Optimizing Vial Pressurization Parameters for the Analysis of <USP 467> Residual Solvents Using the 7697A Headspace Sampler

Application Note

Pharmaceuticals

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Abstract

Several vial pressurization/loop fill schemes of the 7697A Headspace Sampler are evaluated using aqueous solutions of USP <467> residual solvents (Class 1, Class 2A, and Class 2B) at their limit concentrations. Increased sensitivity can be achieved by holding the sample loop at pressures above ambient prior to injection. This is implemented using the 7697A on-board EPC. Two vial pressurization modes, "Flow to Pressure" and "To Pressure" are compared with respect to system repeatability for Class 2A solvents.

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Introduction

Earlier generation static headspace samplers using the valve and loop system were designed to vent the pressurized vial to ambient pressure during the loop fill process. The latest generation Agilent 7697A Headspace Sampler uses an internal PCM (pressure control module) with both forward and back pressure control to handle vial sampling. This makes it possible to control both the initial pressurization setting of the vial as well as the final vial pressure in the sample loop during the loop fill process. Using final vial pressures above ambient can yield a sample concentrating effect and more consistent peak areas since atmospheric pressure fluctuations are removed. USP <467> solvents are used to study the effect of sampling vial pressures on peak area. Lastly, two loop fill modes of the 7697A; flow control (flow limited) to final pressure and fast flow (200 mL/min) to pressure are compared with respect to peak area repeatability.

Experimental

The Agilent 7890A GC system interfaced to a 7697A Headspace sampler was used in this work. Parameters are given in Table 1. The headspace transfer line was 0.45 mm id deactivated fused silica tubing interfaced to a split/splitless inlet through the septum. Carrier gas was controlled by the 7890A s/s inlet EPC routed to the headspace sampler.

Table 1. System Parameters

Agilent 7697A Parameters	
Oven temperature	85 °C
Equilibration time	40 min
Vial Pressurization mode	Flow to Pressure
Vial fill rate	50 mL/min
Loop fill	20 psi/min
Sample loop	1 mL
Headspace vial size	20 mL
Liquid volume in vial	6 mL
Vial pressurized to	15 psi for Class 1 and Class 2B, 20 psi for Class 2A
Final vial pressures for Class 2A	0 (ambient), 2 psi, 5 psi, 8 psi, 10 psi, 12 psi, and 15 psi.
Final vial pressures for Class 1 and Class 2B	0 (ambient), 2 psi, 5 psi, 10 psi
Headspace software	B.01.02 or greater
Agilent 7890A Parameters	
Inlet	Split/splitless at 150 °C, 7:1 split, 4 mm straight liner, no glass wool #5190-2294
Detector	FID, 275 °C
Carrier gas	Helium
Vial pressurization gas	Helium
Column	30 m × 0.25 mm × 1.4 um VF-624ms
Oven program	40 °C (5 min.) to 240 °C (2 min.) @ 16 °C/min.
ChemStation software	B.04.03 or greater

The diagram in Figure 1 details the EPC pneumatics (PCM) for controlling vial and loop pressures. Pressure and flow rate setpoints are input either from the 7697A keyboard or from the GC ChemStation. The forward pressure channel uses PV1 of the vial PCM channel to provide flow or pressure control to pressurize the vial while backpressure can be set during the venting or loop fill process with PV2. Pressure is sensed using PS1.

All experiments were conducted using aqueous solutions of residual solvent to illustrate typical use of the PCM setpoints for controlling headspace sample injection. USP <467> residual solvents, Class 1, 2A, and 2B were prepared in purified water at their limit concentrations according to procedure A of the method. Transfer of solutions at final concentration to 20 mL headspace vials was performed with a Brand Dispensette to remove most variability from the sample prep.

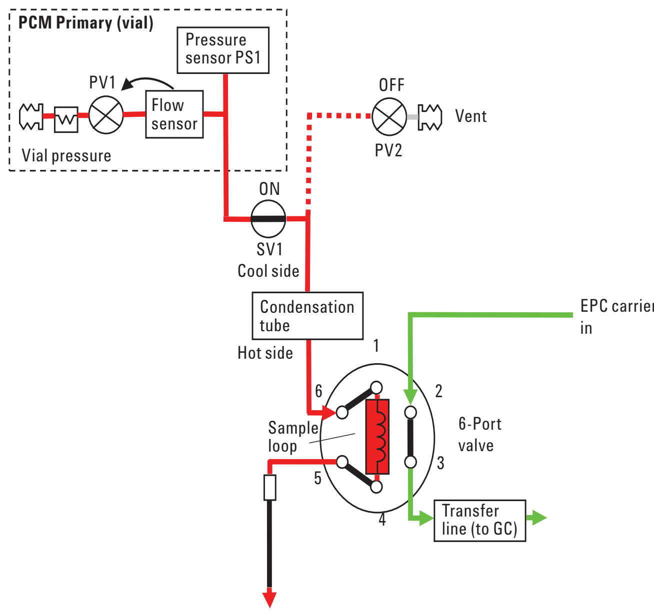


Figure 1. Headspace pneumatic diagram showing detail of vial pressurization and loop fill EPC.

Results

The 7697A uses the well established valve and loop system for headspace sample introduction. This system for filling the sample loop has been enhanced by using both forward and backpressure EPC to control precisely the pressures in the headspace vial and sample loop. Controlling the loop pressure above ambient can increase sensitivity and remove atmospheric pressure variability leading to improved RSD's [1]. Table 2 lists the pressure setpoints used in this study. The Loop Pressure column (Table 2) shows the final pressure in the sample loop just prior to GC injection. A higher initial loop pressure or vial pressurization pressure (20 psi) was used for the Class 2A solvents simply to give additional data points for the area vs. loop pressure plots. The higher the initial vial pressurization setting, the greater the level of analyte dilution in the headspace vial since more helium flows into the vial to reach the higher pressure setpoint. Keep this in mind when developing methods.

When filling the sample loop, care must be taken to choose vial size, volume of sample, vial pressurize pressure and final sample loop pressure so that sufficient gas is swept through the loop to give a representative sample prior to injection. Using the ideal gas law under isothermal conditions, the following equation can be used to check if the final volume sweeps the 1 mL loop at least once.

$$V_2 = (P_1 - P_2)/P_1 \text{ abs} \times V_1$$

Where:

V_1 = headspace volume in vial
P_1 = vial pressurization pressure
P_2 = final vial pressure when loop is filled
abs = absolute pressure

Pressurized loop study

Table 2. Vial Sampling Parameters Used in the Study. Twenty mL Vials Were Used

Solvent set	Vial pressurized to (psi)	Loop pressures (psi)
Class 1	15	0, 2, 5, 10
Class 2A	20	0, 2, 5, 8, 10, 12, 15
Class 2B	15	0, 2, 5, 10

Graphs for all residual solvents at their USP limit concentrations in aqueous solution are shown according the parameters given in Table 2. Class 1, Class 2A, and Class 2B solvents are plotted in Figures 2a, 2b, and 2c, respectively. Solvents are split into a number of plots to make them more legible. In all plots, the "y" axis is area and the "x" axis is loop pressure in psi prior to rotation of the 6 port valve for sample injection. Pressure set points are NTP (25 °C, 14.697psia). A linear relationship is seen as expected from the ideal gas law for all solvents expect 1,4 dioxane which shows some non-ideal behavior. Also, carbon tetrachloride, a class 1 solvent, shows little area enhancement with increasing loop pressure. In general, compounds with low partition coefficients (k) will show the largest slope as such solvents do not partition into the water matrix well.

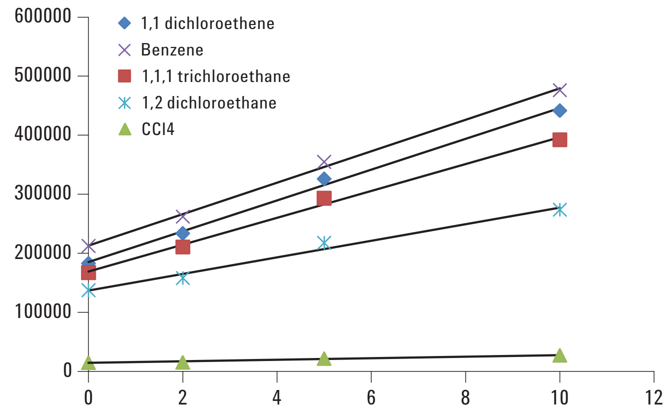


Figure 2a. Class 1 solvents.

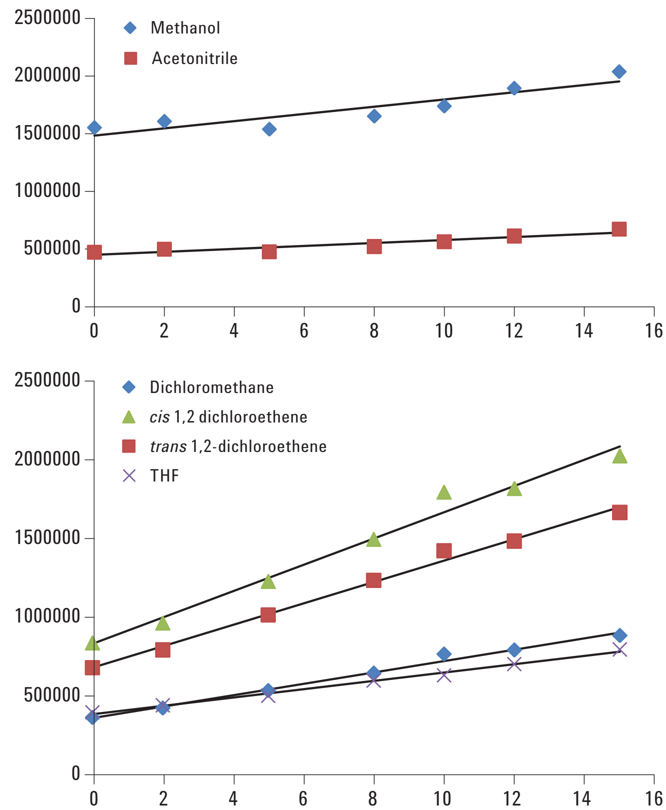
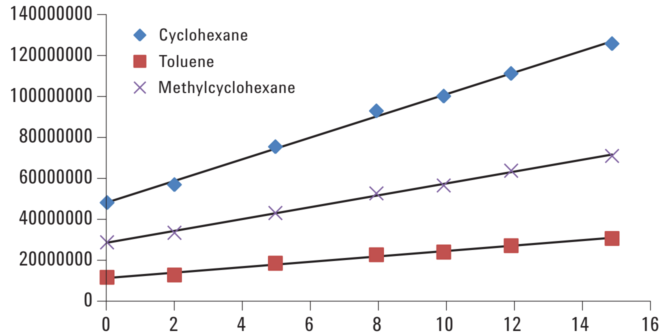
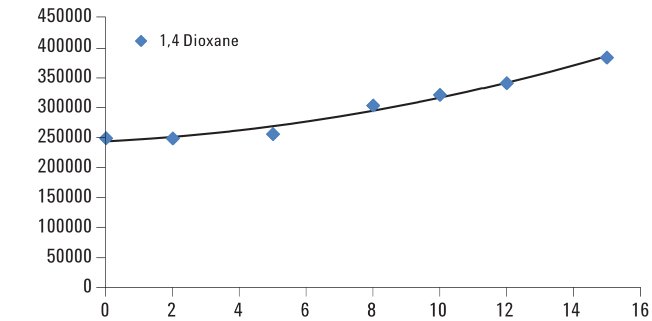


Figure 2b. Class 2A solvents. (Continued)





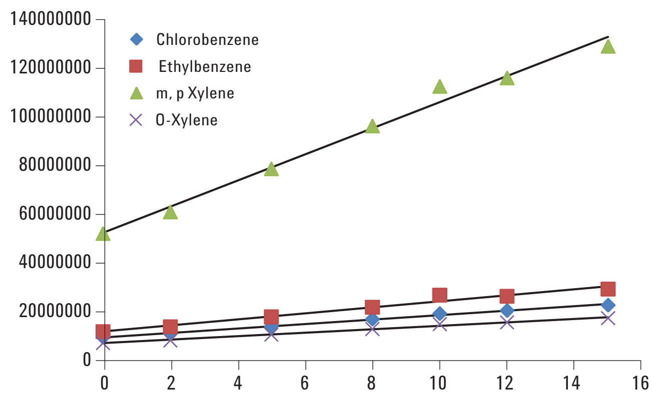
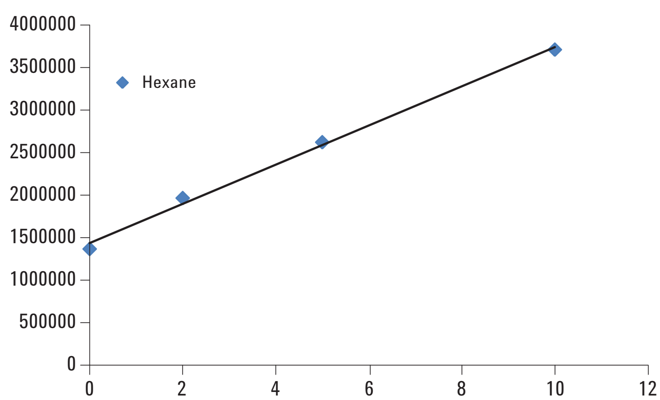
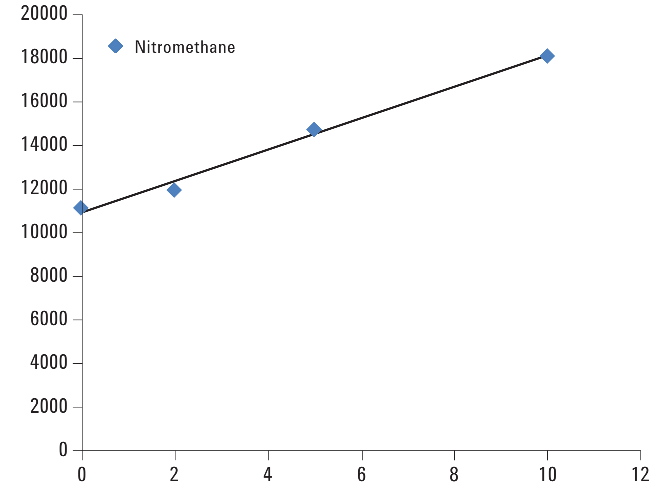
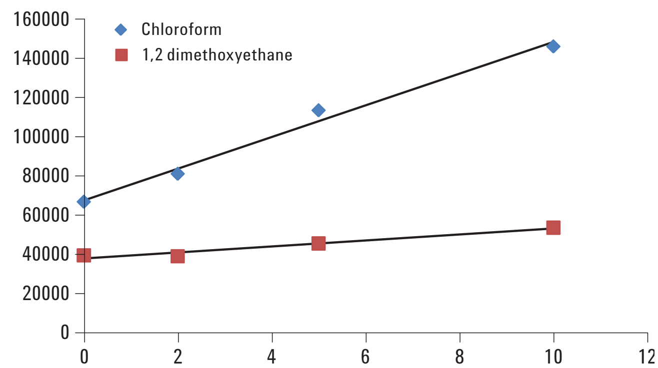


Figure 2b.   Class 2A solvents.







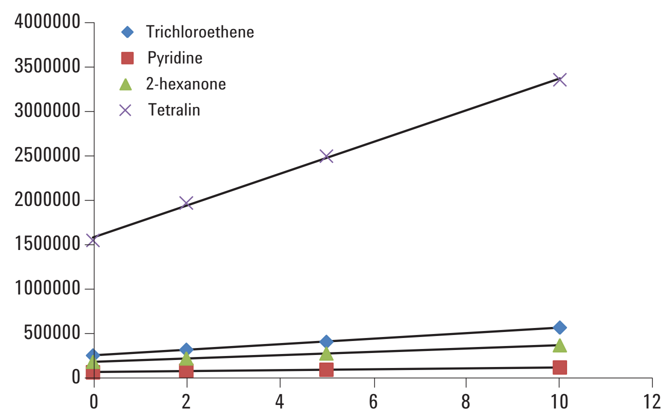


Figure 2c.   Class 2B solvents.

In summary, it is clear from these plots that sensitivity can be enhanced by injecting the headspace sample at pressures above ambient. Generally speaking, a linear relationship is seen between peak area and loop pressure. Slope of the line is dependent on the k value for the analyte/diluent system at a given vial equilibration temperature and time.

Comparison of "Flow to Pressure" and "To Pressure" modes

Two vial pressurization modes, "Flow to Pressure" and "To Pressure" are available on the Agilent 7697A. This study compares these two modes using Class 2A solvents as the test mix. A third mode, "Constant Volume" was not investigated here. The objective was to determine if one mode has advantages over the other in terms of area repeatability. Parameters used in this study are shown in Table 3.

Table 3. Vial Pressurization Parameters

Parameter	Flow to pressure	To pressure
Vial pressurized to (psi)	15	15
Final vial pressure (psi)	5	5
Vial fill	50 mL/min	200 mL/min
Loop fill	20 psi/min	20 psi/min
Time to pressurize (seconds)	43	21
Extracting time (seconds)	32	32

Percent RSD's for all Class 2A solvents (n = 10) at limit concentrations in water are shown in Table 4. This table compares the two vial pressurization modes. A dramatic improvement in repeatability is seen for the two lowest k solvents, cyclohexane and methycyclohexane using the "To pressure" mode which pressurizes the vial in half the time compared to "Flow to Pressure". Otherwise, there is little difference in repeatability for the remaining solvents between the two modes of pressurization.

Table 4. Residual Solvent RSD's for Two Modes of Vial Pressurization

Class 2A compound	Flow to pressure	To pressure
Methanol	1.92	2.27
Acetonitrile	2.09	2.37
Dichloromethane	0.81	1.44
trans-1,2-dichloroethene	1.54	1.84
cis-1,2-dichloroethene	1.00	1.7
THF	1.06	1.47
Cyclohexane	4.88	1.52
Methycyclohexane	5.01	1.43
1,4-dioxane	2.36	2.36
Toluene	1.56	1.81
Chlorobenzene	1.14	1.5
Ethylbenzene	1.99	1.85
m,p--xylene	1.92	1.89
0-xylene	1.56	1.93

Conclusion

Advanced on-board EPC pneumatics in the 7697A Headspace Sampler give the analyst increased flexibility and performance enhancement not possible with previous generation samplers. By setting the sample loop at pressures above ambient in the range of 2 to 10 psi, analyte area counts increase improving the MDL since the moles of a given analyte in the sample loop increases with pressure at constant 1mL loop volume. The technique would gain additional importance if regulations drive allowed drug impurity levels down in the future.

The two modes of vial pressurization compared (flow to pressure and to pressure) using Class 2A solvents are nearly equivalent in repeatability except for cyclohexane and methylcycohexane which have very low k's in water. Many permutations are possible in terms of flow and pressure setpoints when developing a 7697A headspace method. The settings used in the work are typical parameters that will address a wide range of applications.

References

1. Roger L. Firor, "Analysis of USP <467> Residual Solvents with Improved Repeatability using the Agilent 697A Headspace Sampler," Agilent Publication 5990-7625EN, 2011.

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