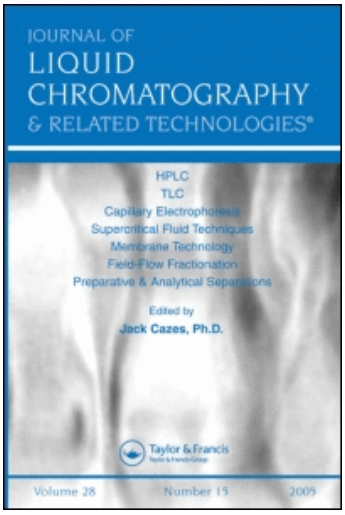

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New Advances in Large-Volume Injection Gas Chromatography-Mass Spectrometry

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Abstract: Gas chromatography-mass spectrometry (GC-MS) with large-volume injection (LVI) is a well-known analytical technique with high sensitivity and specificity, which has been widely used in the identification and quantitation of organic compounds, especially at very low concentrations. This review paper summarizes the new advances of LVI-GC-MS since 2000 and includes the currently available large volume injectors and GC-MS techniques, the sample preparation techniques used with LVI-GC-MS, and the applications of LVI-GC-MS in the analysis of trace organic compounds in a variety of sample matrices.

Keywords: Gas chromatography, Large-volume injection, LVI-GC-MS applications, Mass spectrometry, Sample preparation

INTRODUCTION

Large-volume injection (LVI) is an effective technique widely used for the analysis of trace level organic compounds suitable for gas chromatography (GC) and has a few obvious advantages over conventional hot split/splitless injection with an injection volume of 2 μL or less. First, LVI can improve detection limits without the need for large volumes of samples. Secondly, LVI can eliminate or reduce the need for sample preparation because of the increased sensitivity. Thirdly, LVI can make it possible

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to simplify and/or automate sample preparation steps because of the reduced need for large sample volumes. Finally, LVI can be a suitable interface for online connection of GC to a sample preparation technique.

In the literature, there are a number of peer-reviewed review and research papers in the developments and applications of LVI-GC with various sample preparation and detection techniques. Coupled with flame ionization detection, nitrogen-phosphorus detection, electron capture detection, mass spectrometry (MS), atomic emission detection, and inductively-coupled plasma-MS (ICP-MS) techniques, LVI-GC has been widely used in several analytical fields and has been significantly facilitated by the developments of new sample preparation techniques, particularly small scale sample preparation techniques.

This review paper covers the recent developments and applications of LVI-GC-MS with a focus on the widely used LVI and sample preparation techniques. The literature sources for this review paper mainly consist of peer-reviewed review and research papers published since 2000. Because it is impossible to review and cite all peer-reviewed papers, this review selects representative developments and applications of LVI-GC-MS techniques. Therefore, the injection techniques based on thermal desorption (TD), which may include purge-and-trap, solid-phase microextraction, solid-phase dynamic extraction, and stir bar solvent extraction (SBSE) followed with TD, are not in the scope of this review. A list of acronyms is included in Table 1 as a quick reference to the abbreviations of analytical techniques and other terms discussed in this review.

OVERVIEW OF LARGE-VOLUME INJECTION GC-MS TECHNIQUES

The focal point in LVI is how to remove the solvent vapor resulting from the expansion of a large volume of sample or sample extract. Most efforts are made to efficiently retain and separate analytes from the solvent vapor. LVI techniques generally work well for semi-volatile organic compounds (SOCs) but have limitations with volatile analytes and low volatility or high molecular weight analytes. However, all LVI techniques must deal with one or more problems or challenges in the following important aspects: losses or discrimination of high volatility compounds, ineffective transfer of low volatility compounds, degradation of thermally labile compounds, carryover contamination from previous injections, tolerance of dirty sample matrices, and maximum injection volumes. There may also be negative impacts from moisture in samples or sample extracts on GC and MS. New LVI techniques have been developed to overcome the disadvantages or limitations of early LVI techniques.

Table 1. List of acronyms

ASE	Accelerated solvent extraction
AED	Atomic emission detection
BDE	Brominated diphenyl ether
CI	Chemical ionization
CLLE	Continuous liquid–liquid extraction
CLSA	Closed loop stripping analysis
DMI	Difficult matrix injection
DSI	Direct sample introduction
DSPE	Dispersive solid-phase extraction
EDC	Endocrine disrupting chemical
EI	Electron impact ionization
ESE	Enhanced solvent extraction
GC	Gas chromatography
GCxGC	Two dimensional GC
GPC	Gel Permeation chromatography
HF-LPME	Hollow-fiber liquid-phase microextraction
HRGC	High resolution gas chromatography
HRMS	High resolution mass spectrometry
ICP-MS	Inductively-coupled plasma-mass spectrometry
IDL	Instrument detection limit
ITMS	Ion trap mass spectrometry
LAS	Linear alkylbenzenesulfonate
LC	Liquid chromatography
LD	Liquid desorption
LLE	Liquid–liquid extraction
LOD	Limit of detection
LOQ	Limit of quantitation
LP	Low pressure
LPME	Liquid-phase microextraction
LVI	Large-volume injection
MAE	Microwave-assisted extraction
3-MCPD	3-Monochloropropane-1,2-diol
MDL	Method detection limit
MESI	Membrane extraction with a sorbent interface
MMLLE	Microporous membrane liquid–liquid extraction
MS	Mass spectrometry
PAH	Polycyclic aromatic hydrocarbon
PASE	Pressurized accelerated solvent extraction
PBB	Polybrominated biphenyl
PBDE	Polybrominated diphenyl ether
PCB	Polychlorinated biphenyl
PCDD	Polychlorinated dibenzo-*p*-dioxin
PCDF	Polychlorinated dibenzofuran
PCN	Polychlorinated naphthalene
PDMS	Polydimethylsiloxane
PLE	Pressurized liquid extraction
POP	Persistent organic pollutant
PSE	Pressurized solvent extraction
PSI	Pulsed splitless injection
PTV	Programmed-temperature vaporization/programmable temperature vaporizer
SFE	Supercritical fluid extraction
SAE	Sonication-assisted solvent extraction
SBSE	Stir bar solvent extraction
SD	Solvent desorption
SDME	Single drop microextraction
SE	Solvent extraction
SFE	Supercritical fluid extraction
SLME	Supported liquid membrane extraction
S/N	Signal-to-noise
SOC	Semi-volatile organic compound
SPE	Solid-phase extraction
TCDD	Tetrachlorodibenzo-*p*-dioxin
TD	Thermal desorption
TOFMS	Time-of-flight mass spectrometry
TOTAD	Through oven transfer adsorption desorption
VOC	Volatile organic compound

Early LVI techniques for GC include loop-type injection, on-column injection, and programmed-temperature vaporization injection/programmable temperature vaporizers (PTV). Recent LVI techniques include pulsed splitless injection (PSI)/pressure pulse injection, splitless overflow, at-column injection, direct sample introduction (DSI)/difficult matrix injection (DMI), and through oven transfer adsorption desorption (TOTAD) interface. The developments and applications of LVI techniques have been discussed in several review papers as summarized in Table 2, which also includes two important sample preparation reviews.[1–11] The general advantages and disadvantages of a few current LVI techniques are summarized in Table 3.

PTV

PTV solvent split injection is the predominant LVI technique and can be described as the following steps:[1–5]

1. an aliquot of large volume sample or sample extract is injected into the GC injector at a relatively low temperature;
2. solvent is vaporized and split through a venting valve and analytes are retained and enriched in the injector liner;
3. the injector is rapidly heated in the splitless mode and the retained analytes are desorbed and transferred onto the analytical column, and the oven temperature program starts;
4. the injector remains at high temperature to remove residual matrix interferences and residual solvent vapor from the liner in a splitting mode.

The solvent-split injection approach in PTV-LVI is simple, flexible, robust, and allows rapid at-once injection, multiple or repeated injections, and speed-controlled injection. Multiple and speed-controlled injections are effective for maximizing injection volumes because analytes can be simply retained and enriched in the injector liner after the excess solvent is removed through venting of solvent vapor. The maximum injection volumes are critically dependent on the selection of injector liners and packing materials as well as the optimization of multiple PTV-LVI conditions.

The selection of packing materials or sorbents is often based on the properties of analytes and solvents for a particular application. Several types of packing materials are commercially available. Undeactivated glass wool and beads appear to have strong water affinity. Silanized or Siltek deactivated glass wool is applicable for a wide range of SOCs. Carbofrits have strong affinity to polyaromatic compounds but

Table 2. Overview of peer-reviewed review papers dealing with LVI techniques for GC

Subject	LVI technique	Application	Reference
PTV techniques in GC	Splitless/split injection, vapor overflow, and as an on-column LVI interface	Analytes in organic solvents, water and gas samples	[1]
Injectors for GC	On-column injection, PTV, PSI, at-column injection, and MDI	Environmental analysis	[2]
LVI techniques in GC	On-column injection, PTV, splitless overflow, DSI/DMI, at-column injection, and TOTAD	Environmental, food, agricultural, pharmaceutical, and biological analysis	[3]
Methods and applications of LVI in GC	Loop-type injection, on-column injection, and PTV	Environmental, food, pharmaceutical, and biological analysis	[4]
Online coupling of extraction with GC	Loop-type injection, on-column injection, and PTV	Not specified.	[5]
Advances in GC analysis of persistent organic pollutants	LVI (on-column injection and PTV) was also discussed.	Persistent organic pollutants (POCs) in the aquatic environment	[6]
Direct coupling of RPLC to GC	Loop-type interface, on-column interface, PTV, and vaporizer/pre-column solvent split/gas discharge interface	Environmental and food analysis.	[7]
Developments and applications of GC with AED plus MS	Different extraction techniques with GC injection techniques including on-column injection and PTV.	Environmental analysis	[8]
Membrane extraction for GC applications	Various membrane extraction techniques were Reviewed. LVI was also discussed.	Environmental analysis	[9]
LPME in pesticide residue analysis	Various LPME techniques were reviewed.	Environmental analysis	[10]
Sample preparation for analysis of VOCs	Membrane extraction was also reviewed.	Air and water analysis	[11]

Table 3. Primary advantages and disadvantages of various LVI techniques

LVI	Advantages	Disadvantages
Loop-type	1. Simple configuration and easy parameter optimization	1. Losses of volatile compounds
	2. Suitable for thermally labile compounds	2. Not very rugged with dirty sample matrices
	3. Injection volumes mainly depend on the sample loop size.	3. Difficult to control "shooting" of sample liquid into the column
On-column	1. Good precision	1. Relatively complex configuration and parameter optimization
	2. Suitable for thermally labile compounds	2. Not rugged with dirty sample matrices
	3. Suitable for volatile compounds depending on conditions	
	4. Injection volumes mainly depend on the retention gap size.	
PTV	1. Simple, flexible, and robust	1. Complex parameter optimization
	2. Rugged with dirty sample matrices	2. Considerable losses of thermally labile and volatile compounds
	3. Injection volumes depend on the liner size, packing material, injection approach, and solvent vapor venting conditions.	3. Possible low injection efficiency of heavy compounds
		4. Possible carryover contamination
PSI	1. Simple and flexible	1. Not very rugged with dirty sample matrices
	2. Suitable for thermally labile and volatile compounds	2. Limited injection volume, up to 10 μL
At-column	1. Suitable for thermally labile compounds	1. Relatively complex configuration and parameter optimization
	2. Rugged with dirty sample matrices	2. Losses of volatile compounds
	3. Restricted "shooting" of sample liquid into the column	

(*Continued*)

Table 3. Continued

LVI	Advantages	Disadvantages
	4. Injection volumes depend on the injector liner size, injection approach, and solvent vapor venting conditions.	
DSI/DMI	1. Simple	1. Complex parameter optimization
	2. Rugged with dirty sample matrices	2. Considerable losses of volatile compounds
	3. Less carryover contamination	3. Variations of different microvials
		4. Limited injection volumes, up to 30 μL

release most high boiling point compounds. Organic polymer Tenax or cross-linked polystyrene resists water but strongly retains analytes with a range of volatilities. PTFE wool is inert but does not tolerate high temperature. Polyimide wool is more adsorptive to organophosphorous pesticides. Critical PTV-LVI conditions typically include sample volume and injection speed, solvent venting (injector) temperature and time, vent gas flowrate and split ratio, splitless time and injector temperature after analyte transfer, etc. Because excessive solvent vapor entering the analytical column can affect peak shapes and result in more column bleed, a short deactivated fused silica capillary used as a guard column is often connected to an analytical separation column to focus analytes.

On-Column Injection

In conventional on-column injection, an aliquot of large volume sample or sample extract is injected onto a deactivated capillary retention gap through an on-column injector at a temperature below the solvent boiling point. As the liquid spreads in the retention gap, large volumes of solvent are expended and evaporated, and less volatile analytes are condensed and separated from the solvent. The maximum injection volume is usually dependent on the size of the retention gap. However, the injection volume can be increased by using an early solvent vapor exit (SVE) or a partially concurrent solvent evaporation (PCSE) technique through speed-controlled injection.[2,3] The SVE can be placed between the

retention gap and the analytical column. Both the SVE and the PCSE techniques enable increased solvent evaporation rates which protect the analytical column and detector from excessive solvent vapor. However, similar to PTV-LVI, the SVE technique may cause losses of relatively high volatility analytes. The efforts to reduce the loss of volatile analytes include using a small amount of different solvent with a high boiling point to co-trap more volatile analytes, installing a retaining pre-column between the retention gap and the SVE to restrict the solvent evaporation rate, using a small SVE or narrow bore solvent vapor outlet to restrict the solvent evaporation rate, and closing the SVE prior to the end of solvent evaporation.

At-Column Injection

At-column injection is a recently developed LVI technique that can be described as the following steps:[2,3,12]

1. an aliquot of large volume sample or sample extract is injected into an empty liner with a solvent vapor venting hole at the top of the injector and an approximately 1 mm diameter glass bead used as a liquid flow restrictor in the bottom section. The liner is kept at an initial temperature below the solvent boiling point;
2. the sample slowly enters a short deactivated fused silica capillary precolumn connected to an analytical column. The initial GC oven temperature is above the solvent boiling point;
3. the evaporated solvent creates overflow vapor pressure in the precolumn, which pushes the liquid back toward the cooler liner due to the temperature gradient;
4. the excessive solvent vapor is removed via the injector solvent vapor vent; and
5. at the end of injection, the liner is heated to remove the carry-over resulting from matrix interferences.

The most critical condition for at-column injection is the initial injector temperature. Like PTV-LVI, maximized injection volumes can be achieved by using speed-controlled or multiple injections. Because of the combined features, that is, the flexibility and robustness of PTV, the inertness of on-column injection, and the vapor overflow mechanism of loop-type injection, at-column injection can overcome most drawbacks of other LVI techniques and demonstrates promising applications for a wide range of compounds from very volatile compounds, heavy compounds, and even thermally labile compounds.[12]

Direct Sample Introduction

In DSI, a disposable microvial containing a small amount of liquid or solid sample is introduced into a PTV-LVI GC-MS system using a manual probe or an autosampler.[3,13–15] DSI is also referred to as difficult matrix injection (DMI) when a liquid sample is injected into the microvial placed in a PTV injector liner using an autosampler.[2,3,16] The maximum injection volume is dependent on the size of the microvial, normally 10–20 μL. The optimization of DSI/DMI conditions is similar to the PTV solvent split technique. The microvial is removed and discarded after a GC run. Recently the microvial placed in the DSI probe was successfully used as a small online reactor for the online injection port ion-pair derivatization of acidic organic compounds.[17–20] A small volume of tetrabutylammonium salt solution used as the derivatization reagent or catalyst was added into the microvial along with an aliquot of liquid sample or sample extract. The derivatization was performed by optimizing the PTV conditions, particularly the injector temperature and derivatization time. LVI-GC-MS with DSI online injection port derivatization provided sensitive, fast, and reproducible results.

Pulsed Splitless Injection

Pulsed splitless injection (PSI), also referred to as pressure pulse injection, is a simple and flexible LVI technique with a limited injection volume of up to 20 μL.[2,3,21,22] The injection volume is typically dependent on the liner size, solvent type, injection temperature, and inlet pressure. PSI can reduce solvent vapor volume formed in the liner through the programmed elevation of column head pressure for a short period of time during injection. The higher carrier gas flowrates resulting from the pressure pulse can reduce the residence time of analyte in the hot injection port, which subsequently reduces the degradation of thermally labile compounds and the adsorption of analytes in the injector liner.

Large-Volume Injection GC-MS

LVI-GC-MS studies and applications are commonly carried out using quadrupole or ion trap (IT) MS with electron impact ionization (EI) or chemical ionization (CI) and classic analytical bore capillary columns. A fast GC-MS method using a narrow bore capillary column and PTV-LVI with an injection volume of 125 μL was recently

reported for analyzing polybrominated diphenyl ethers (PBDEs).[23] The resulting retention times were as short as 6.4 min for the last eluting compound, decabrominated diphenyl ether (BDE-209). A fast and sensitive Supersonic GC-MS method using a Supersonic Molecular Beam interface, a fly-through EI ion source, and PTV-LVI with an injection volume of 5–15 μL was also developed to analyze a broad range of pesticides in complex agricultural matrices.[24] One of the main advantages of the Supersonic GC-MS was an enhanced molecular ion (M^+) in the resulting mass spectra with a significant reduction of matrix interferences. The Supersonic GC-MS was suitable for a high carrier gas flowrate. With these features, pesticides at 20 ng/g in a spice matrix were analyzed in 6 min. Two dimensional GC-Time-of-Flight (TOF) MS using PTV-LVI with an injection volume of 10 μL was used for the analysis of pesticides and contaminants in animal feed.[25] ICP-MS coupled with PSI-LVI-GC was used for the speciation of high boiling point analytes. With an injection volume of 20 μL, the limits of detection (LODs) for organotin were 68–250 fg absolute and in the pg/L range for 80 mL water samples extracted with 1 mL of solvent.[21] High resolution GC-high resolution MS (HRGC-HRMS) using PTV-LVI with an injection volume of 20 μL was used for the analysis of dioxins in human milk and plasma.[26] GC-CI-MS-MS using PTV-LVI was used for the analysis of nitrosoamines at ng/L concentration levels in drinking water.[27] A GC-MS-MS method using PTV-LVI was developed as an alternative and complimentary method for dioxin monitoring in food and animal feed.[28] With an injection volume of 10 μL, the method provided an instrument detection limit (IDL) of 200 fg/μL with a signal-to-noise (S/N) ratio of 5:1 for tetrachlorodibenzo-*p*-dioxin (TCDD). Low pressure (LP) GC-MS with an injection volume of up to 5 μL was also evaluated for the analysis of multiple pesticides in food.[29,30]

SAMPLE PREPARATION TECHNIQUES

Sample preparation is a particularly important step for LVI-GC-MS applications not only because analytes need to be enriched but also because water and certain sample matrices are not compatible to GC-MS. First, water vapor can quickly deteriorate the stationary phase of a capillary GC column. Secondly, water vapor can significantly affect the ionization and sensitivity. Pumping down the ion source is very time-consuming. Thirdly, water is not a suitable solvent for wetting the surfaces of the commonly used stationary phases of capillary GC columns as well as the retention gaps and/or precolumns. The wetting can greatly affect peak shapes and sensitivity,

particularly for highly volatile organic compounds. Furthermore, water can form a much larger volume of vapor per volume of liquid than many organic solvents commonly used for GC, which can make the solvent venting process very time-consuming. As a result, complete drying of samples or sample extracts must be performed prior to GC-MS analysis.

Liquid–Liquid Extraction

Liquid–liquid extraction (LLE) is still widely used in the routine preparation of aqueous samples because of its simplicity, robustness, and wide acceptance in many standard methods.[31] However, traditional single or multiple-step LLE is quite labor-intensive and time-consuming, requires large volumes of high purity hazardous solvents, and can cause losses of volatile organic compounds (VOCs) because of their low boiling points close to the boiling points of extraction solvents. Therefore, relatively small scale LLE is often performed. In an in-vial LLE,[32] 800 μL water containing chlorophenoxy acid herbicides in a small autosampler vial was directly derivatized with 800 μL dimethyl sulfate and tetrabutylammonium salts used as an aqueous phase methylation catalyst. The methylated chlorophenoxy acid herbicides were then extracted with 800 μL hexane in the same vial and analyzed using on-column LVI-GC-MS with an injection volume of 200 μL. The limits of quantitation (LOQs) based on a signal-to-noise (S/N) ratio of 6:1 were 10–60 ng/L. Relative standard deviations ranged from 8 to 15% ($n = 7$) for analyte concentrations of 0.5 μg/L in surface water. When the efficiency of a single extraction is very low or multiple batch extractions are impractical due to a large quantity of sample, continuous LLE (CLLE) can be used to extract polar analytes from aqueous samples. In CLLE, a small volume of fresh organic solvent is recycled continuously in the form of droplets passing through the sample. CLLE with PTV-LVI-GC-MS was successfully used to analyze earthy-musty off-flavor problems present in different types of water samples at sub-part-per-trillion (ppt) levels.[33]

The current trends in LLE are toward the simplification, miniaturization, and automation of sample preparation. Liquid-phase microextraction (LPME) gains great interest and developments are being made to reduce the analysis steps, to increase the sample throughput, and to improve the quality and sensitivity of analytical methods, particularly in conjunction with LVI-GC-MS.[9–11] Emerging LPME techniques include single drop microextraction (SDME) and membrane LPME. SDME is based on the distribution of analytes between an aqueous solution and a small drop of organic solvent at the tip of a microsyringe needle.

Membrane LPME is based on the distribution of analytes between an aqueous solution and a water immiscible film trapped in the membrane. Similar to traditional LLE, the selectivity and efficiency of the LPME process is governed by the selection of the two immiscible phases, and is affected by important extraction conditions including the type and volume of solvent film or drop, extraction time, sample ionic strength, sample pH value, and stirring rate.

Two formats of membrane LPME have been used in conjunction with LVI-GC-MS. They are membrane-assisted solvent extraction (MASE) using a hydrophobic membrane bag containing a trapped organic solvent for the analysis of organic contaminants in a variety of sample matrices[34–38] and microporous membrane liquid-liquid extraction (MMLLE) for the analysis of pesticides in grapes.[39] Other types of membrane LPME include membrane extraction with a sorbent interface (MESI), hollow-fiber liquid-phase microextraction (HF-LPME), and supported liquid membrane extraction (SLME) using a flat porous membrane sheet.[9] In theory, MESI, HF-LPME, and SLME can also be used with LVI-GC-MS but no reports have been seen. In addition, a simple and inexpensive polysiloxane tube instead of a membrane bag was also used to extract 10 mL water placed in a 15 mL vial,[40] followed with liquid desorption (LD) using 200 μL organic solvent. The extract was then analyzed using PTV-LVI-GC-MS with an injection volume of 50 μL. The LODs were in the range of 0.5–5 ng/L for 14 organic compounds with a broad range of polarities including atrazine and polychlorinated biphenyls (PCBs).

Solid-Phase Extraction

Solid-phase extraction (SPE) is a standard sample preparation technique alternative to LLE for aqueous sample preparation. SPE is superior to LLE in extraction efficiency, solvent consumption, and ease of automation. A variety of SPE sorbents and formats are used in the extraction of aqueous samples. Conventional manual SPE techniques involving multiple procedures are still widely used in LVI-GC-MS and MS-MS analyses of various sample matrices.[27,41–44] Dispersive SPE can be used for the cleanup of the solvent extracts from complex samples such as animal feeds.[25]

Like LLE, modern trends in SPE also move toward simplification, miniaturization, and automation. Micro-scale SPE methods can simplify the operating steps and in conjunction with LVI-GC-MS provide sufficient sensitivity.[45,46] Automated SPE methods significantly improve accuracy, precision, and throughput. However, most current

automated SPE techniques are not applicable for online GC-MS. Online automated microscale SPE LVI-GC-MS becomes more attractive because no sample manipulation is required between extraction and analysis, which significantly reduces the risk of losses and contamination, and the exposure to hazardous solvents and other chemicals.[47,48] The online micro-scale SPE LVI-GC-MS method, based on a x–y–z robotic technique using 96-well SPE plates, provided method detection limits (MDLs) of less than 0.1 μg/L and could be used for the in-situ analysis of multiple SOCs in tap water, well water, and river water.[47]

Recent developments and applications of SPE LVI-GC-MS techniques also include SBSE that is simple, flexible, robust, and cost-effective. SBSE uses a small stir bar (typically, 1 cm length) coated with polydimethylsiloxane (PDMS) or other phases such as polyurethane foams[49] to extract analytes from aqueous samples. After extraction, stir bars are removed, rinsed with reagent water, and dried with air or clean tissues. SBSE-LD or solvent desorption (SD) instead of TD can be used in combination with LVI-GC-MS for enhanced sensitivity.[25,46,50–54] The experimental conditions affecting adsorption and desorption efficiency of SBSE often include adsorption equilibration time, desorption equilibration time, agitation speed, pH and ionic strength of sample, salting-out effects, and partition coefficients of analytes. The drawbacks of SBSE include potential carryover contamination from repeated use of the stir bars and potential losses due to the adsorption of analytes on the inner surfaces of the sample containers.

Pressurized Liquid Extraction

Pressurized liquid extraction (PLE) is also known as pressurized solvent extraction (PSE), accelerated solvent extraction (ASE), pressurized accelerated solvent extraction (PASE), and enhanced solvent extraction (ESE). Conventional solvent extraction (SE) is a very simple technique for the extraction of solid samples. In SE, organic compounds can be directly extracted into a small amount of organic solvent from a solid matrix. In PLE, the sample is placed in a closed extraction vessel and the extraction solvent is pumped into the extraction vessel that is heated by an external oven.[5] The hot solvent in the vessel quickly removes analytes from the liquid or solid sample matrix. After extraction, the solvent containing analytes is pumped out or purged into a collection vial for further preparation and analysis. The critical conditions often include the pressure and temperature of the extraction chamber, the extraction solvent, and the total solvent volume. PLE combined with

LVI-GC-MS was used to analyze PAHs in airborne particulate matter, soils, and sediments,[55,56] chloroanilines in complex soil samples,[57] 4-nonylphenol in sediments,[13] and linear alkylbenzenesulfonate (LAS) residues in sediments.[17]

Microwave-Assisted Extraction

Microwave-assisted extraction (MAE) uses an organic solvent in a closed extraction vessel.[5] The solvent absorbs the microwave radiation and is heated internally. The temperature in the vessel is dictated by the extraction solvent. As the temperature of the solvent in the closed vessel rises, the pressure rises above atmospheric pressure. MAE is a very simple, inexpensive, fast, and effective extraction technique for the extraction of polar and medium polar organic compounds in solid samples. However, the solvents used in MAE must be dielectric, such as water and alcohols. Combined with PTV-LVI-GC-MS, MAE was used to analyze PBDEs, polybrominated biphenyls (PBBs) and polychlorinated naphthalenes (PCNs) in sediments.[58]

Other Sample Preparation Techniques

Closed loop stripping analysis (CLSA) is a conventional preparation technique typically used for the analysis of VOCs in liquid samples and has a limited enrichment factor. However, combined with the sensitivity enhancement feature of LVI, modified CLSA with PTV-LVI-GC-MS was applicable for the analysis of earthy-musty odorous compounds in water at concentrations of 15–50 pg/L.[59] Online supercritical fluid extraction–liquid chromatography (SFE-LC) was also effectively used to collect atmospheric particles for GC-MS analysis.[60] The aerosol sample extracted by SFE was fractionated into four different LC fractions (280 μL, 840 μL, 840 μL, and 840 μL, respectively) according to polarity, which were subsequently analyzed by GC-MS for nonpolar compounds, polycyclic aromatic hydrocarbons (PAHs), alkyl-PAHs, and more polar compounds, respectively. Ultrasonic or sonication-assisted solvent extraction (SAE) is also a very simple, inexpensive, fast, and effective extraction technique for the extraction of organic compounds with a wide range of polarities in solid samples. Unlike MAE, the solvents used for SAE are less restricted. Therefore, SAE is also suitable for nonpolar organic compounds and was used to extract PBDEs after the analytes were collected on a pumping filter from air.[23]

LVI-GC-MS APPLICATIONS

Environmental Analysis Applications

Environmental analysis has been a primary application area for LVI-GC-MS. Table 4 represents examples of LVI-GC-MS applications published in peer-reviewed papers since 2000 for a variety of environmental sample matrices including various waters, soils, sediments, sludge, airborne or atmospheric particles, and fly ash. As shown in Table 4, PTV with different sample extraction techniques is the predominant LVI used for these analyses. The applications of PTV-LVI-GC-MS include:

1. emerging contaminants including endocrine disrupting chemicals (EDCs) in water,[41,50,52] estrogens in sludge and sediments,[61] and PBDEs as brominated flame retardants in air and sediments;[23,58]
2. PAHs in marine sediments,[62] airborne particles,[56] water and beverage,[37] and soils and sediments;[55]
3. halogenated persistent organic pollutants (POPs) from PCBs in river water and other matrices[34] to PBDEs, PBBs, and PCNs in sediments;[58]
4. a wide range of SOCs in waters for pesticides,[63], phenols,[36,64] phthalates,[54] acidic and polar organic contaminants,[53] triazines and other semi-volatile contaminants,[35] and 14 organic compounds covering a broad range of polarity from atrazine to PCB 138;[40]
5. volatile taste and odor compounds in waters;[33,59] and
6. other organic compounds in fly ash[65] and chloroanilines in soils.[57]

With the use of MAE, PTV-LVI-GC-MS was used to analyze 47 environmental contaminants including triazines, organochlorine, and organophosphorus compounds in several complex samples such as natural and synthetic wastewater, bacterial culture, and orange juice.[38] In addition, PTV-LVI was also coupled with GC-ICP-MS for the speciation of organotin in waters and sediments.[66]

Several papers have reported the studies and applications of large volume DSI with GC-MS, for example, sediment analyses for linear alkylbenzenesulfonates (LAS)[17] and 4-nonylphenol as an EDC,[13] and water analyses for naphthalenesulfonic acids,[20] acidic herbicides,[19] and acidic pharmaceuticals.[18] Only a few applications used PSI and on-column LVI-GC-MS techniques. PSI-LVI-GC-MS was used for the analysis of PBDEs, PBB, PCBs, and other halogenated compounds in NIST Standard Reference Material (SRM).[67] Coupled with GC-ICP-MS, PSI-LVI was also used for the speciation of organotin in waters and sediments using an extra-long liner, retention gap, pulse time, purge time, and solvent trapping time.[21] On-column LVI was used for the analysis of herbicides in water[32] and pesticides in air.[68]

Table 4. Applications of LVI-GC-MS in environmental analyses

Analyte	Matrix	Extraction	Instrumentation	Notes/comments	Reference
Chloroanilines	Soil	PLE	On-column & PTV-LVI-GC-MS	For standard solutions of chloroanilines, the LODs were 0.05–0.5 μg/L for on-column LVI of 100 μL and 0.2–12 μg/L for PTV-LVI of 20 μL.	[57]
EDCs	Water	SBSE-LD	PTV-LVI-GC-MS	The LOD was 0.1 μg/L for 60 EDCs with an injection volume of 20 μL.	[50]
EDCs	Water	SBSE-LD	PTV-LVI-GC-MS	The LODs were 0.01–0.24 μg/L with an injection volume of 200 μL. Aldrin, dieldrin, 4,4′-DDE, and 4,4′-DDT were detected in river samples.	[52]
EDCs	Water	SPE	PTV-LVI-GC-MS	The LOQs (10xSD) were 0.5–20 ng/L for 12 EDCs, with an injection volume of 40 μL.	[41]
Estrogens	Sludge & sediment	SE & derivatization	PTV-LVI-GC-MS-MS	An extract cleanup procedure was performed after solvent extraction. Estrogens were analyzed with an injection volume of 5 μL after derivatization.	[61]
Herbicides	Water	In-vial LLE	On-column LVI-GC-MS	The analytes were in-situ derivatized with dimethyl sulfate with tetrabutylammonium salts as catalyst for the methylation of chlorophenoxy acid herbicides. The LOQs (S/N = 6:1) were 10–60 ng/L with an injection volume of 200 μL.	[32]

(*Continued*)

Table 4. Continued

Analyte	Matrix	Extraction	Instrumentation	Notes/comments	Reference
Herbicides	Water	SPE	DSI-LVI-GC-MS	The analytes were online derivatized with tetrabutylammonium salts in the injection port. The LOQs were 0.1–0.2 μg/L with an injection volume of 10–20 μL.	[19]
LAS	Sediment	PLE	DSI-LVI-GC-ITMS	The analytes were online derivatized with tetrabutylammonium salts in the injection port. The LOQ (S/N = 10) was 0.05 μg/g for total LAS Residues with an injection volume of 10–20 μL.	[17]
Naphthalene-sulfonic acids	Water	SPE	DSI-LVI-GC-MS	The analytes were online derivatized with tetrabutylammonium salts in the injection port. The injection volume was 10 μL. The analytes were quantitated at 0.05 μg/L for wastewater and river water.	[20]
4-Nonyl-phenol	Sediment	PLE	DSI-LVI-GC-MS	After PLE, a cleanup procedure was applied to the extract. The LOQ (S/N = 10:1) was 0.01 μg/g with an injection volume of 20 μL.	[13]
Organics	Atmo-spheric particles	Online SFE-LC	LVI-GC-MS	The identification of a wide range of organic compounds were performed by collecting and analyzing four LC fractions with volumes of 280, 840, 840, and 840 μL, respectively.	[60]
Organics	Fly ash	SE	PTV-LVI-GC-MS	The injection volumes were 10–100 μL.	[65]

Organotin	Water	Derivatization	PSI-LVI-GC-ICP-MS & LLE	The analytes were derivatized with sodium tetrapropylborate. The LODs were 68–250 fg or in the pg/L range with an injection volume of 20 μL.	[21]
Organotin	Water & Sediment	LLE & LSE	PTV- LVI-GC-ICP-MS	The LODs were 0.019–0.85 pg/L for water and 0.23–0.48 ng/g for sediments with an injection volume of 100 μL.	[66]
PAHs	Marine sediment	MAE	PTV-LVI-GC-MS	The LODs were 0.05–1.08 μg/L for 26 PAHs with an injection volume of 25 μL.	[62]
PAHs	Airborne particles	ASE	PTV-LVI-GC-MS	After ASE, a cleanup procedure using GPC was applied. The LODs (S/N = 3:1) were 0.26–3 pg/m^3 with an injection volume of 70 μL.	[56]
PAHs	Water & beverage	MAE	PTV-LVI-GC-MS	The LODs were in the ng/L range for aqueous samples, milk, juice, and wine, and varied with the different fat content with an injection volume of 100 μL.	[37]
PAHs	Soil & sediment	PLE	PTV-LVI-GC-MS	The at-once injection volume was 50 μL. The LODs were 1–9 ng/g for the majority PAHs.	[55]
PBDEs	Air	MAE & SPE	PTV-LVI-GC-MS	The air samples were collected on a pumping filter. The injection volume was 50 μL. The LODs were from 0.04 pg for BDE-100 to 0.87 pg for BDE-209 that correspond to 0.8 fg/μL and 17.4 fg/μL.	[23]
PBDEs, PBBs	Sediment	MAE & PCNs	PTV-LVI-GC-MS-MS	The LODs were 4–20 pg/g with an injection volume of 70 μL.	[58]

(*Continued*)

Table 4. Continued

Analyte	Matrix	Extraction	Instrumentation	Notes/comments	Reference
PCBs	Water & beverage	MAE	PTV-LVI-GC-MS	The injection volume was 100 μL. The LODs in the ng/L range for river water samples, juice, and wine, varied with the different fat content.	[34]
Pesticides	Water	SPE	LVI-GC-MS	The injection volume was 10 μL. 5 pesticides could be identified and quantitated at 1.2–3.0 ng/L in marine and coastal waters.	[42]
Pesticides	Water	Micro LLE	PTV-LVI-GC-NICI-MS	The LODs were 0.004 to 2.2 ng/L for river water with an injection volume of 100 μL.	[63]
Pesticides	Air	PLE	On-column LVI-GC-NCI-MS	The air sample is collected using a sampler a polyurethane foam plug/sorbent cartridge and a glass fiber filter. The MDLs were 1.0–5.0 μg/L with an injection volume of 10–100 μL.	[68]
Phenols	Water	MAE	PTV-LVI-GC-MS	The LODs were 1–10 ng/L for 7 phenols with an injection volume of 100 μL.	[36]
Phenols	Water	Derivatization & LLE	PTV-LVI-GC-MS	Phenols were derivatized with acetic anhydride. Followed with LLE, the corresponding phenyl acetate esters were analyzed. The LODs were in the low ng/L range for all compounds.	[64]

Pharma-ceuticals	Water	SPE	DSI-LVI-GC-MS	The analytes were online derivatized with tetrabutylammonium salts in the injection port. The LOQs were 1.0–8.0 ng/L with an injection volume of 10 μL. Clofibric acid, ibuprofen, carbamazepine, naproxen, ketoprofen, and diclofenac at 30–420 ng/L were in WWTP effluents and river waters.	[18]
Phthalates	Water	SBSE-LD	PTV-LVI-GC-MS	The injection volume was 20 μL. The LODs were 3–40 ng/L for drinking water.	[54]
POPs	NIST SRM & SAE	Soxhlet extraction	PSI-LVI-GC-MS	With an injection volume of up to 120 μL, the LODs were pg-fg levels for the persistent organic pollutants (POPs) including PDBEs, PBB, PCBs, hexachlorocyclohexane isomers, and hexachlorobenzene.	[67]
SOCs	Complex matrix	MAE	PTV-LVI-GC-MS	The LOD was 2–10 ng/L for organochlorine compounds with an injection volume of 100 μL.	[38]
SOCs	Sediment	SE & online SPE	Loop-type LVI-GC-MS	The injection volume was 150 μL. The methanol or ethyl acetate extract of the dried sediments was filtered and then diluted. The diluted extract was then loaded onto online SPE GC-MS, which provided semi-quantitative detection at low- to sub-μg/L for PAHs and other contaminants.	[48]

(*Continued*)

Table 4. Continued

Analyte	Matrix	Extraction	Instrumentation	Notes/comments	Reference
SOCs	Water	SBSE-LD	PTV-LVI-GC-MS	The LODs were 1–800 ng/L for 46 acidic and polar organic contaminants with an injection volume of 200 μL.	[53]
SOCs	Water	PTSE-LD	PTV-LVI-GC-MS	The injection volume was 50 μL. The LODs were in 0.5–5 ng/L for 14 SOCs including 7 PCBs, atrazine, and others. PTSE = Polysiloxane tube sorptive extraction.	[40]
SOCs	Water	MAE	PTV-LVI-GC-MS	The LODs were 1–10 ng/L for triazines and other SOCs with an injection volume of 100 μL.	[35]
Taste & Odor	Water	CLSA	LVI-GC-MS	The LODs were 15–30 pg/L with an injection volume of 10–250 μL.	[59]
Taste & Odor	Water	CLLE	PTV-LVI-GC-MS	The injection volume was 100 μL. The MDLs were from 0.05 ng/L for geosmin, 0.34 ng/L for MIB, to 0.035–0.07 ng/L for haloanisoles. The recovery ranged from 58% to 96% with a relative standard deviation of 4.7–15.1%.	[33]

Agricultural and Food Analysis Applications

Table 5 represents examples of LVI-GC-MS applications published in peer-reviewed papers since 2000 for a variety of agricultural and food sample matrices. Similar to the environmental analysis applications, PTV is the predominant LVI used for these analyses. DSI/DMI, PSI, and on-column LVI are also used in agricultural and food analyses. Primary LVI-GC-MS applications include:

1. pesticides in vegetables and fruits,[16,22,39,46] eggs,[14] and animal feed;[25]
2. wine analyses for aldehydes,[69] ethyl carbamate,[70] and VOCs;[71] and
3. volatile off-flavor compounds including 2,4,6-trichloroanisole and 2,4,6-tribromoanisole.[45]

PTV-LVI-GC-MS-MS with different sample preparation and cleanup techniques was used for the analysis of PCBs in fast food menus;[72] dioxin in milk powder, yolk, animal feed, and serum;[28] and 3-monochloropropane-1,2-diol (3-MCPD) in food.[73] Acrylamide in various food matrices was analyzed by DSI-LVI-GC-MS with a microscale solvent extraction (SE) technique and acrylamide-d_3 used as an internal standard. Testosterone in bovine bile was analyzed by PTV-LVI-GC-MS with SPE and LC for extract purification.[44]

Other Analysis Applications Since 2000

LVI-GC-MS is also used for biological and pharmaceutical sample analyses. PBDEs in human adipose tissue were analyzed by PTV-LVI-GC-MS with Soxhlet extraction and a cleanup procedure using two successive SPE cartridges for sample preparation and a narrow-bore capillary column for separation.[74] With an injection volume of 100 μL, the method allowed the determination of five major PBDE congeners (BDE 28, BDE 47, BDE 99, BDE 100, and BDE 153) at concentrations below 1 ng/g lipid weight within a short analysis time (up to 10 min). The obtained LODs in the selected ion mode were 0.05–0.3 ng/g lipid weight, depending on the degree of bromination. Multiple dioxins in human milk and plasma were analyzed by PTV-LVI-HRGC-HRMS with a sample extraction, purification, and fractionation procedure. With an injection volume of 20 μL, the LODs were 0.02–0.1 pg/g for representative isomers including polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), *non-ortho* PCBs, and *mono-ortho* PCBs.[26] Cannabinoids in plasma were analyzed by PTV-LVI-GC-MS with SPE sample preparation.[43] With an injection volume of 20 μL, the LODs were 0.7–0.8 ng/mL.

Table 5. Applications of LVI-GC-MS in food and agricultural analyses

Analyte	Matrix	Extraction	Instrumentation	Notes/comments	Reference
Acrylamide	Food	Micro SE	DSI-LVI-GC-MS	A 20 μL aliquot of sample extract from various food matrices was analyzed with acrylamide-d_3 as an internal standard and resulted in a lowest calibration level of 25 ng/g.	[15]
Aldehydes	Wine	Derivatization	PTV-LVI-GC-MS & SPE	The LODs were 0.002 to 0.73 μg/L for nine aldehydes previously derivatized with PFBHA with an injection volume of 40 μL.	[69]
Dioxin	Complex matrix	Soxhlet extraction PLE, & SPE	PTV-LVI-GC-MS-MS	The injection volume was 10 μL. The IDL (S/N = 5:1) was 200 fg/μL for milk powder, yolk, animal feed, and serum.	[28]
Ethyl carbamate	Wine	SPE	PTV-LVI-GC × GC-MS	The LOD was 0.1 ng/mL. The LOQ was 1 ng/L.	[70]
3-Monochloropropane -1,2-diol	Food	SE	PTV-LVI-GC-MS-MS	With a chromatographic column purification, the LOD (S/N = 3:1) was 0.044 ng/mL with an injection volume of 70 μL.	[73]
PCBs	Food	PSE	PTV-LVI-GC-MS-MS	After PSE, a cleanup procedure using LLE and GPC was applied, followed with SPE Fractionation. The LODs were 0.3–1.2 pg/g for fast food menus with an injection volume of 80 μL.	[72]
Pesticides	Egg		DSI-LVI-GC-MS-MS	The injection volume was 10 μL (5 mg). The LODs were <10 ng/g.	[14]

Pesticides	Vegetable & fruits	SE & SPE	PTV-LVI-GC-MS	After solvent extraction, the extract was diluted and followed with SPE. The injection volume was 10 μL. The method was used to detect and quantitate over 100 pesticides in fruits & vegetables at 0.01 mg/kg.	[46]
Pesticides	Animal feed	Micro SE	PTV-LVI-GCxGC-TOFMS	After solvent extraction, a cleanup procedure using GPC and dispersive SPE was applied to the extract. The injection volume was 10 μL. The LOQs were 1–20 μg/kg for most analytes. The recoveries were 70–110% with RSDs below 20% for majority of 106 pesticides and others.	[25]
Pesticides	Grape	PLE & MMLLE	On-column LVI-GC-MS	The LOQs were 0.3–1.8 μg/kg.	[39]
Pesticides	Vegetable	Micro SE	PSI-LVI-GC-MS	The LODs were 0.01–0.05 mg/kg with an injection volume of 10 μL.	[22]
Pesticides	Lettuce	SE	DMI-LVI-GC-TOFMS	The lowest calibration level was 5 μg/kg or 2.5 ng/mL with an injection volume of 10 μL.	[16]
TCA & TBA	Wine	SPE	PTV-LVI-GC-MS	The injection volume was 40 μL. The LODs were 0.2 μg/L for 2,4,6-trichloroanisole (TCA) and 0.4 ng/L for 2,4,6-tribromoanisole (TBA).	[45]
Testosterone	Bovine bile	SPE	PTV-LVI-GC-IRMS	The SPE extract was further purified by LC prior to analysis.	[44]
VOCs	Wine	SBSE-LD	PTV-LVI-GC-MS	The LODs were 0.05–9.09 μg/L for nine VOCs with an injection volume of 20 μL.	[71]

CONCLUSIONS

The current trends in analytical chemistry include the development of high sensitivity and high throughput analytical systems. LVI-GC-MS is a very powerful technique because GC provides high separation efficiency, MS provides high sensitivity and specificity detection, and LVI provides enhanced analyte enrichment. PTV is obviously the most popular LVI technique used with GC-MS for the analysis of a wide range of organic compounds in environmental, agricultural, food, biological, and other sample matrices. The merits of PTV are also seen in promising innovative LVI techniques, such as at-column injection and DSI/DMI. At-column injection retains the advantages of PTV and improves the applicability of LVI for volatile and thermally labile compounds. DSI/DMI retains the advantages of PTV and improves the applicability of LVI for complex sample matrices.

LVI-GC-MS applications are facilitated by the development of more sensitive, accurate, precise, and robust sample preparation techniques. The simplification, miniaturization, high concentration enrichment, and automation of sample preparation procedures make routine analysis of a large number of samples easy, fast, and inexpensive. Microscale LLE, SPE, and emerging sample preparation techniques (LPME, MASE, HF-LPME, and SBSE) are replacing labor-intensive and time-consuming classic techniques, such as LLE and Soxhlet extraction for aqueous samples. Simplified and miniaturized SE, PLE, and MAE have become more attractive for solid sample analyses. Online LVI-GC-MS analyses are significant. The online coupling of sample preparation and LVI-GC-MS can provide better precision and substantial cost savings associated with labor, reagents, materials, etc. A recent online microscale SPE PTV-LVI-GC-MS method was able to allow on-site and real-time trace analysis of SOCs in waters. Direct coupling of LC to LVI-GC-MS is still a very powerful technique. Because of the high sample capacity and a wide range of separation mechanisms, modern LC is an appealing online approach for selective fractionation and/or sample cleanup. Finally, LVI-GC-MS also moves toward a wider range of applications because of the advanced LVI and sample preparation techniques and the increased demands for high sensitivity and specificity analyses of various sample matrices.

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