents that are likely to be present (LTBP) per the original risk assessment made by the product manufacturer [2]. Hence, this “cross talk” can be eliminated through use of an appropriate subset of analytes and calibration of individual solvents or use of less complex calibration mixtures. Of course, such decisions should be made product by product during method development and validation—i.e., when the SIFT-MS procedure is tested on a new product, with supporting full-scan analysis.

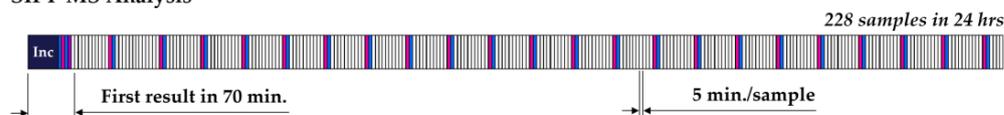
The present study is clearly of limited scope in that it has only compared GC-FID and SIFT-MS performance for water-soluble articles and hence does not broadly address industry requirements [2,4]. An upcoming publication will establish the concentration ranges over which six compatible non-aqueous diluent solvents can be used with SIFT-MS and thus support extending the applicability of SIFT-MS to non-aqueous and mixed aqueous/organic solvent systems. This evaluation is necessary because headspace is introduced continuously into the SIFT-MS instrument and all solvent present in the gas phase is potentially reactive with the reagent ions.

Despite these challenges, SIFT-MS potentially provides a significant step forward for residual solvents analysis in water-soluble matrices. Applying the benefit of faster sample analysis (Figures 2–4) to a real-world testing scenario that includes daily calibration, it is evident that a SIFT-MS instrument provides significantly faster time to results, as well as much higher sample throughputs (Figure 8). Additionally, the cost of ownership is reduced through elimination of the chromatographic column (and related maintenance and replacement). For pharmaceutical companies investing in scale-up of their manufacturing processes, the increased analytical capacity achievable with a single automated SIFT-MS instrument may provide significant economic benefits as a high-throughput screening tool for water-soluble articles due to a single SIFT-MS instrument replacing multiple GC-FID instruments.

GC-FID Analysis



SIFT-MS Analysis



Legend:

Inc. Incubation time Cal Calibration/QCC Blk Blank SST System suitability test S Sample

Figure 8. Daily sample schedules for GC-FID and SIFT-MS analysis of Class 2A and 2B residual solvents.

5. Conclusions

This study compared the performance of a SIFT-MS-based alternative procedure [12] with the standard USP <467> [2] GC-FID procedure for analysis of Class 2A and 2B residual solvents. Both techniques comfortably met the acceptance criteria for linearity and precision (repeatability). However, SIFT-MS outperformed GC-FID for accuracy and recovery measurements, with just one compound failing for SIFT-MS versus ten for GC-FID. It is postulated that this is due to FID signal levels and significantly longer wait times for GC-FID analysis compared to SIFT-MS (see Figure 2), which may result in losses of volatiles and hence increased failures. In addition to reducing the wait time (five-fold faster time to deliver the first analytical result), SIFT-MS can provide operators with a daily sample throughput 15-fold greater than GC-FID, delivering lower cost per sample.

Although SIFT-MS is a DIMS technique—that is, it analyzes headspace directly without pre-separation using chromatography—it provides specific analysis through application of multiple orthogonal reagent ions [10,11]. Where possible, SIFT-MS methods use several quantitation ions and software cross-compares these independent measurements to overcome matrix effects. However, at times, matrix complexity and/or reaction chemistry can be a limiting factor (here, hexane could not be analyzed effectively in the oral suspension). As part of best-practice application of a SIFT-MS analytical method to a new ingredient or formulation, the matrix should be assessed using full scan analysis in addition to targeted analysis of residual solvents. With appropriate method development

and validation, SIFT-MS could provide a useful alternative to GC-based approaches for residual solvent analysis, especially in environments where fast test results and/or high sample throughputs are required.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/appliedchem3020018/s1>: Figures S1–S6; Tables S1–S26. These comprise the entire dataset for this article.

Author Contributions: Conceptualization, M.J.P., S.E.W. and V.S.L.; methodology, M.J.P., C.H. and S.E.W.; investigation, M.J.P., C.H. and S.E.W.; resources, M.J.P.; data curation, M.J.P., C.H. and V.S.L.; writing—original draft preparation, V.S.L.; writing—review and editing, M.J.P., C.H., S.E.W. and V.S.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the findings of this study are available in full in the Supplementary Materials.

Conflicts of Interest: M.J.P. and C.H. are employees of Element Materials Technology (formerly Anatune) in Cambridge, United Kingdom, a distributor of commercial SIFT-MS instruments in the United Kingdom and the Republic of Ireland. S.E.W. and V.S.L. are employees of Syft Technologies Limited, a manufacturer of commercial SIFT-MS instruments.

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