Headspace Sampling in Gas Chromatography

Clayton B'Hymer
U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, Division of Applied Research and Technology, Cincinnati, Ohio, U.S.A.

INTRODUCTION

Headspace sampling is a type of analysis in which the volatile analytes are separated from a sample matrix prior to their introduction into a gas chromatograph (GC). The gaseous phase or "headspace" above the sample matrix within a sealed system is collected and then analyzed by the GC. Headspace sampling represents an indirect method to measure volatile components of the sample matrix, that is, the gaseous phase above a sample matrix is measured, not the sample matrix itself. In the general technique, an aliquot of gas (vapor) phase sampled is in equilibrium with the liquid or solid phase of the sample matrix. In equilibrium, the distribution of the analytes between the two phases is dependent upon their partition coefficients; thus, the quantity of the original analyte in the sample can be determined from the analytical results of the headspace aliquot. Dynamic (purge-and-trap) and static headspaces are the two main classic types of headspace sampling techniques currently used. In the last decade, solid-phase microextraction (SPME) has also been developed to sample headspace volatile. An equilibrium is established between the gas phase above the sample matrix and the solid-phase of the SPME fiber in SPME. Applications of headspace sampling are extensive and include the analysis of volatile components in the food and flavor industry, pharmaceuticals, cosmetics, biomarkers of chemical exposure or ingestion, environmental testing, and volatile monomers from plastics. Headspace sampling and analysis represent a broad analytical field with continued growth in numerous applications.

HISTORICAL BACKGROUND

Since the inception of gas chromatographic analysis, the need to analyze volatile components from a nonvolatile sample matrix has often been encountered. When a nonvolatile sample matrix is directly introduced into a gas chromatograph, the sample remains within the injector, thus contaminating it. Headspace sampling was a logical development to avoid this sample matrix problem. Headspace sampling was initially applied to other analytical techniques before being used with gas chromatography, and this chronological description has been reported elsewhere.[1] The first apparent reported combination of headspace sampling with GC analysis was by Bovijn, Pirotte, and Berger[2] in 1958; they used the technique to monitor trace concentrations of hydrogen in water present in a power plant high-pressure boiler. The terms "headspace," "headspace sampling," and "headspace analysis" have been attributed to the food packaging industry where the gas layer above the food in sealed containers was described as the headspace. This terminology was first used in the early 1960s by Stahl and his coworkers while at the McCormick & Company, Inc. (Baltimore, Maryland, U.S.A.). In Stahl's work, the oxygen content within the headspace of metal food cans was determined by headspace sampling GC, and Stahl's work has been described within the historical context of headspace sampling.[1] Headspace analysis gained wide use within the food industry with the development of more sensitive detectors for GC in the late 1950s. Initial headspace sampling was performed manually using syringes, but automated instrumentation was quickly devised by major manufacturers for commercial sale. The need of forensic analysis has been one of the main driving forces for accurate quantitative headspace sampling instrumentation; exact quantitative results have been demanded by the court system for blood alcohol analysis. Blood alcohol analysis has been a common application for headspace sampling for several decades. Regulatory requirements by the Food and Drug Administration in the U.S.A. and by the European drug regulatory agencies have also generated demand within the pharmaceutical industry for accurate quantitative measurements of residual solvents and volatile components of drug products.[3,4]

TYPES OF HEADSPACE SAMPLING

As mentioned in "Introduction," there are basically three headspace sampling techniques. Dynamic or purge-and-trap headspace sampling and static headspace sampling are the two classical techniques. Solid-phase microextractionis the third headspace sampling technique, which will be discussed. These three

Encyclopedia of Chromatography DOI: 10.1081/E-ECHR-120042205

methodologies have been described extensively in the literature[1,3–5] and their basic designs are diagramed in Fig. 1. The sample matrices can be gas, liquid, or solid. Most often, liquids or liquid/solid mixtures are used because of better sample homogeneity and the relatively quick establishment of an equilibrium of the gas phase above the sample matrix. Solid samples may require additional time for a volatile to diffuse out of the solid matrix; residual solvents may be entrapped within a solid crystal structure. (The use of a dissolution solvent to release the analytes within a solid is done frequently in headspace analysis.) Finally, derivatization/reaction headspace sampling is a variation of headspace sampling and will also be discussed.

Dynamic Headspace Sampling

In dynamic headspace analysis, a continuous flow of gas is swept over the surface of the sample matrix. The sample may be heated during this cycle. The volatile components of the sample are swept into a trap where these analytes are accumulated prior to GC analysis (Fig. 1A). The trap consists of a column containing a sorbent such as Tenex®, Chromosorb®, Porapak®, Amerlite® XAD resins, or activated carbon. Tenex is most often used because of its superior thermal stability. A rapid thermal desorption cycle of the trap is initiated, and a carrier gas takes the desorbed analytes into a GC for analysis. Cold trapping can be used as an alternative to the sorbent trap in dynamic headspace sampling. After collection of the volatile, the cold trap is then heated and the analytes are introduced into a GC by a carrier gas. Other terminology and variations of dynamic headspace sampling are thermal desorption sampling (TDS) or direct thermal extraction. These last two sampling methods can involve more extreme heating cycles of the sample matrix.

Dynamic headspace sampling has several advantages over static headspace analysis. Dynamic headspace analysis is particularly suitable for the determination of volatile analytes at very low concentrations from the sample matrix. Lower detection limits are obtained because the "total" amount of a volatile substance can be extracted, trapped, and analyzed at one time. The detection limits for dynamic headspace sampling have been noted as being substantially lower than those for static headspace sampling.[6] Also, dynamic headspace sampling has the advantage of avoiding an equilibrium between the gas phase and the sample matrix, as is required with static headspace and SPME techniques. In the specific case of solid samples being thermally decomposed, an advantage of dynamic headspace analysis is that the use of a dissolution solvent and, thus its associated peak, can be avoided in the chromatogram.[7] The most frequently cited disadvantage of dynamic headspace sampling is the problem of artifact volatile collection in the trap. This is common for the purge-and-trap technique and can be minimized by complete desorption of the trap. This could include desorption cycles having higher temperatures or extending for longer periods to remove the artifacts. Numerous dynamic headspace sampling instruments are commercially available for the easy use of this technique.

Static Headspace Sampling

Static headspace analysis is probably the most widely practiced form of headspace analysis. In static headspace sampling, a liquid or solid sample is placed into

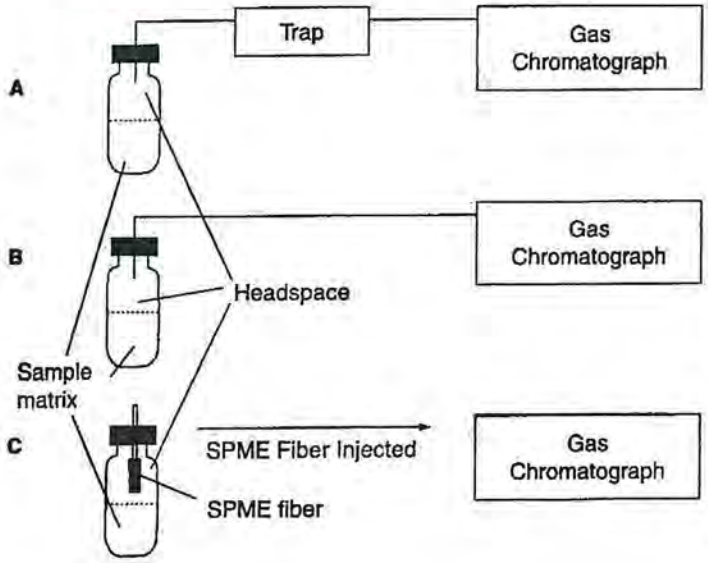

Fig. 1 Comparison of dynamic, static, and SPME headspace sampling. (A) Dynamic headspace sampling uses a sorbent or cold trap to concentrate volatile analytes before analysis by the GC; (B) Static headspace sampling uses direct transfer of a volume of gas from the headspace above the heated sample vial directly to the GC for analysis. Injection designs are illustrated in Fig. 2; (C) SPME headspace sampling uses a fiber support with solid-phase coating. The fiber is placed in the headspace and reaches equilibrium with the headspace volatile analytes. The SPME fiber is transferred by means of a syringe and thermally desorbed in the injector of the GC for analysis.

a sealed vial. The vial is heated for a time until an equilibrium of the volatile between the sample and the gas phase is reached. An aliquot of the headspace gas is sampled and injected into the GC for analysis. The basic physicochemical properties and gas laws are applied in this technique and need not be detailed in this entry. Higher temperatures will promote higher partial pressure and concentration of volatile with the headspace of a given sample; polarity considerations of solutes vs. solvents also will come into play. In pharmaceutical testing, static headspace sampling is preferred when the liquid or solid samples are soluble (or extractable) in solvents such as water, benzyl alcohol, dimethyl formamide (DMF), or dimethyl sulfoxide (DMSO).[4,8] A liquid sample matrix offers a system in which the partitioning equilibrium is more readily established and reproducible. The repeated gas-extraction method first described by McAullife[9] can be used in the case when the partition coefficients (the partition coefficient, k, equals the ratio of the concentration of the volatile analyte in the sample matrix divided by the concentration of the volatile in the gaseous headspace at equilibrium) and the equilibrium time are not well known. Kolb and Posipsil[10] popularized this technique, but referred to it as multiple-headspace extraction (MHE). In MHE, the headspace sample is extracted several times with a gas to obtain exponentially decreasing peak area responses. This allows for the calculation of the total residual solvent or volatile in the original sample, assuming that the thermodynamic equilibration was reached during the multiple extractions. Kolb and Posipsil[10] proposed MHE with solid or certain insoluble samples requiring external calibration. Multiple-headspace extraction as a headspace sampling technique has fallen out of current usage and is not very common.

The main disadvantages of static headspace sampling over dynamic headspace sampling are in higher detection limits and lower sensitivity. Detection limits and sensitivity can be improved by pH control, salting-out, or increasing the equilibrium temperature during sample heating.[11–15] Salting-out is done simply by adding an inorganic salt to an aqueous sample matrix. High salt concentrations in aqueous samples decrease the solubility of polar organic volatiles and thus promote their transfer into the headspace. Some common salts used for salting-out include ammonium chloride or sulfate, sodium chloride, citrate, or sulfate, magnesium sulfate, or potassium carbonate. The magnitude of the salting-out effect is not the same for all compounds. Generally, volatile polar compounds in aqueous matrices will experience the largest increase in partitioning into the gaseous headspace and have higher responses after the addition of a salt. Increasing the sample heating temperature will increase the analyte response until exceeding the boiling point temperature of the analytes.[16] The case in which water is chosen as the dissolution medium, nonpolar analytes are enriched in the headspace and have higher GC responses, while polar analytes have lower GC responses. Dennis, Josephs, and Dokladalova[17] showed enrichment in the headspace up to a factor of 50 for trace nonpolar solvents in water, while polar analyte responses in the headspace of polar sample matrices dropped by up to a factor of 4. Use of multiple internal standards may be necessary in static headspace sampling to match the solubility and partitioning of the analytes in the sample matrix. The purity of the dissolution solvent is another common problem encountered with static headspace sampling. A small impurity in the dissolution solvent may produce an interference peak in the chromatogram.

Instrumental design for static headspace samplers

Automated headspace systems have been offered by several manufacturers for many years, including Thermo Electron Corporation (San Jose, California, U.S.A.), Perkin-Elmer (Wellesley, Massachusetts, U.S.A.), Tekmar (Mason, Ohio, U.S.A.), and Agilent Technologies (Palo Alto, California, U.S.A.). There are essentially three injection techniques for static headspace sampling: gas-tight syringe, balanced-pressure, and pressure-loop injection (Fig. 2). All these techniques are used on commercial headspace systems and will be described.

The gas-tight syringe injection technique can be done manually, although Thermo Electron-Finnigan offers some autosamplers which can perform this technique. A syringe draws a sample of the headspace after equilibrium has been achieved above the sample; then the syringe is used to inject the headspace gases directly into a GC (Fig. 2A). Volatile sample loss can occur unless precautions are taken. The syringe must be heated correctly to ensure that no analytes condense inside the syringe; reproducibility problems can occur from sample loss using the syringe. Some sample loss may occur owing to the pressure changes between the heated headspace vial and the atmospheric conditions. Early static headspace analysis was performed manually using hand held gas-tight syringes, but reproducibility of injections and analyte condensation were significant problems until automated systems were available. The Finnigan TRACE model HS2000 headspace autosampler uses the gas-tight syringe design.

The balanced-pressure injection entails the headspace vial being pressurized and allowed to reach an equilibrium; then a valve is switched to direct part of the sample into the transfer line and the GC for a specific time interval (Fig. 2B). The absolute volume of the sample injected into the GC is unknown because this

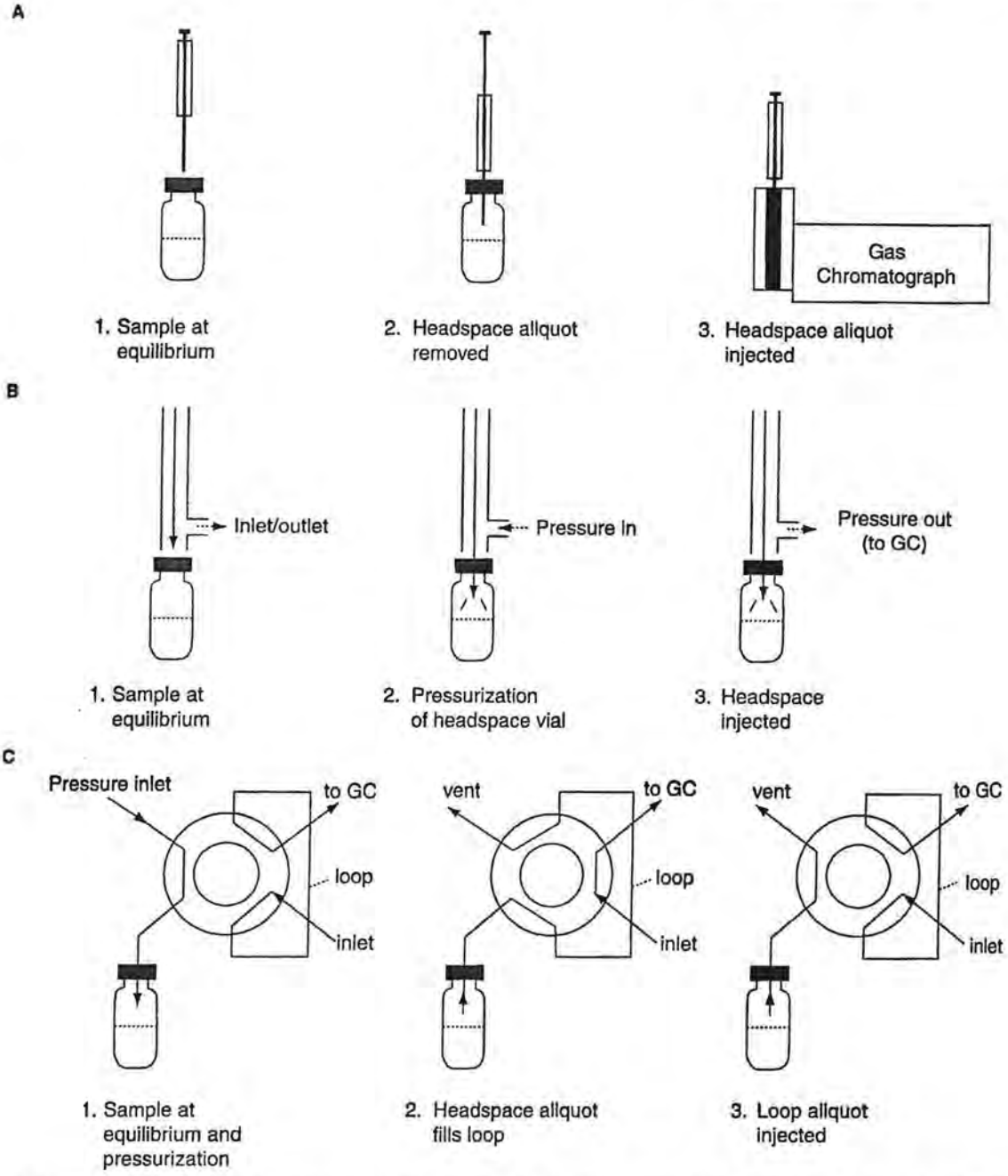

Fig. 2 The three designs of static headspace injection systems. (A) The gas-tight syringe system uses a syringe to collect and transfer a headspace aliquot to the GC; (B) The balance-pressure system pressurizes the vial after thermal equilibrium, and then releases the pressurized headspace into the GC; (C) The pressure-loop system pressurizes the headspace vial, fills a fixed volume loop with a headspace aliquot, and then the loop contents are flushed into the GC.

technique uses a theoretical value amount of time to inject the sample. The number of contact parts is minimized in this design, which should in theory lessen the chance of analyte adsorption or condensation within the system. An example of an instrument utilizing the balanced-pressure technique is the Perkin-Elmer TurboMatrix model HS-40.

The pressure-loop system uses a known amount of sample, unlike the pressure-balance injection technique. After the sample vial has reached an equilibrium and

has been pressurized, a fixed volume loop is filled with an aliquot of the headspace gases. This sample loop is flushed with carrier gas and the volatile analytes are carried by means of the transfer line into the GC (Fig. 2C). Typically, this technique uses a six-port valve system much like those used on high-performance liquid chromatographic injection systems. Loop volumes are generally 1 ml and slightly larger. The loop is flushed between injections, but may cause ghost peaks because of sample carryover from a previous analysis. Analyte condensation is minimized by heating the sample loop and transfer line, although adsorption problems are possible in the sample loop and various transfer lines. The pressure-loop system is noted for its good run-to-run reproducibility and precision of duplicate injections. The pressure-loop injection design is used by the Tekmar model 7000HT and by Agilent Technologies in their models G1888 and 7694E static headspace sampling systems.

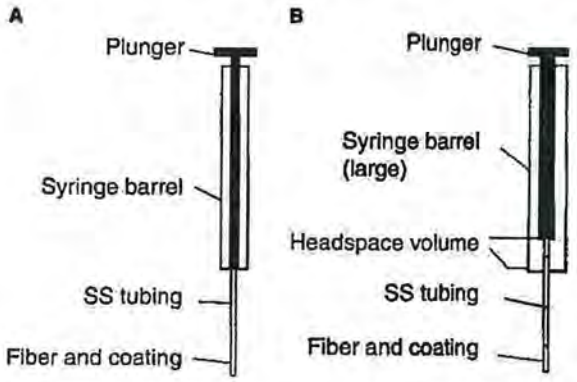

Fig. 3 Injection modes of SPME using a manual syringe. (A) The gas-tight SPME samples a small volume of the sample headspace by using a small syringe. Most of the volatile analytes are collected on the coating of the SPME fiber. (B) Headspace SPME syringe collects a larger volume of the sample's headspace gases along with the volatile analytes collected on the SPME fiber. The headspace aliquot and the analytes adsorbed to the fiber are injected into the GC.

SPME Headspace Sampling

In SPME headspace sampling, a small amount of extracting phase, a stationary phase (described as the solid phase), is coated on a support most commonly a fused silica fiber. The extraction phase is placed in the headspace of a sealed vial containing the sample matrix and heated until concentration equilibrium is reached. The analytes reach equilibrium between the sample matrix, the headspace above the sample matrix, and the extraction solid phase of the SPME fiber (Fig. 1C). Once the equilibrium is reached, continued exposure of the SPME fiber does not lead to any additional accumulation of the analytes. The fiber is usually attached to a sampling device, which is basically a syringe. The SPME fiber is attached to the plunger and is extended during sampling and is withdrawn into the syringe before insertion into a GC. The fiber is extended into the inlet of a GC, and the volatile analytes are thermally desorbed from the extracting phase of the fiber and swept onto the GC column for analysis. The SPME sampling by direct contact or immersion with a liquid sample matrix has also been done to measure volatile components, but this technique is not true "headspace sampling" and will not be discussed.

"Gas-tight" and "headspace injection" SPME are the two types of injection techniques used. In gas-tight SPME, only a small volume of headspace gas is removed from the sample vial for injection. In headspace injection SPME, a larger volume of headspace gas is removed from the sample vial along with the SPME fiber (Fig. 3). Camarasu, Meqei-Szuts, and Varga[6] conducted an extensive comparison test of these techniques along with static headspace sampling of common

Table 1 Detection limit comparison of headspace sampling methods (ng/ml)

Residual solvent	Headspace SPME (PDMS/DVB)	Gas-tight SPME (PDMS/DVB)	Static headspace
Acetonitrile	0.1	0.05	2
Benzene	0.01	0.01	0.1
Chloroform	0.01	0.007	7
1,2-Dichloroethylene	0.01	0.02	7
Dichloromethane	0.01	0.005	0.5
1,4-Dioxane	2	2	20
Trichloroethylene	0.01	0.01	7
Pyridine	0.05	0.7	30

PDMS/DVB, polydimethylsiloxane/divinylbenzene coated fiber; SPME, solid-phase microextraction.
(From Ref.[6].)

solvents found in pharmaceutical products which are listed in Table 1. Gas-tight SPME was found to be the most sensitive technique for acetonitrile, dichloromethane, and chloroform in the Camarasu study. This was attributed to the inherent selectivity of the SPME fiber (polydimethysiloxane/divinylbenzene). Volatile residual solvents commonly found in pharmaceuticals were shown to have detection limits nearly two orders of magnitude lower when using gas-tight SPME over the detection limits determined for static headspace sampling GC.[6] The main limitation of SPME headspace sampling is in the capacity of the fiber itself. Overloading the SPME fiber is possible and the equilibrium time of both the headspace and the SPME fiber in the headspace must be experimentally determined.

Solid-phase microextraction headspace sampling has the advantage of concentrating the analytes, thus lowering detection limits of volatiles. In recent years, SPME headspace analysis has gained a solid reputation as a valid alternative to traditional headspace GC because of the simplicity of execution of the procedure and the low cost of the hardware.[18] Utilization of SPME headspace sampling is increasing with the availability of commercial devices. Supelco (Avondale, Pennsylvania, U.S.A.) has offered a manual syringe SPME system. Varian offers SPME capability in their Combi PAL autosampling system. Many autosampler designs can be adapted to SPME injection because it is analogous to the operation of a common hand held syringe. Another advantage of this technique is that SPME fibers can be cleaned easily and are ready for reuse after thermal desorption which simplifies their adaptation to automation. Solid-phase microextraction has been reviewed in the literature.[19,20]

Derivatization/Reaction Headspace

Chemical derivatization is a technique that can be used to increase the headspace sampling/chromatographic response of specific compounds, which may lack volatility if not derivatized. Compounds with the capability of hydrogen bonding (i.e., alcohols, acids, and amines) are difficult to volatilize and analyze by direct GC. Derivatization can be performed in the actual headspace sample vial to form the more volatile derivatized analyte, which can in turn be sampled in the gaseous headspace. One common example is the use of methanol and boron trifluoride to derivatize fatty acids to the corresponding methyl esters. The major disadvantage of this approach is that the derivatization reagents and associated by-products from the derivatization reaction may be volatile and can partition into the headspace along with the desired derivatized compounds. This may cause difficulties with interfering peaks which might coelute with the compounds of interest. Pressures within the headspace/reaction vial may also cause problems by exceeding the pressure sealing abilities of the septum or the vial's structure.

Example Applications of Headspace Sampling in GC

There are multiple areas in analytical chemistry which utilize headspace sampling and headspace analysis with GC. Food analysis has been briefly discussed in this manuscript in the historical development of headspace analysis. Headspace analysis is widely practiced in environmental analytical chemistry; it is often used in the analysis of volatile organic chemicals in water,

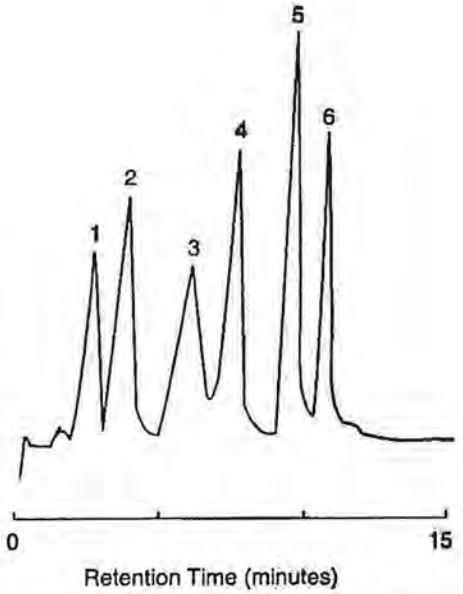

Fig. 4 Gas chromatogram of a standard alcohol mixture. The concentration of each alcohol is at 1000 nmol m/l aqueous solution. Peaks: 1) ethanol; 2) *n*-propanol; 3) 2-propen-1-ol (allyl alcohol); 4) *n*-butanol; 5) 3-methyl-1-butanol (isoamyl alcohol); 6) *n*-pentanol (*n*-amyl alcohol). Manual static headspace sampling was used with the following conditions: 0.2-ml aliquot of sample added to 9-ml serum bottle containing 200 mg of potassium carbonate and heated for 20 min at 70°C. A 0.2-ml headspace aliquot was injected. The Hewlett-Packard Model 5880 GC was equipped with a cryogenic attachment (carbon dioxide cooling) and a 50 m × 0.2 mm (ID) Carbowax 20M (HP) column. Initial column temperature was 20°C with a 6-min hold, then increased at a rate of 5°C/min to 40°C/min, then increased at a rate of 10°C/min to a final temperature of 90°C and held for 5 min. A flame ionization detector (FID) was used. (From Ref.[22].)

waste water, and soil. Plastic material testing for volatile monomers in finished plastic products has been performed using headspace analysis. Forensic chemists are utilizing SPME headspace sampling for use in testing traces of residual accelerants from residue ash or post fire debris. The SPME fibers are replacing the activated charcoal strips previously used in sampling headspace of collected fire debris. Dynamic and static headspace analysis as well as cryogenic focusing have been used in arson analysis.[21] The three examples that is briefly discussed for this entry are clinical/toxicological analysis, industrial health and hygiene exposure analysis, and pharmaceutical analysis. Many applications obviously exist and can be readily found in the literature.

Clinical/toxicological analysis

Clinical/toxicological analysis is another important area for headspace sampling including blood alcohol analysis, although forensic analysis of blood alcohol levels for court cases is one of the most common uses of headspace sampling. Clinical testing and testing of blood for volatile alcohol in support of toxicology studies are equally significant. In Fig. 4, a chromatogram of typical blood alcohol analysis is displayed; in this particular example, rat blood was analyzed using manual syringe headspace sampling.[22] In addition to ethanol, longer chain alcohols were analyzed simultaneously using this procedure. Blood alcohol testing, in general, has been reviewed in the literature,[23] and headspace sampling offers an ideal technique for the analysis of volatile components. This is also true for many toxicological analyses where the blood, tissue, or sample matrix is not applicable to the direct injection into a GC. The Doizaki and Levit[22] procedure cited above was also applied in the determination of alcohols in human stool specimens.

Industrial Health and Hygiene Biomonitoring Exposure Analysis

Headspace sampling is being used to monitor the internal exposure of human subjects to chemicals in their work environment. Test methods have been devised to measure residual parent compounds or their metabolites (biomarkers for exposure) in human blood or urine samples taken from the exposed population. In a recently published work, a method to measure urinary 1- and 2-bromopropane was validated.[16] 1-Bromopropane is a commonly used industrial solvent, and 2-bromopropane is often found as an impurity component in industrial grade 1-bromopropane. 1-Bromopropane has numerous industrial applications including cleaning metal, optical instruments, and electronics as well as being a component in spray adhesives. Both compounds are a health concern for exposed workers owing to their chronic toxicity. Because of the extensive use of 1-bromopropane in the industrial setting, workers can be exposed to 1-bromopropane by both vapor and liquid including direct dermal contact. In the example chromatogram displayed in Fig. 5, 1- and 2-bromopropane were analyzed using static headspace sampling of spiked urine samples.[16] Headspace sampling of adsorbent material used to monitor the workplace environment is also done. The other forms of headspace sampling are finding applications in the industrial health and hygiene monitoring field.

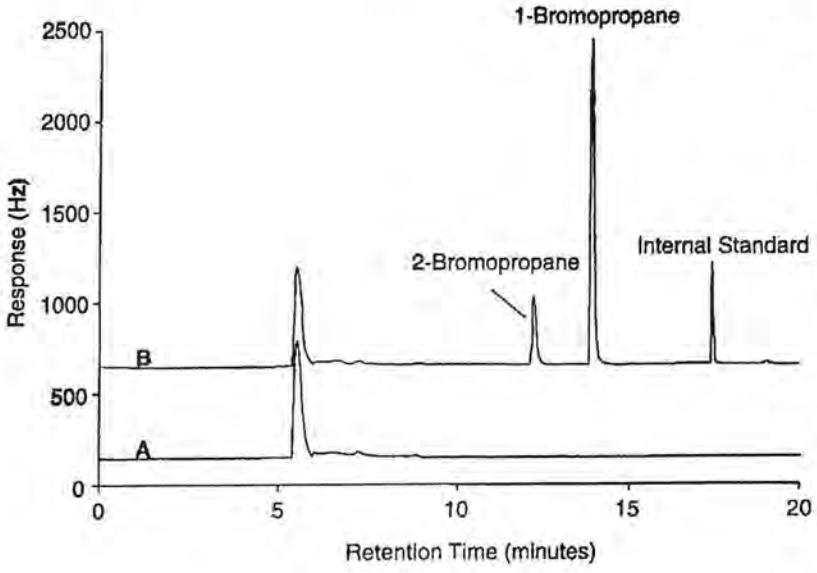

Fig. 5 Gas chromatograms of blank (A) and spiked; (B) human urine samples containing 1-bromopropane, 2-bromopropane, and 1-bromobutane as the internal standard. Static headspace sampling was used with the following conditions: Tekmar model 7000 HT headspace sampler with 1.0-ml sample loop and platen temperature of 75°C and a valve/loop temperature of 120°C. Sample equilibrium time was 34 min. The Agilent Technologies Model 6890 GC was equipped with an Agilent J&W DB-1 (dimethylpolysiloxane) column with a 1 μm film thickness. Initial column temperature was 45°C with a 10 min hold, then increased at a rate of 12.5°C/min to a final temperature of 170°C. A microelectron capture detector (μ-ECD) was used. (From Ref.[16].)

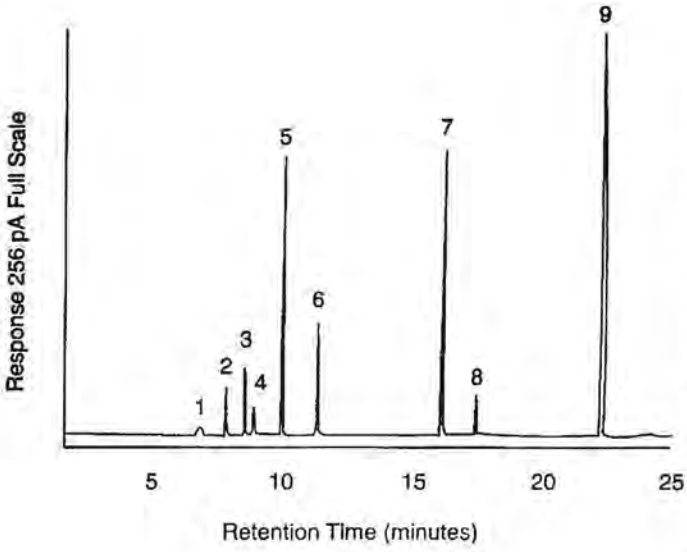

Fig. 6 Gas chromatogram of a vigabatrin drug substance sample spiked with possible processing solvents. Peaks: 1) methanol; 2) ethanol; 3) acetone; 4) isopropanol; 5) methylene chloride; 6) 1-propanol (internal standard); 7) 1,2-dichloroethane (internal standard); 8) butanol; 9) toluene. Static headspace sampling was used with the following conditions: Hewlett-Packard/Dani Model 19395A HS sampler with 1.0-ml sample loop with a bath temperature of 60°C and a valve temperature of 70°C. Sample equilibrium time was 30 min. The Hewlett-Packard Model 5880 GC was equipped with a 60 m × 0.32 mm (ID) Supelco SPB-1 (dimethylpolysiloxane) column with a 1 μm film thickness. Initial column temperature was 35°C with a 12 min hold, then increased at a rate of 10°C/min to a final temperature of 175°C. A flame ionization detector (FID) was used. (From Ref.[24].)

Pharmaceutical Analysis

Pharmaceutical products are extensively tested for residual solvents, and headspace analysis has been often used. Residual solvents in pharmaceuticals are generally volatile chemicals that are used in and are produced during the synthesis of drug substances or can be in the excipients used in the production of drug formulations. These residual volatile chemicals can be remains from processing agents. Many of these volatile organic substances cannot be completely removed by standard manufacturing processes and are left behind, usually at low or trace levels. High levels of residual organic solvents can play a role in the physicochemical properties such as crystallinity of the bulk drug substance. Residual solvents also present a risk to human health because of their toxicity. Some odor problems have also been associated with finished drug products having high levels of residual volatiles. Therefore, the main purpose of pharmaceutical residual solvent testing is in its use as a monitoring check for further drying of bulk drug substance or as a final check of a finished product. In Fig. 6, a chromatogram of a headspace GC method to quantify the levels of various residual solvents in the bulk pharmaceutical product Vigabatrin is shown.[24] The solvents detected in this chromatogram are possibly present in bulk drug as they were used in its synthetic route or used to recrystallize the final bulk product. Static headspace sampling was used for this specific chromatographic test method analysis, but dynamic headspace sampling has been applied to analytical problems within the pharmaceutical industry. The SPME headspace sampling is a more recent development and has been applied to pharmaceutical residual solvent analysis.[6]

CONCLUSIONS

Headspace sampling in gas chromatographic analysis is a highly useful technique and has been widely practiced in multiple analytical fields over the past four decades. The advantages of avoiding direct sampling of sample matrices which would contaminate the operation of a GC make headspace sampling a valuable technique. Coupling this sampling technique with today's greater availability of both more sensitive and more specific GC detectors including mass spectrometry will only lead to continued use and growth in the future. The use of SPME headspace sampling will certainly increase, as commercial instrumentation becomes more available and the technique becomes more accepted in the different fields of analysis. The two best works on the basics and theory of headspace sampling and analysis are books by Hachenberg and Schmidt[11] and by Kolb and Ettre.[5] Solid-phase microextraction headspace sampling has been best described by the associated works of Pawliszyn et al.[19,20,25] For further information on pharmaceutical applications of headspace sampling, the review articles by Witschi and Doelker[4] and B'Hymer[3] may be referred.

ACKNOWLEDGMENTS

The author would like to thank Anne P. Vonderheide, Dennis W. Lynch, Lisa S. Milstein and David C. Ackley for their editorial comments and help during the preparation of this manuscript.

DISCLAIMERS

Mention of company names and/or products does not constitute an endorsement by the CDC. The findings and conclusions in this manuscript are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

REFERENCES

1. Ettre, L.S. The beginnings of headspace analysis. LC-GC N. Am. 2002, *20*, 1120–1129.
2. Bovijn, L.; Pirotte, J.; Berger, A. Determination of hydrogen in water by means of gas chromatography. In *Gas Chromatography, 1958*, Proceedings of the 2nd Symposium (Amsterdam), Desty, D.H., Ed.; Butterworths: London, 1958; 310–320.
3. B'Hymer, C. Residual solvent testing: a review of gas-chromatographic and alternative techniques. Pharmaceut. Res. 2003, *20*, 337–344.
4. Witschi, C.; Doelker, E. Residual solvents in pharmaceutical products: acceptable limits, influences on physicochemical properties, analytical methods and documented values. Eur. J. Pharm. Biopharm. 1997, *43*, 215–242.
5. Kolb, B.; Ettre, L.S. *Static Headspace Gas Chromatography: Theory and Practice*; Wiley-VCH, Inc.: New York, 1997.
6. Camarasu, C.C.; Meqei-Szuts, M.; Varga, G.B. Residual solvents in pharmaceutical products by GC-HS and GC-MS-SPME. J. Pharm. Biomed. 1998, *18*, 623–638.
7. Wampler, T.P.; Bowe, W.A.; Levy, E.J. Dynamic headspace analysis of residual volatiles in pharmaceuticals. J. Chromatogr. Sci. 1985, *23*, 64–67.
8. Mulligan, K.J.; McCauley, H. Factors that influence the determination of residual solvents in pharmaceuticals by automated static headspace sampling coupled to capillary GC-MS. J. Chromatogr. Sci. 1995, *33*, 49–54.
9. McAullife, C.D. GC determination of solutes by multiple phase equilibration, Chem. Tech. 1971, *1*, 46–51.
10. Kolb, B.; Posipsil, P. A gas chromatographic assay for quantitative analysis of volatiles in solid materials by discontinuous gas extraction. Chromatographia 1977, *10*, 705–711.
11. Hachenberg, H.; Schmidt, A.P. *Gas Chromatographic Headspace Analysis*; Heyden Press: Rheine, Germany, 1977.
12. Drozd, J.; Novak, J. Headspace gas analysis by gas chromatography. J. Chromatogr. 1979, *165*, 141–165.
13. Poole, C.F.; Schuette, S.A. Isolation and concentration techniques for capillary column gas chromatographic analysis. J. High Res. Chromatogr. 1983, *6*, 526–549.
14. Nunez, A.J.; Gonzalez, L.F.; Janak, J. Pre-concentration of headspace volatiles for trace organic analysis by gas chromatography. J. Chromatogr. 1984, *300*, 127–162.
15. Vitenberg, A.G. Methods of equilibrium concentration for the gas chromatographic determination of trace volatiles. J. Chromatogr. 1991, *556*, 1–24.
16. B'Hymer, C.; Cheever, K.L. Development of a headspace gas chromatographic test for the quantification of 1- and 2-bromopropane in human urine. J. Chromatogr. B 2005, *814*, 185–189.
17. Dennis, K.J.; Josephs, P.A.; Dokladalova, J. Proposed automated headspace method for organic volatile impurities (467) and other residual solvents. Pharm. Forum 1993, *19*, 5063–5066.
18. Croan, S.A.; Giannellini, V.; Furlanetto, S.; Banbagiotti-Alberti, M.; Pinznuti, S. Improving gas chromatographic determination of solvents in pharmaceuticals by combined use of headspace solid-phase microextraction and isotopic dilution. J. Chromatogr. A. 2001, *915*, 209–216.
19. Kataoka, H.; Lord, H.L.; Pawliszyn, J. Application of solid-phase extraction in food analysis. J. Chromatogr. A. 2000, *880*, 35–62.
20. Lord, H.; Pawliszyn, J. Evolution of solid-phase microextraction technology. J. Chromatogr. A. 2000, *885*, 153–193.
21. Reeve, V.; Jeffery, J.; Weihs, D.; Jennings, W. Developments in arson analysis: a comparison of charcoal adsorption and direct headspace injection techniques using fused silica capillary gas chromatography. J. Forensic Sci. 1986, *31*, 479–488.
22. Doizaki, W.M.; Levit, M.D. Gas chromatographic method for the determination of the lower volatile alcohols in rat blood and in human stool specimens on a fused silica capillary column. J. Chromatogr. 1983, *276*, 11–18.
23. Tagliaro, F.; Lubli, G.; Chielmi, S.; Franchi, D.; Marigo, M. Chromatographic methods for blood-alcohol determination. J. Chromatogr. Biomed. Appl. 1992, *580*, 161–190.
24. B'Hymer, C. Static headspace gas chromatographic method for the determination of residual solvents in Vigabatrin drug substance. J. Chromatogr. 1988, *438*, 103–108.
25. Pawliszyn, J. *Solid-Phase Microextraction: Theory and Practice*; Wiley-VCH, Inc.: New York, 1997.