APPLICATION OF SELECTED ION FLOW TUBE MASS SPECTROMETRY (SIFT-MS) TO THE CONTAINMENT PERFORMANCE OF CLOSED SYSTEM TRANSFER DEVICES (CSTDs)

APPLICATION NOTE AS-238

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Abstract

This Application Note describes the use of SIFT-MS to measure small volume leaks from Closed System Transfer Devices (CSTDs). Using propylene glycol methyl ether (PGME) as a surrogate, it has been shown that SIFT-MS can detect sub-microlitre volume leaks from these devices, following the testing protocols developed by NIOSH. Depending on the concentration used, the limits of detection for this technique suggest that leaks as small as 10 nanolitres should detected, significantly lower than current techniques such as FTIR. Additionally, the real-time capabilities of SIFT-MS gives it excellent temporal response, sensitivity and selectivity of detection, covering the ideal requirements of detection in a single instrument. The operation of the SIFT-MS is also straightforward, when compared to TD-GC-MS – another suggested technique for this type of analysis, which can achieve good sensitivity but is not capable of real-time detection.

INTRODUCTION

Hazardous drugs delivered by the parenteral route pose a significant risk to healthworkers during both drug reconstitution and administration. To mitigate this risk, medical devices referred to as closed system transfer devices (CSTDs) have been developed to contain hazardous drug materials and protect healthworkers from accidental exposure.

In 2015, the US National Institute for Occupational Safety and Health (NIOSH) released a draft performance-based test for physical barrier CSTDs[1]. The objective of the test was to be able to evaluate the containment performance of CSTDs under simulated pharmacy (task 1) and administration (task 2) related tasks performed by healthworkers. An updated universal test protocol was released in draft form in 2016 by NIOSH based on the use of thermal desorption-gas chromatography-mass spectrometry (TD-GC-MS) along with a list of nine potential challenge agents[2]. The universal protocol (2016, NIOSH) was applicable to both physical barrier and air-filtration CSTDs, allowing assessment of containment for all commercially available devices using a single test[2].

The protocol requires that releases are measured from the vapour, so it is an essential requirement that the challenge agent is relatively volatile and will evaporate from a liquid leak. Real time detectors (RTD) provide continuous data, in contrast with TD-GC-MS which is a time weighted average detector. RTD offer the possibility of temporal tracking of the release, but most commercial instruments are limited in terms of sensitivity, typically ~1ppm as a limit of quantitation for an FTIR instrument (Gasmet).

Implementation of USP<800> has presented an urgent need for a robust scientific test to assess the containment performance of CSTDs when used for drug preparation and administration[3]. Furthermore, the test must demonstrate sufficient sensitivity to measure microlitre (or smaller) volume liquid leaks from CSTDs. Previous work published by Wilkinson *et al* based on the 2016 draft NIOSH protocol showed CSTD containment to be sub-microlitre[4]. Recent experimental work highlights the advantages of propylene glycol methyl ether (PGME), an analogue of propylene glycol (2016 NIOSH list) that quickly evaporates, supporting quantitative measurement of liquid leaks.

This application note describes some preliminary work assessing the ability of SIFT-MS to detect sub-microlitre release of aqueous/ethanolic solutions of PGME from CSTDs, when operated according to the latest 2019 draft NIOSH protocol as per task 1 (drug reconstitution).

EXPERIMENTAL

Instrumentation

SIFT-MS: Syft Technologies Dual Polarity Voice200*ultra*

138L NIOSH testing chamber (constructed according to the instructions supplied by NIOSH in 2015[1] and validated by BSTL ltd - BSTL 79). A limited number of modifications were made to improve integrity and performance of the testing chamber, and these are documented in a publication by Wilkinson et al[4]. The chamber was operated both with and without a PC cooling fan (Noctua, FN-A9 5V PWM) operating from a 5V usb powerpack which was employed to assist with mixing inside the NIOSH chamber.

Figure 1a: *Syft Technologies' Voice200ultra SIFT-MS*

Figure 1b: *138L NIOSH Testing chamber*

METHOD

Details of the SIFT-MS technique can be found in Application Note AS191.

The Voice200*ultra* SIFT-MS was interfaced to a 138L test chamber (NIOSH), via a short length of 1/8" Teflon tubing. For the initial chamber testing, small droplets of PGME, in 30:70 ethanol:aqueous solution were placed in the chamber and allowed to volatilise, either with or without fan-assistance. The SIFT-MS was used in selected ion mode (SIM) for ethanol and PGME. Following assessment of detection limits in the chamber, an air-filtration CSTD was used to perform the 2019 NIOSH task 1 (drug reconstitution) using PGME in 30:70 ethanol:water. The CSTD containment performance was assessed over a range of PGME concentrations from 0.1 Molar to 1 Molar. The manipulations were carried out in the NIOSH chamber and liquid release was assessed in real time using SIFT-MS. The concentrations measured were then related to total mass release and subsequently converted to notional droplet volumes. Details of this process are provided in the results below.

To enable accurate quantitation of the gas phase concentration, standards of both ethanol and PGME were prepared and analysed. Measured concentrations for PGME and ethanol were approximately 82% and 87%, respectively, of the expected concentrations. All data presented is corrected for this assumed difference. It should be noted that the calibration includes a margin of error due to the nature of the standards used and values should be assumed to be indicative only. A more thorough calibration should be carried out for future analyses.

RESULTS

To assess the ability of SIFT-MS to quantitate releases of PGME from the air-filtration CSTD at suitably low levels, a series of PGME standards were prepared in 30:70 ethanol:water as diluent and analysed. Microlitre quantities of each solution, either at 0.1M or 1M PGME, were aliquoted into a weighing boat, which was placed in the middle of the NIOSH chamber. Sufficient time was allowed for volatilisation and vapour diffusion to occur inside the chamber, either with or without the inclusion of a mixing fan.

The following samples were analysed –

1 µL drop of 0.1M PGME in 30:70 ethanol:water (no fan)
1 µL drop of 1M PGME in 30:70 ethanol:water (no fan)
1 µL drop of 1M PGME in 30:70 ethanol:water (fan assisted)
10 µL drop of 1M PGME in 30:70 ethanol:water (no fan)
10 µL drop of 1M PGME in 30:70 ethanol:water (fan assisted)

From the solution volumes and concentrations, it was possible to calculate the expected total mass released from full evaporation of the analytes, and suitable processing of the SIFT-MS concentration data converted the usual parts-per-billion by volume (ppbV) concentration value, to total mass release for both PGME and ethanol. This process is detailed below.

In all subsequent figures, the rapid drop in concentration towards the end of the measurement corresponds to the point in the measurement when the NIOSH chamber lid was removed to vent the chamber at the end of test.

Figure 2a shows the data obtained for a 1µL droplet of 1M PGME solution. This is converted to µg/m^3 using the appropriate molar volume calculation (figure 2b). From this a total PGME mass was calculated, by dividing by the chamber volume and subtracting a suitable baseline signal (figs 2c and 2d). Finally, the measured amount was amended by applying the concentration conversion factor, described in the method section. This yields the total mass of PGME released, versus the expected value (figure 2e). A similar conversion from ppbV to µg released was also performed for ethanol. For brevity, calculations for ethanol are not included in this application note and all subsequent data should be assumed to have gone through the above processing. Ethanol was not present as a challenge agent but as a co-solvent to mimic hazardous drug compositions where the drug is poorly soluble

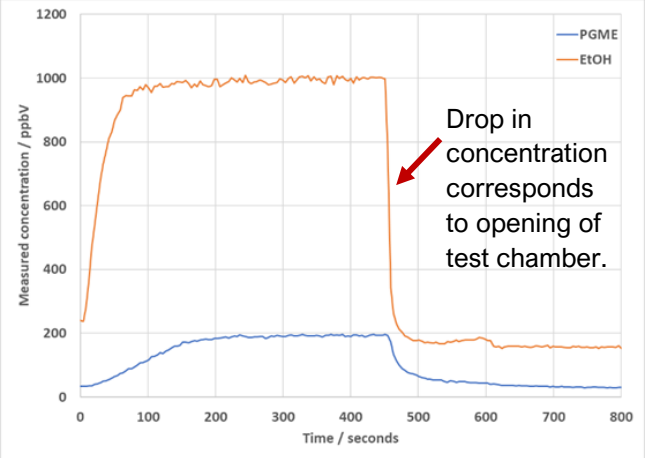

Figure 2a: *Measured concentrations for PGME and ethanol from a 1µL drop of 1M PGME in 30:70 ethanol:water with fan assisted evaporation.*

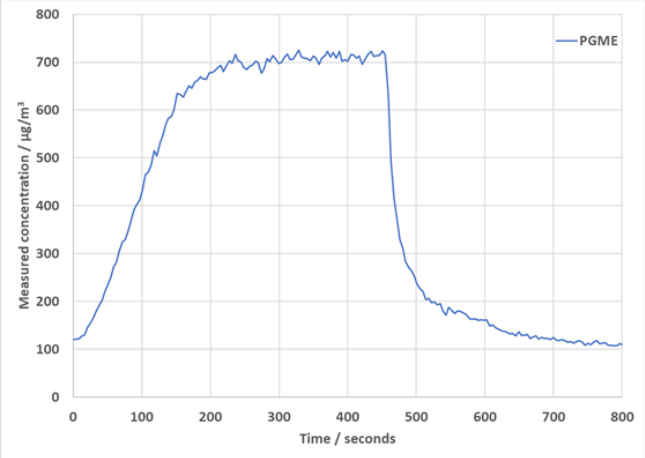

Figure 2b: *Conversion of PGME concentration from ppbV to µg/m³.*

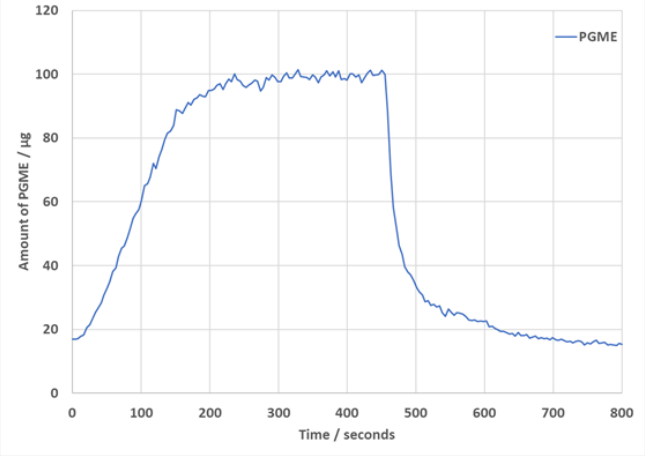

Figure 2c: *Conversion of PGME concentration to mass, based on chamber volume of 138L.*

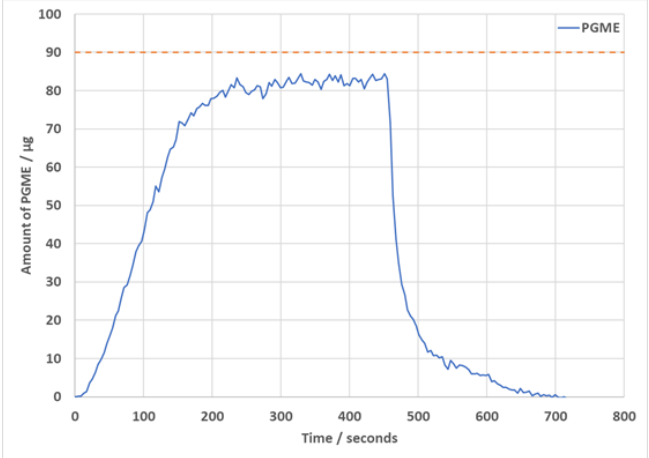

Figure 2d – *Baseline subtraction of data presented in figure 2c (dotted line shows expected mass based on solution concentration and volume).*

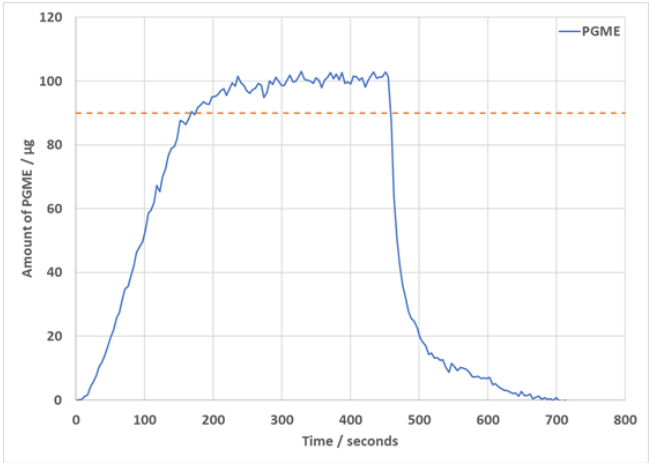

Figure 2e – *Data from figure 2d amended to account for the apparent undermeasurement of PGME, as shown in figure 2d.*

Figures 3 to 7 below show the results for the chamber tests on the samples described in the results section, with Table 1 showing maximum concentrations and equilibration times. In the following figures, the dashed line shows the expected level of PGME, based on the concentration and droplet size.

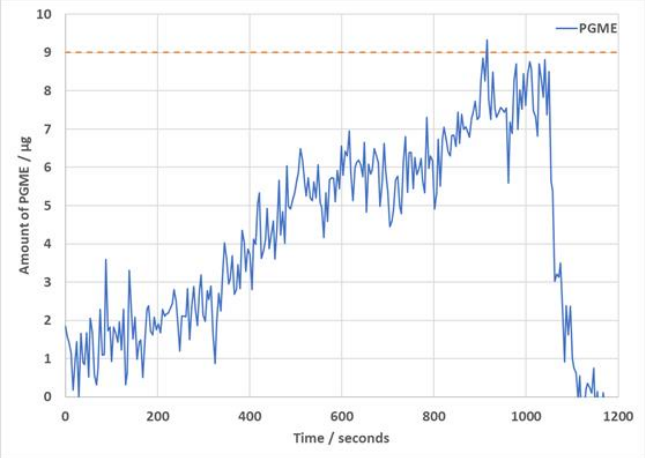

Figure 3: *Amended PGME release from a 1µL drop of 0.1M PGME in 30:70 ethanol:water, with no fan in the chamber*.

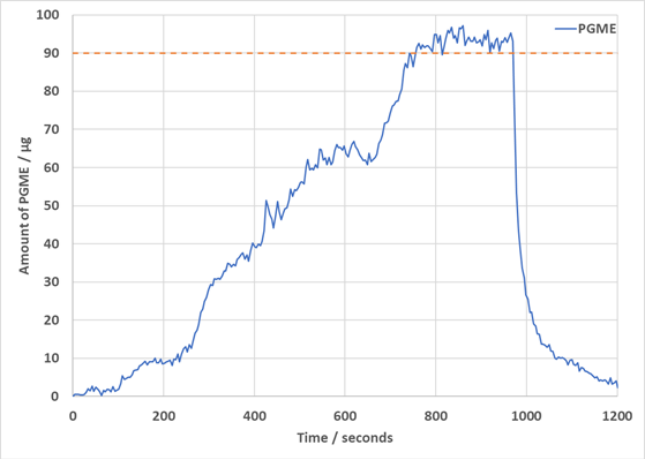

Figure 4: *Amended PGME release from a 1µL drop of 1M PGME in 30:70 ethanol:water with no fan in the chamber.*

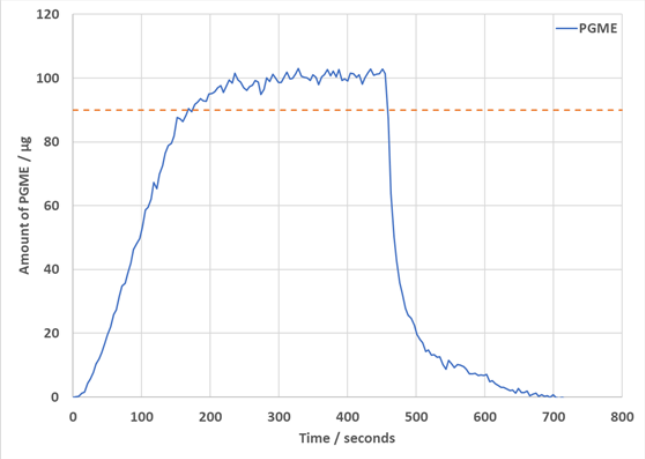

Figure 5: *Amended PGME release from a 1µL drop of 1M PGME in 30:70 ethanol:water with fan assisted evaporation in the chamber.*

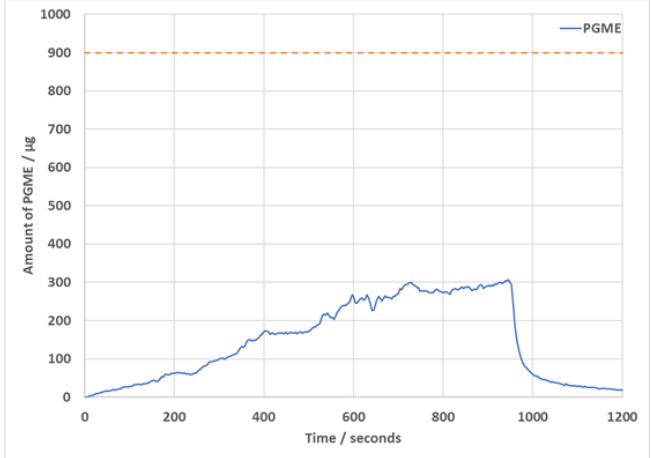

Figure 6: *Amended PGME release from a 10µL drop of 1M PGME in 30:70 ethanol:water, with no fan in the chamber.*

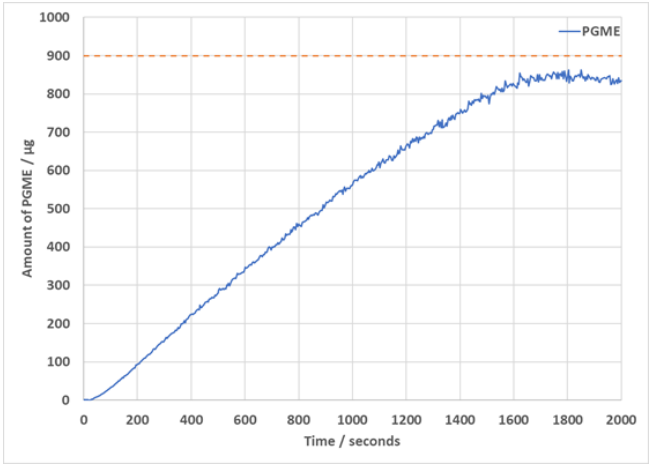

Figure 7: *Amended PGME release from a 10µL drop of 1M PGME in 30:70 ethanol:water with fan assisted evaporation in the chamber.*

From the above data, and Table 1 below, it can clearly be seen that SIFT-MS is sufficiently sensitive to detect the release of small volumes of PGME following volatilization in the NIOSH chamber. The data presented here demonstrates sub-microlitre releases of PGME from CSTD devices can be accurately quantified. It is also apparent that for effective volatilisation and diffusion, a fan is required to achieve robust data, compare figures 4 and 5. For the 10 microlitre drop size experiments, even with fan assistance, some material was observed in the weighing boat at the end of the measurement (>2000 seconds).

Sample	Amount of PGME / expected amount of PGME	Time to reach equilibrium	Amount of ethanol / expected amount of ethanol	Time to reach equilibrium
0.1M soln. 1 µL drop No fan	8 µg / 9 µg	1000 sec	120 µg / 237 µg	300 sec
1M soln. 1 µL drop No fan	95 µg / 90 µg	800 sec	220 µg / 237 µg	300 sec
1M soln. 1 µL drop With fan	100 µg / 90 µg	200 sec	230 µg / 237 µg	150 sec
1M soln. 10 µL drop No fan	300 µg / 900 µg	1000 sec	1900 µg / 2370 µg	600 sec
1M soln. 10 µL drop With fan	850 µg / 900 µg	1800 sec	2000 µg / 2370 µg	600 sec

Table 1: *Results from chamber evaporation tests.*

SIFT-MS reports concentrations of PGME challenge agent inside the NIOSH chamber directly from the instrument. However, it was useful to perform an external check of concentration measurements using standards of PGME prepared in 30:70 ethanol:water as diluent. Droplet sizes from 1 microlitre to 10 microlitres were aliquoted on to a weighing boat inside the NIOSH chamber and allowed to evaporate until their achieved steady state concentrations.

From the data shown in figure 8 show, there is a linear relationship between release amount of PGME in micrograms and concentration with a fixed volume of droplet size (0.1 microlitre). The amounts of PGME release correspond with the maximum theoretical amount of PGME contained within the 0.1 microlitre aliquot released (within experimental error and errors in preparing the standard solutions).

It is worth noting the slight discrepancies between the expected and measured concentrations for both analytes, *ie*. PGME appears to overreport the concentration, whilst ethanol appears to underreport. This is likely to be related to a difference between the literature reported and instrument specific reaction rate 'k' for ethanol generated by the initial calibration, as the standard generation detailed in the method section above relies on an accurate measurement of vapour pressure at a given temperature. This is easily adjusted for with more accurate calibration standards being used, *eg*. certified gas standards or permeation tubes. For this reason, the overmeasurement for PGME for the 1µL drop experiments is probably due to inaccuracy in the droplet size, as this was added to the weighing boat manually using a 10 µL GC (Hamilton) syringe.

From the above data, it is clear that, so long as we are confident of full volatilistion of the PGME challenge agent when released from the CSTD during use, it is possible to convert the measured concentrations into an equivalent liquid volume.

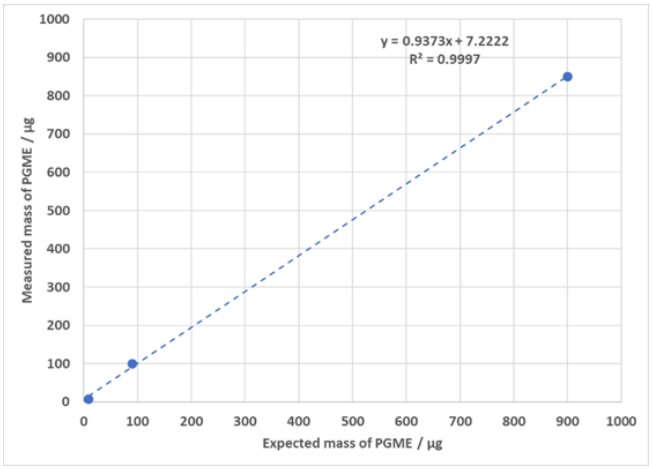

Figure 8: *Release of PGME from external calibration of the 138L NIOSH chamber apparatus.*

CSTD containment analysis

Following the method sensitivity assessments, measurement of leakage from air-filtration CSTD was then assessed when used to perform task 1 of the 2019 NIOSH protocol[5]. All manipulations of the CSTD devices were performed in strict accordance with the 2019 NIOSH protocol task 1 for drug reconstitution using PGME in 30:70 ethanol:water as challenge agent. This involved a transfer of 45 mL volume of PGME in 30:70 ethanol:water challenge agent from vial 1 to vial 2 using CSTD components under instructions for use (IFU). Following completion of the task 1 a second task 1 was performed to provide a further challenge to the CSTD. Finally, a third action consisting of the transfer of a further 30mL of challenge agent was performed between the two vials before ending the procedure. It should be noted that in the normal operation of these devices according to 2019 NIOSH task 1 only a single 45 mL transfer would be performed, and therefore we are presenting the data from this first step only. However, to assess whether the containment efficacy of an air-filtration CSTD reduced following subsequent manipulations additional tasks were assessed. Data (not shown) showed identical releases to the first time use of the CSTD components indicating that containment performance was maintained. All processes took place inside the NIOSH chamber. Figures 8a – c shows an example of the data generated and the process used to convert the measured chamber concentration into notional liquid/droplet size release.

In figure 9a a 1M PGME in 30:70 ethanol:water solution was used as the challenge agent for task 1. This presents an extreme challenge to an air-filtration CSTD with approximately 39.8 mL of volatile organic solvent per 100 mL of challenge agent (40%). Figure 9a clearly shows the release of the two markers: ethanol and PGME for the 45 mL transfer following the 2019 NIOSH task 1. The lower level PGME release is difficult to see on the same scale used for ethanol.

From this plot, the PGME concentration is extracted and converted to mass of PGME released (figure 9b), using the same process as detailed above for the droplet experiments (figures 2a – 2e). The calculations reveal that the release is equivalent to a mass of 12.7 micrograms of PGME released from the air-filtration CSTD during drug reconstitution (2019 NIOSH task 1). It is then possible to convert the mass of 12.7 micograms into volume of released challenge agent, as the concentration of PGME in the solution is known. This is shown in figure 9c below.

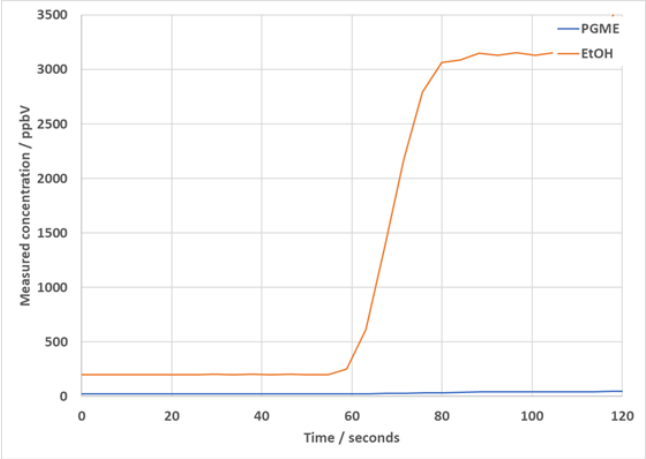

Figure 9a: *Measured concentrations for PGME and ethanol released from an air-filtration CSTD testing to 2019 NIOSH task 1.*

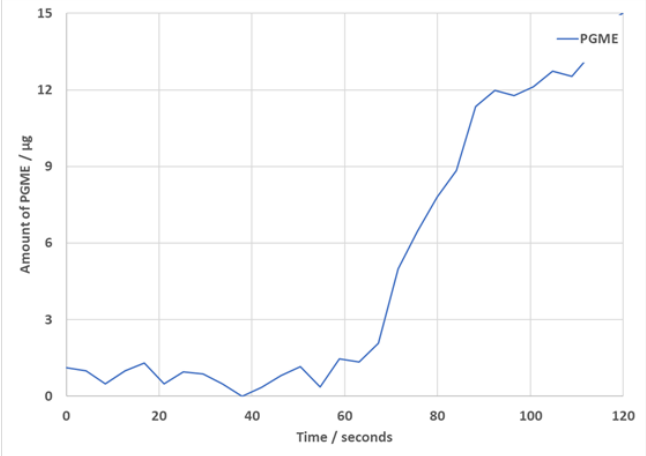

Figure 9b: *Conversion of concentration into mass release for PGME for performing 2019 NIOSH task 1, as described in initial data analysis example.*

Figure 9c below, shows that around 139 nL of challenge agent (liquid) were released during the 2019 NIOSH CSTD protocol task 1 for drug reconstitution using the air-filtration CSTD components when 1M PGME as challenge agent was employed in 30:70 ethanol:water as diluent.

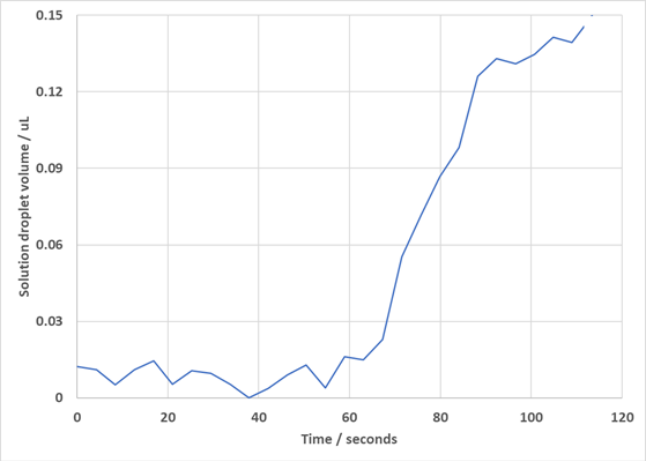

Figure 9c: *Conversion of mass release for PGME to notional drop size, assuming a 1µL drop of 1M PGME will release 90 µg of PGME.*

It is interesting to note that analysis of the release volume from the same CSTD components when a further 45 mL transfer is performed yields an equivalent volume of challenge agent release of 198 nL. This is very similar to the first release volume, within the experimental error of the test, showing remarkable consistency between transfers (data not shown).

Figure 10 shows the first 120 seconds of PGME release data from performing 2019 NIOSH task 1 (as in figure 9c above), together with the ethanol marker data seen earlier in figure 9a, arbitrarily scaled to fit the y-axis scale. From the rise and plateau in both PGME and ethanol concentration, it is clear that the release only occurs during the CSTD component manipulations and that there is no evidence of continual "bleed" of PGME or ethanol from the device at the end of test. This is an important observation because with both physical barrier and air-filtration CSTDs there is potential for release of challenge agent at the membrane surfaces following connection and disconnection of syringe adaptor and vial adaptor components. In the case of an air-filtration CSTD however release could also occur via the air cleaning apparatus, but the release data shown in figure 10 appears to discount this as the dominant mechanism of release for the device studied. In data obtained (not shown) further manipulations of the air-filtration CSTD produce identical behavior for both release of PGME challenge agent and ethanol indicating that the containment performance of these types of CSTD remains constant even when challenged beyond the requirements of 2019 NIOSH task 1.

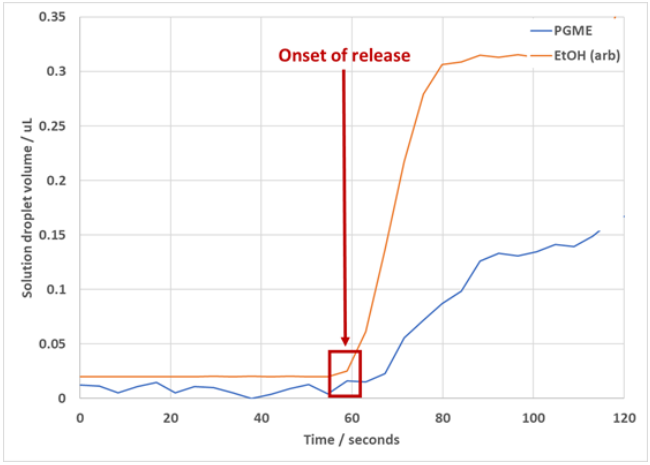

Figure 10: *Plot of PGME challenge agent release shown in figure 9c, with ethanol release data overlaid (arbitrary scaling to fit).*

Figure 11 to 13 below, shows the results of PGME challenge agent leakage from the same air-filtration CSTD device, using three increasing PGME concentrations spanning an order of magnitude. The PGME concentrations evaluated were: 0.1M, 0.3M and 1M PGME in 30:70 ethanol:water as diluent representing an increasing challenge to the air-filtration CSTD. The same process as described above was carried out, and once again the plot shows only the manipulations required to complete the 2019 NIOSH protocol task 1 for drug reconstitution, *ie.* 45 mL transfer from one vial to another. The green, yellow, and orange traces are the arbitrarily scaled ethanol releases (as a marker only) for each of the PGME solutions, to show the point at which the first signs of liquid release occurred. Owing to the more volatile nature of ethanol solvent it has a higher temporal response compared with PGME, requiring almost zero time to volatilize in the NIOSH chamber. The ethanol marker effectively provides a measure of the time constant for the NIOSH test apparatus *i.e.* the minimum time required for the release to reach equilibrium concentration inside the NIOSH chamber.

From figure 11 below, it can be seen that regardless of PGME concentration some leakage of challenge agent occurs from the CSTD, with the signal detected dependent on the challenge agent (PGME) concentration

used. When this amount of signal is converted from micrograms to a volume of challenge agent in microlitres, using the PGME concentration, the volume released for all three challenge tests is broadly identical – approximately 110 nL in all three cases. This is an important finding because it shows that the release is independent of challenge agent concentration in the range studied from 0.1M to 1M PGME. This is further evidence to support a lack of involvement of the air cleaning apparatus of the CSTD in being responsible for the accidental releases of challenge agent. When the amount of released PGME is plotted versus the challenge agent concentration, good linearity is observed. This is shown in figure 12.

Finally, the data presented in figure 13 shows that when normalized to account for differences in PGME concentration, the volume of challenge agent release is identical in all three tests confirming that it is concentration independent. The releases are all approximately of the order of 110 nL for PGME. Ethanol *(*yellow, orange, and green) is present only as a marker of the onset of release due to its higher volatility.

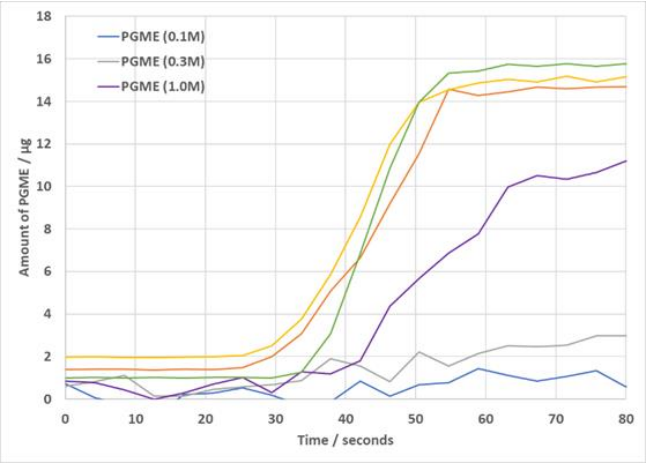

Figure 11: *Release of PGME from three device tests, using three PGME challenge agent concentrations in the range 0.1 to 1 Molar. Total mass of PGME detected is displayed. Ethanol (yellow, orange, and green) is used as a marker for release only and indicates consistency in release behavior and onset time.*

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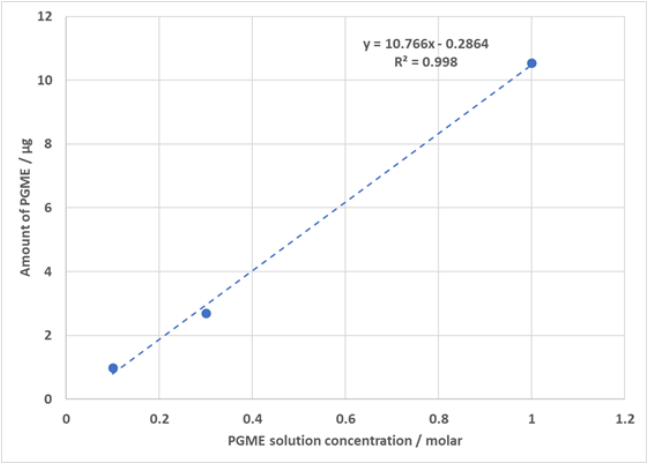

Figure 12: *Release of PGME at a range of challenge agent concentrations in the range 0.1 to 1M.*

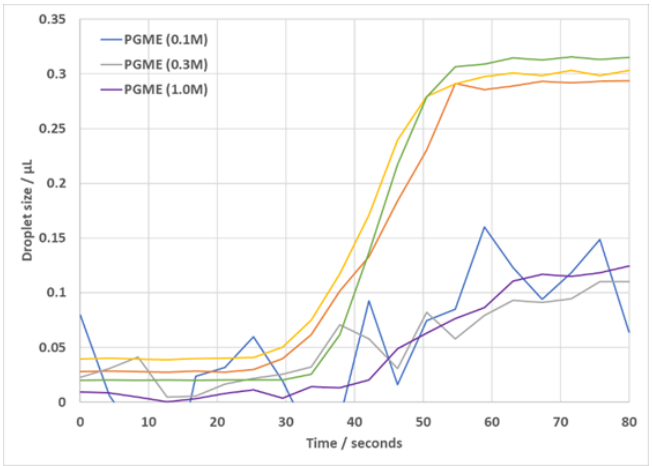

Figure 13: *Data from figure 11, converted to a PGME release liquid volume, based on PGME solution concentrations used.*

DISCUSSION

Since the first draft NIOSH protocol was released in 2015 to assess the containment performance of physical barrier CSTDs,· NIOSH have evaluated both infrared (Miran Saphire, Thermofisher) and TD-GC-MS (various) instruments within the NIOSH protocols. Whilst infrared instruments provide real time data they are limited to ppm sensitivity of detection. TD-GC-MS on the other hand is capable of sub ppb level quantification but is not a real time detector (time weighted average).

SIFT-MS enables both real time assessment of containment of CSTDs (demonstrated in this application note using an air-filtration CSTD) as

well as ppt sensitivity for releases when PGME is used as the challenge agent.

Although SIFT-MS has a higher price point compared with the other two commercial technologies, there are significant benefits to using SIFT-MS for assessment of containment performance of CSTDs. SIFT-MS has excellent temporal response, sensitivity and selectivity, covering the ideal requirements of detection in a single instrument. The operation of the SIFT-MS is also straightforward, when compared to TD-GC-MS.

As demonstrated, SIFT-MS allows the use of a binary system where the detection signals differ by orders of magnitude as shown with PGME in 30:70 ethanol:water diluent. Although ethanol was only used as a marker it allows early detection of onset of release where PGME is the challenge agent released, see figure 9 above. This provides useful temporal information regarding the release mechanism. The use of ethanol as a marker in this application also helps to confirm that the nature of release was liquid rather than vapour. Ethanol is not an appropriate molecule for use as a challenge agent as it is not a good model for hazardous drugs whereas PGME can represent these classes of parenteral drugs. Therefore, PGME release can indicate the accidental release from CSTDs when hazardous drugs are used, extrapolating data obtained from the 2019 NIOSH protocol for tasks 1 and 2 (drug reconstitution and administration).

The data obtained using PGME at concentrations from 0.1-1 Molar in 30:70 ethanol:water showed accidental releases of ~110 nL (liquid) form an air-filtration CSTD when tested according to the 2019 NIOSH task 1. Both release of PGME and ethanol were consistent with this volume of release. No further release of PGME challenge agent (or ethanol) was observed following the final 45 mL addition step (task 1). More aggressive testing of the same CSTD components did not result in increased releases of PGME (or ethanol) or “bleed” of challenge agent vapour directly following manipulation of the CSTD components according to NIOSH task 1.Data obtained supports the hypothesis that mainly liquid release occurs and that the source of release is disconnection of the CSTD device components at the end of task 1.

Normalisation of the different release data over a range of PGME concentrations showed that the volume of liquid release ~110 nL is independent of PGME concentration in the range 0.1-1 Molar. The PGME concentrations studied equate to a drug concentration range of 9 - 90mg/mL for hazardous drugs. This represents a credible challenge for the CSTD components. Testing was also performed in the presence of 30% ethanol. For the case where hazardous drugs are poorly soluble ethanol can be present in the diluent up to 30% by volume. Ethanol can therefore further challenge the containment apparatus of air-filtration CSTDs during NIOSH testing although it should be noted that ethanol is not hazardous and does not need to be contained by the CSTD.

The absence of a signal for ethanol release prior to disconnection of CSTD components during task 1, supports the hypothesis that it is a liquid release rather than a vapour release produced during NIOSH testing. The faster rise in signal from ethanol release is due to the volatility of ethanol and allows a better estimate of the onset time for release during testing.

The ability of SIFT-MS to quantify releases down to nL of PGME allows the use of lower concentrations of challenge agent (0.1M) to be employed making the testing more representative of actual hazardous drug concentrations without compromising sensitivity. Detection was demonstrated down to 110 nL even when 0.1M PGME was used as challenge agent.

CONCLUSIONS

This work clearly demonstrates that PGME is a very effective challenge agent for use within the 2019 NIOSH test protocol for assessing the containment of both physical barrier and air-filtration CSTDs. Challenge agent concentrations were employed in the range 0.1-1 Molar with identical containment results and excellent sensitivity allowing sub-microlitre (~110 nL) release volumes to be quantified using SIFT-MS. A unique benefit of SIFT-MS is that it can span several orders of magnitude

concentration and allows the use of a volatile marker such as ethanol to be employed alongside the challenge agent PGME. In this way ethanol can be used as an additional temporal marker to identify the earliest onset of release from the CSTD without impacting the accuracy of the release data for PGME. SIFT-MS is a real time detector and is able to detect both vapour and liquid releases of challenge agent when CSTD performance is assessed using the 2019 NIOSH tasks 1 and 2. SIFT-MS is both selective (based on mass of ions) and sensitive (detects ppt level leaks) and therefore demonstrates significant advantages over alternative real time detectors such as Gasmet infrared detectors (ppm level detection) which can only detect releases on the microlitre volume scale. Time weighted average detectors such as TD-GC-MS whilst more sensitive than infrared for PGME detection (ppb or better), cannot operate in real time and would also not support the use of ethanol as an additional marker due to its poor capture efficiency on typical sorbent materials.

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