

Source Apportionment and Quantification of Liquid and Headspace Leaks from Closed System Transfer Devices via Selected Ion Flow Tube Mass Spectrometry (SIFT-MS)

Introductory Information

Closed system drug-transfer devices (CSTDs) are devices which replace traditional needles, septa, and other connectors used for transferring hazardous drugs (HDs). NIOSH recommends using CSTDs to limit occupational exposure to hazardous materials and sharps when compounding and administering these drugs (NIOSH 2004). One of the engineering challenges associated with CSTDs is management of the headspace that is either compressed or displaced when transferring liquids in and out of drug vials. CSTD designs and components employing various technologies include creating a physical barrier to contain the displaced volume of air or filters to clean the displaced volume of air when transferring HD solutions. In 2015, NIOSH developed a protocol to test material containment of barrier type CSTDs (NIOSH 2015). NIOSH presented a plan to update the testing protocol so that it was applicable to both barrier and air cleaning types of CSTDs (NIOSH 2016). Both barrier type CSTDs and air cleaning type CSTDs may be susceptible to either liquid or headspace vapor leaks. Air-cleaning type CSTDs allow free passage of air but are expected to remove semi-volatile hazardous drugs (HD)s from the exiting airstream. Barrier type CSTDs have been designed to contain air rather than clean it, and it is reasonable to conclude that a headspace leak with a barrier type CSTD would contain the drug at the same concentration as the headspace inside the vial. As a result, the procedure described in this paper can adequately assess the efficacy of barrier type CSTDs based on the volume of liquid and headspace vapor leak measured. However, the volatile compounds used in this procedure will readily pass through an air-cleaning CSTD, regardless of the ability to retain a semi-volatile HD. Therefore, testing the efficacy of an air-cleaning CSTD requires coupling the procedure described herein with an assessment of the ability of air cleaning CSTDs to retain an appropriate semi-volatile surrogate when volumes of headspace containing that surrogate are passed through the CSTDs. The difference in the amount of HD contained in liquid versus headspace vapor leaks may be several orders of magnitude. The work presented herein is a test method that can distinguish the origin and volumetric quantity of liquid and headspace vapor leaked.

CSTD evaluation involves operation of CSTDs during normal use tasks, such as transferring a solution between two drug vials (NIOSH 2015). A test solution containing two volatile organic compounds (VOCs), acetone and methyl t-butyl ether (MTBE), was used in the evaluation. Leaks were measured by detecting the VOCs in a glove chamber using Selected Ion Flow Tube Mass Spectrometry (SIFT-MS) as the detector. Liquid and headspace leaks are differentiated by the ratios of the two VOCs measured as a result of leaks from the CSTD. The compounds, acetone and MTBE, at equal concentrations in a test solution have a concentration ratio in the headspace vapor of the test solution that is very different, as predicted by their Henry's constants. The ratio of acetone to MTBE detected in the glove chamber can be used to elucidate the source, liquid or headspace, and the magnitude of a leak. The analytical strategy is similar to stable isotope mixing models used to determine contributions from various sources by measuring isotopic ratios (Phillips and Gregg 2001). Propylene glycol (PG) was included in the testing solution as a surrogate for a HD component, though it was not quantified. At the outset of this project, we had chosen propylene glycol as one of two HD surrogates, which could be a marker for liquid leaks while a second HD surrogate (tentatively tetraethylurea (TEU)) could be a marker for headspace vapor leaks. This was because there was very little PG detectable in the headspace leaks, but substantially more TEU detectable in the headspace. Both PG and TEU have relatively similar vapor pressures of 0.129 mmHg and 0.208 mmHg, respectively. Unfortunately, PG from liquid leaks evaporated very slowly. We felt that extending the sampling time to wait for complete and quantitative evaporation of the PG was not a workable scenario. While it may be possible to quantify with semi-volatile compounds, we opted to quantify leaks using the rapidly quantifiable dual-VOC, SIFT-MS system presented herein. Fluorescein was included as a visual qualitative indicator of a liquid leak location. SIFT-MS offers low limits

of detection and real-time response. The real-time response has the benefit of enabling leaks to be temporally correlated with tasks involving manipulation of CSTD components.

Methods Collection

1. Instrumentation

- A Syft Technologies, Selected Ion Flow-Tube Mass Spectrometer (SIFT-MS) model Voice 200 ultra with an HPI inlet was used to measure concentrations of vapor phase acetone and methyl t-butyl ether.

2. Experimental Setup

- Experiments were done in a glove chamber.
- PGAB Calibration solution consisted of 0.3 M acetone, 0.3 M methyl t-butyl ether, 2 M propylene glycol, and 3 mM sodium fluorescein in water.

3. Calibration of vapor phase acetone and methyl t-butyl ether

- Aliquots of PGAB liquid were released inside the glove chamber.
- Vapor phase concentrations and concentration ratios of acetone and methyl t-butyl ether were correlated to PGAB liquid and headspace volumes.

4. CSTD Testing

- 100 mL vials with a rubber septum were filled with 50 mL of PGAB solution.
- Inside of glove chamber, CSTDs were used to transfer 45 mL of PGAB solution from one vial to second empty vial.
- The SIFT-MS response to acetone and MTBE were recorded and magnitude and ratio of acetone to MTBE responses were correlated with leak volumes.

References

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Publications

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