Evaluation of Propylene Glycol Methyl Ether as a Potential Challenge Agent for Leak Detection of Liquid and Headspace from Closed System Drug Transfer Devices using Fourier Transform Infrared Spectroscopy

Materials.

Ethanol and 1-methoxypropan-2-ol (PGME) were from the Sigma-Aldrich Co (Saint Louis, MO). Water was deionized to > 18 MΩ-cm using an Evoqua Water Technologies (Pittsburgh, PA) water purification system. Gasmet DX4040 FTIR Gas Analyzer and Calcmet software were from Gasmet Technologies Oy (Vantaa, Finland). Adsorbent Tube Injector System (ATIS) was from Supelco. Syringe pumps were from Cole-Parmer (Vernon Hills, IL). Gas-tight syringes were from Hamilton Company (Reno, NV). A Bios DryCal Defender flowmeter was from Mesa Labs (Lakewood, CO).

A Secador® Techni-dome® 360 Large Vacuum Desiccator from Bel-Art Products (Pequannock, NJ) was customized by adding a 30 cm tall cylinder the same diameter as the desiccator between the desiccator halves. Glove ports (20 cm dia.) in the cylinder enabled the desiccator to be used as a glove chamber with a volume of 131 liters. A fan was used to circulate air within the chamber. The configuration of the chamber including the cylinder with glove ports will be referred to as the NIOSH chamber.

Calibration of the FTIR.

A calibration apparatus was constructed as depicted in Figure 1. Two syringe pumps were fitted with glass syringes, with one containing PGME and the other containing ethanol. The syringes were connected to PEEK tubing which was inserted through the septum of the ATIS. Bottled nitrogen gas, controlled by a regulator on the N_2 tank and needle valve on a ball flow meter, was connected to the inlet of the ATIS. The ATIS temperature was set to 50 °C. The flow rate of gas exiting the ATIS was set to 2.40 L/min as measured using a calibrated Bios DryCal flowmeter. The rates of the syringe pumps were adjusted to achieve the desired final concentration of PGME and/or ethanol when mixed with the nitrogen flow. The effluent from the ATIS was connected to the sample inlet port of the FTIR spectrometer. The FTIR spectrometer was operated with a cell temperature of 30°C. FTIR measurements in the calibration apparatus used a background spectrum of N_2 gas.

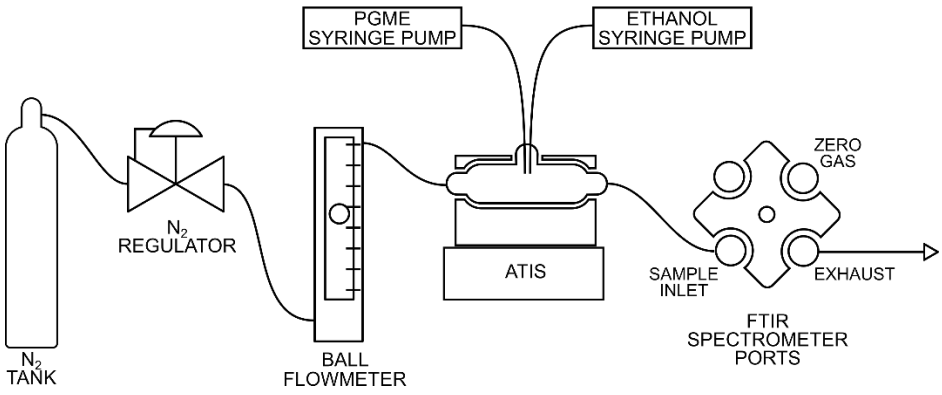

Figure 1. Calibration apparatus connections where nitrogen gas metered from a regulator flowed into a ball flow meter, then into the ATIS where it was mixed with PGME and/or ethanol from syringe pumps. The effluent from the ATIS was routed to the FTIR sample inlet port.

Gravimetric analysis of the evaporation of 2.5 M aqueous PGME.

Estimates of the evaporation times for various volumes of PGME solution were made by gravimetric analysis and observation. A single drop of PGME solution was placed on a tared watch glass in an analytical balance. With the balance doors open, a fan was used move air over the solution to aid evaporation and simulate conditions used in later experiments inside the NIOSH chamber. The doors were closed at one-minute intervals and the mass was recorded. The time for complete evaporation was confirmed by visual observations indicating that the solution aliquot was gone from the watch glass.

Measurements of PGME vapor in the NIOSH Chamber.

A port on the upper section of the NIOSH chamber was connected to the FTIR sample inlet via ¼ inch PTFE tubing. The FTIR instrument had a sample flow rate of 2.5 liters per minute. FTIR is not a destructive analysis method, so to reduce the loss of atmosphere due to sampling, the exhaust of the FTIR was returned to the chamber as shown in Figure 2.

A fan (3.5 inch dia.) was used to circulate the air inside the NIOSH chamber to promote evaporation of the PGME solutions and homogeneity of the atmosphere. When measuring PGME in the chamber, FTIR background spectra were recorded in lab air, so that the PGME signal was discernable without needing to subtract water and other background components as part of the post collection analysis of the spectrum. FTIR measurements of PGME vapor from a liquid source inside the NIOSH chamber were done after dispensing aliquots of 2.5 M PGME from syringes onto a watch glass where they could evaporate.

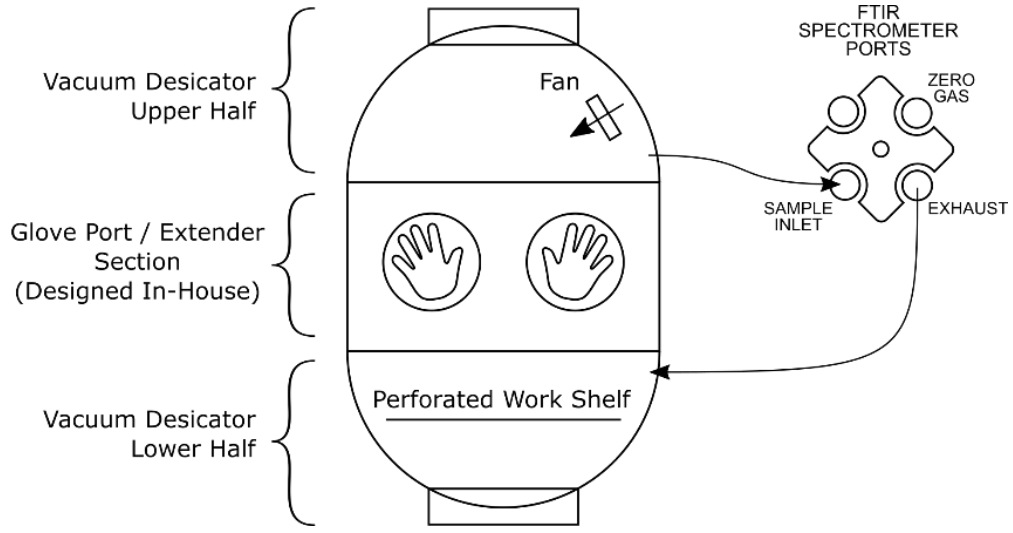

Figure 2. NIOSH chamber depicting the configuration including location of the fan, glove ports, work shelf, and connections to the FTIR spectrometer.

Headspace from above a 2.5 M PGME solution was measured in the NIOSH chamber. Measurements were made of PGME vapor generated from the headspace using a 100 mL drug vial with a crimp-cap septum containing 50 mL of 2.5 M PGME solution. A needle, on a 50 mL syringe filled with lab air, was inserted

through the septum of the drug vial. A second needle was inserted into the septum to provide a path for headspace effluent. From the syringe, 50 mL of air was pushed into the drug vial, which forced headspace from the vial via the second needle. After pushing the air from the syringe, both needles were removed from the septum.