Dynamic headspace GC-MS method to detect volatile extractables from medical device materials

Milani R. Wijeweera Patabandige and Samanthi Wickramasekara
US Food and Drug Administration, Silver Spring, MD

Plain Language Summary

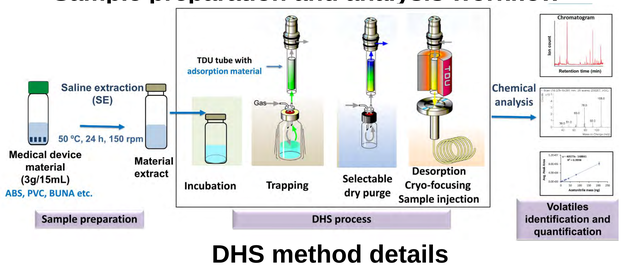
Volatile extractables that can diffuse from medical devices can be harmful to the patients. Current volatile-analysis methods provide higher variability in signal responses leading to incorrect safety assessment. We evaluated the performances of dynamic headspace(DHS) analysis as an alternative to achieve the sensitivity suitable for safety assessment of volatile extractables.

Introduction and Overview

- Volatile extractables released from medical devices can expose patients to harmful levels of toxic compounds.
- The Analytical Evaluation Threshold (AET) is used to determine the analytical sensitivity to support toxicological risk assessment.
- Direct injection gas chromatography-mass spectrometry (GC-MS) and static headspace GC-MS are the most used analytical methods for volatile/ semi-volatile analysis.
- Current volatile analysis methods provide higher variability in signal responses leading to incorrect safety assessment.
- This study was designed to evaluate the performance of dynamic headspace (DHS) GC-MS analysis to achieve the sensitivity levels suitable for proper toxicological risk assessment for volatiles extracted from medical devices.

Experimental Methods

Sample preparation and analysis workflow



DHS method details

System component	Parameters	Low-volume conditions (0.1 mL)	High-volume conditions (5 mL)
DHS incubation	Incubation temperature and time	37 °C for 2 min	37 °C for 10 min
Pre-concentrator	Focusing trap packing	Multibed graphitized carbon (Carbopack B/X)	Multibed graphitized carbon (Carbopack B/X)
	Trapping temperature, volume, and time	30 °C; 100 mL for 5 min	30 °C; 750 mL for 15 min
Thermal Desorption Unit (TDU)	Desorption conditions	40 °C (0.4 min); 720 °C/min (30 s); 325 °C (5 min)	40 °C (0.4 min delay); 720 °C/min (30 s); 325 °C (5 min)
		Glass wool liner; Split 30:1	Glass wool liner; Split 20:1
Cooled Injection System (CIS)	Cryo cooling (liquid N2)	-120 °C (0.2 min); 12 °C/s; 275 °C (3.0 min)	-120 °C (0.2 min); 12 °C/s; 275 °C (3.0 min)
Chromatography Conditions	Column	DB-624 (60 m × 0.25 mm-I.D.× 1.4 µm film thickness) (6% cyanopropyl-phenyl and 94% dimethyl polysiloxane) Column flow (1.4 mL/min)	
	GC oven temperature and program	40 °C (2 min); 8 °C/min; 240 °C (3 min)	
Mass spectrometer	Ionization mode and other temperature parameters	Ionization – Electron Impact (EI) Scan mode Mass range - (m/z 35 – 500) MSD transfer line temperature – 250 °C Ion source temperature - 230 °C Quadrupole temperature – 150 °C	
Instrumentation	1. Gerstel Dynamic Headspace system with Thermal desorption unit 2. Agilent 7890 B Gas chromatography system 3. Agilent 5977B Mass spectrometer		

Method development was conducted using Residual Solvents Class 3 mix A (24 components from Restek) and applicability was tested using other volatile standard mixes (a total of 71 compounds).

Results

Trapping volume optimization

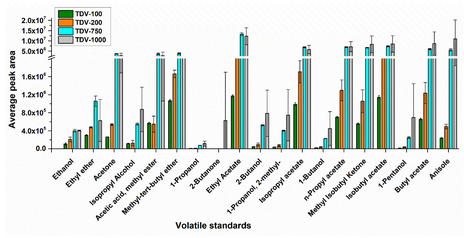


Figure 1: Trapping volume optimization for the standard mix; trapping flow is constant (50 mL/min) and the trapping time varied from 2-20 min. Even though 1000 mL of trapping volume gave higher extraction efficiency, the variation in signal response was larger compared to the smaller volume. Selected 750 mL as the best option.

Volatile calibration

Elution order	Compound name	Linear dynamic range (ng/mL)	Linear regression equation	R^2	m/z (quantification)	Henry's Law Constant at 25°C (atm*m³/mole)
1	n- Pentane	5.00 - 500	Y=2610.5x+7589.2	0.97	43	1.25E+00
2	Ethanol	5.00 - 500	Y=9489.2x-134504	0.97	45	5.00E-06
3	Ethyl ether	5.00 - 500	Y=27952x+127509	0.97	59	1.23E-03
4	Acetone	5.00 - 500	Y=57982x-95944	0.98	43	3.97E-05
5	IPA	5.00 - 500	Y=10107x-182208	0.99	45	8.10E-06
6	Ethyl formate	100 - 375	Y=439.72x+15420	0.85	44	2.87E-04
7	Methyl acetate	5.00 - 500	Y=89872x-2000000	0.99	43	1.15E-04
8	Methyl-tert-butyl ether (MTBE)	5.00 - 500	Y=121449x-596436	0.99	73	5.87E-04
9	1-Propanol	5.00 - 500	Y=1729x-38928	0.94	41	7.41E-06
11	Ethyl acetate	5.00 - 375	Y=189279x-111298	0.99	43	1.34E-04
12	2-Butanol	5.00 - 500	Y=11643x-249207	0.99	45	9.06E-06
13	Isobutanol	5.00 - 500	Y=6505x-77382	0.99	41	9.78E-06
14	Isopropyl acetate	5.00 - 375	Y=140268x-709239	0.99	43	2.78E-04
16	1-Butanol	5.00 - 500	Y=3307.5x-13678	0.98	41	8.80E-06
17	Propyl acetate	5.00 - 250	Y=137964x-1000000	1.00	43	2.18E-04
19	4-Methyl-2-pentanone	5.00 - 250	Y=98255x-549780	1.00	43	1.38E-04
20	Isobutyl acetate	5.00 - 250	Y=131304x-548492	0.99	43	4.54E-04
21	1-Pentanol	5.00 - 500	Y=3187.5x-33584	0.89	55	1.30E-05
22	Butyl acetate	5.00 - 250	Y=101007x-482345	0.99	43	2.81E-04
24	Anisole	5.00 - 200	Y=150650x-1000000	0.99	108	2.76E-04

Table 1: Calibration information for the standard mix using optimized high volume DHS analysis method. Most compounds gave R^2 >0.97 with the dynamic range of 5-500 ng/mL.

Adsorption material efficiency- Carbopack B/X vs. Tenax TA

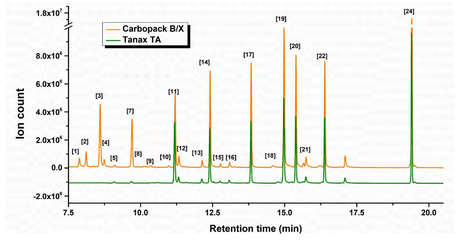


Figure 2: Comparison of extraction efficiency of standard mix with different adsorption materials. Tenax TA material showed low sensitivity (~5 to ~200 times) towards the early eluting volatile compounds compared to Carbopack B/X. (compound Id's are listed in the Table 1).

Volatile recovery with SDS addition

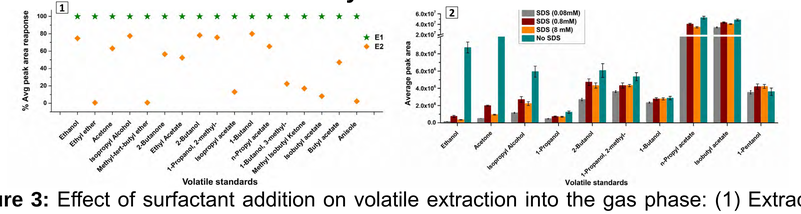


Figure 3: Effect of surfactant addition on volatile extraction into the gas phase: (1) Extraction efficiency with separate injection (2) Exploring the effect of sodium dodecyl sulfate (SDS) at its critical micelle concentration (CMC-8mM) and its dilutions against no SDS samples.

Analyses of materials

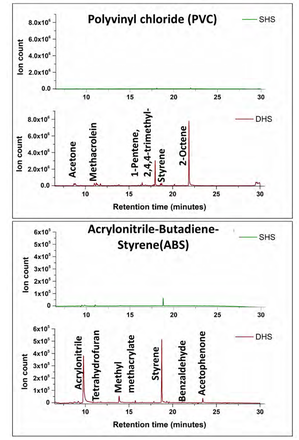


Figure 4: Analysis of PVC and ABS material extracts using both static (green) and dynamic (red) headspace methods (data were plotted on the same scale).

#	RT (min)	Compound	DHS	SHS
		PVC		
1	8.69	Acetone		
2	10.40	methacrolein		
3	11.03	Propanal, 2,2-dimethyl-		
4	11.26	2-Butanone		
5	11.39	1,3-Dioxolane		
6	11.72	Tetrahydrofuran		
7	13.66	2-Pentanone		
8	15.44	Toluene		
9	15.59	2-Pentanone, 3-methylene-		
10	17.73	Benzene, chloro-		
11	17.99	1-pentene, 2,4,4-trimethyl-		
12	18.74	Styrene		
13	21.85	2-Octene		
		ABS		
1	9.79	Acrylonitrile		
2	10.98	Propane, 2-ethoxy-2-methyl-		
3	11.74	Tetrahydrofuran		
4	13.88	Methylmethacrylate		
5	18.79	Styrene		
6	21.10	Benzaldehyde		
7	23.45	Acetophenone		

Table 2. Volatile identification comparison between static (green) and dynamic (red) headspace methods for both materials.

Discussion

- Low-volume samples behave similarly to the high-volume samples with the optimized methods, but the sensitivity was lower for the low-abundance compound identification.
- For high-volume samples, increased trapping time (10 min) led to back inlet pressure shutdown issues towards the end of the sample queue due to vapor accumulation. Addition of vent step is necessary for increased trapping times.
- No effect was observed with SDS addition. Additional surfactants will be explored to improve the extraction efficiency.
- DHS-Material analysis improved sensitivity by one order of magnitude. We will be applying this method to device extracts next.
- If the developed system produces undefined uncertainty factors (UF), alternative approaches will be applied to achieve AET.

Feedback

- We welcome any feedback and comments on whether/how this method works for you and on any hurdles during its application.
- For feedback or questions feel free to contact Samanthi.Wickramasekara@fda.hhs.gov or Milani.Patabandige@fda.hhs.gov

Acknowledgements and Disclaimer: We would like acknowledge Drs. Keaton Nahan, Jacob Hill and Adrijo Chakraborti for their help in data processing. This research was funded in part by CDRH Critical Path initiative and an appointment to the Research Participation Program administered by the Oak Ridge Institute for Science and Education (ORISE) through an interagency agreement between the U.S. Department of Energy and the U.S. FDA. The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any agency determination or policy. The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by Department of Health and Human Services.