The road to lower detection limits

By: Dotse Selali Chormey, Buse Tuğba Zaman, Sezgin Bakırdere

The rapid advancement in technology and industrialization has led to major breakthroughs in healthcare, goods and services, transportation, housing, utilities and communication. With the majority of start-up materials being of synthetic sources, hazardous wastes are generated during production and when the products are not properly disposed into the environment. These actions have the potential to negatively impact humans and other organisms in different habitats of the ecosystem. Pesticides in agriculture, pharmaceuticals in medicine, heavy metals in mining and metallurgy, and phenolic compounds in household products are some common chemical classes that have been recognized to pose toxicological threats above their safe limits. Some chemicals with well-established toxicological effects are categorized as priority contaminants and regulatory authorities are enforcing strict adherence to recommended limits. Emerging contaminants on the other hand are those that are of concern and are being monitored and studied to establish their toxicological effects. In the last three decades, major advancements have been made in liquid phase and solid phase microextraction strategies that serve as efficient sample preparation methods for the preconcentration of organic and inorganic contaminants from environmental, biological, food and medical samples. These microextraction strategies augment analytical instruments to achieve very low detection limits for contaminants, which in effect aid analysts in meeting the low limits set by regulatory authorities.

POLLUTANTS are chemical entities that are introduced intentionally or unintentionally into the ecosystem through natural occurrences (e.g. volcanic gases, forest fires) and anthropogenic activities (e.g. mining, burning of fossil fuel). Anthropogenic sources account for the highest percentage of pollutants that enter the environment relative to natural sources. The onset of the industrialization age led to significant strides in meeting the ever increasing needs of humans such as housing, utilities, goods and services, transportation and health care. It is without a doubt that the quality of finished goods has significantly improved over the years, but disposal of the wastes associated with the production of these goods remain a major challenge. Inorganic/organic materials derived from nature, and synthetically produced starting materials are used as basic components of useful industrial and domestic products. Since the wastes generated from industrial processes cannot be deposited back into nature in their original forms, proper and safe disposal has become a very sensitive topic. The release of contaminants into the environment finds its way back to humans through drinking contaminated water and consuming plants that grow in contaminated soil. These pollutants when exposed to humans and other organisms are capable of altering the regular function of their systems, resulting in adverse health effects and death under extreme conditions. Regulatory authorities therefore play a vital role in ensuring the safety of humans and other organisms, especially in aquatic habitats.

Analytical chemistry plays a very important role in performing acute toxicity assessment of contaminants, which helps to set permissible limits, and the monitoring of contaminants in environmental/food samples. Long term exposure to contaminants even at low concentrations could lead to dire effects, and it is therefore important to utilize analytical instruments that are capable of performing trace determinations. The initial maximum contamination level (MCL) of arsenic set by the World Health Organization (WHO) in 1958 was 200 µg/L. However, the emergence of epidemiological evidence to support the chronic toxicity from constant exposure to lower levels of arsenic led to the lowering of the MCL on two occasions, first from 200 µg/L to 50 µg/L and finally to 10 µg/L [1].

Flame atomic absorption spectrometry (FAAS) and gas chromatography-mass spectrometry (GC-MS) were developed several years ago, and became commercially available in the ensuing years for the determination of metals and volatile organic compounds, respectively. These two instruments

Prof. Sezgin Bakırdere
Prof. Bakırdere is currently a full professor at the Chemistry Department of Yildiz Technical University. In 2001, he graduated with BSc. in Chemistry from Fırat University. He received his MSc. in Analytical Chemistry from the same university in 2003, and then earned his PhD from the Chemistry Department at Middle East Technical University in 2009. His research background over the past 20 years has been mostly focused on metal speciation, microextraction strategies, hydride generation systems, food analysis, waste water treatment and chromatography. In regard to his expert areas, he has published over 300 papers in internationally respected journals. He has over 200 presentations in national/international conferences in addition to 2 books in CRC Press/Taylor&Francis Group and Elsevier. He is an Associate Member of the Turkish Academy of Science and a full member of the Global Young Academy. He is also a Fellow of the Royal Society of Chemistry (FRSC).

Ms. Buse Tuğba ZAMAN
Ms. ZAMAN successfully obtained her Bachelor of Science in Chemistry from Yildiz Technical University (İstanbul-Türkiye) in the year 2016. In 2018, Ms. Zaman was conferred with the academic distinction of Master of Science from the Analytical Chemistry program, which is housed under the Chemistry Department of Yildiz Technical University (İstanbul-Turkiye). Ms. Zaman has conducted scientific investigations focused on developing analytical methodologies for quantifying inorganic and organic analytes in diverse sample matrices using spectrometric and chromatographic methods. Ms. Zaman has authored over 40 publications that have been published in internationally recognized peer-reviewed journals, as well as presented about 40 scientific researches at both national and international conferences. Ms. Zaman is currently a PhD candidate at Yildiz Technical University, pursuing her doctoral studies in Analytical Chemistry.

Dotse Selali Chormey
Dr. Chormey obtained his Bachelor of Science in Chemistry from the University of Science and Technology (Kumasi – Ghana), after which he performed his national service at the Food Research Institute of the Council for Scientific and Industrial Research (Accra – Ghana). He then proceeded to the Graduate School of Nuclear and Allied Sciences at the University of Ghana, where he obtained his Master of Philosophy in Nuclear and Radiochemistry. He worked briefly at the National Nuclear Research Institute of the Ghana Atomic Energy Commission, before pursuing his doctoral studies in Analytical Chemistry at Yıldız Technical University (İstanbul – Turkiye). After obtaining his PhD., he worked as the Laboratory and R&D Manager at Innova Gold Group for four years and is currently the R&D Manager at Neutec Pharmaceutical, both in İstanbul. His area of expertise includes the determination of priority contaminants in biological, environmental, food and pharmaceutical samples using chromatographic and spectroscopic instruments. He has contributed over 90 scientific publications in reputable journals and served as editor for a book in the Comprehensive Analytical Chemistry series of Elsevier.

are robust, yield precise and accurate results, and are still being used for routine analysis due to their simplicity, relatively low purchase cost and low operational cost. However, they are not sensitive enough to meet the constantly decreasing contaminant limits set by regulatory authorities. Major advancements in analytical instrumentation over the years have now equipped analysts with sophisticated and sensitive instruments that are capable of detecting contaminants at levels that could not be achieved with the classical determination techniques. These contemporary instruments though capable of meeting the required low limits are very expensive and the cost associated with their operation and maintenance are also on the high end.

With sample preparation being a prerequisite to instrumental measurement, compelling efforts have been made to introduce novel methods that preconcentrate contaminants from bulk samples into low volumes that make the contaminants detectable even by the classical instruments. Extraction has become synonymous with sample preparation in analytical chemistry due to its prominence over other techniques. **Liquid-liquid extraction** (LLE) and **solid phase extraction** (SPE) are the two classical extraction methods whose underlying principles have formed the basis for **liquid phase microextraction** and **solid phase microextraction** (LPME and SPME). Disadvantages of the classical LLE and SPE methods such as prolonged and tedious procedures, large sample volume, high solvent consumption and low extraction output are mitigated by the microextraction methods [2].

SLOTTED QUARTZ TUBE (SQT) coupled with the FAAS system was first reported in the literature by Watling in 1977, where the basic quartz accessory was placed on the flame unit of the instrument to significantly enhance the precision and detection sensitivity of ten elements [3]. It is well known that the nebulizer unit is the *Achilles' Heel* of the FAAS system, where up to 90% of aspirated liquid sample exits the system as waste. For the 10% of liquid sample that reaches the flame, atomization and subsequent absorption occurs in split-seconds, and this limited interaction with radiation from the light source accounts for the low sensitivity of FAAS systems. With the nebulizer unit being an intrinsic and unchangeable component of the instrument, sensitivity can be increased by mitigating the rapid exit of analyte atoms from the flame, and the SQT accessory suits this purpose.

Increasing the residence time of atoms in the flame is the first working area of SQTs, and it yields about 2 – 5 folds enhancement in detection sensitivity for some metals. A typical SQT for residence time enhancement as presented in Figure 1a has an entry slot that fits the flame length and an exit slot that is usually shorter than the entry slot. By placing the SQT on the burner head, the dynamics of the flame and the zones for atomization can be altered and this accounts for the varying enhancement factors for different elements due to their peculiar atomization temperatures. Recent SQT-FAAS applications have therefore explored different exit slots to optimize the flame conditions for elements under study. In place of the conventional single line exit slot as shown in Figure 1a, different designs have been reported in the literature and some examples are presented in Figures 1b, 1c and 1d. The use of SQTs to enhance the residence times of atoms has been reported for the past three decades in the literature and the "Bakırdere Research Group (BRG)" has been one of the major contributors on the use of different SQT designs to enhance the detection sensitivity of several elements. The study reported by Erarpat et al. is a typical example that shows the relevance of SQT in lowering the quantification limit of the FAAS system to 9.0 μg/L, allowing it to satisfy the 10 μg/L limit set for lead in drinking water [4].

The second working principle of the SQT is atom trapping, and this mode of operation has the potential to enhance the detection sensitivity of the FAAS system up to several thousand folds [5]. In the trapping procedure, the SQT is customized only with an entry slot to prevent the escape of analyte atoms through the exit slot, and this facilitates their adsorption onto the walls of the tube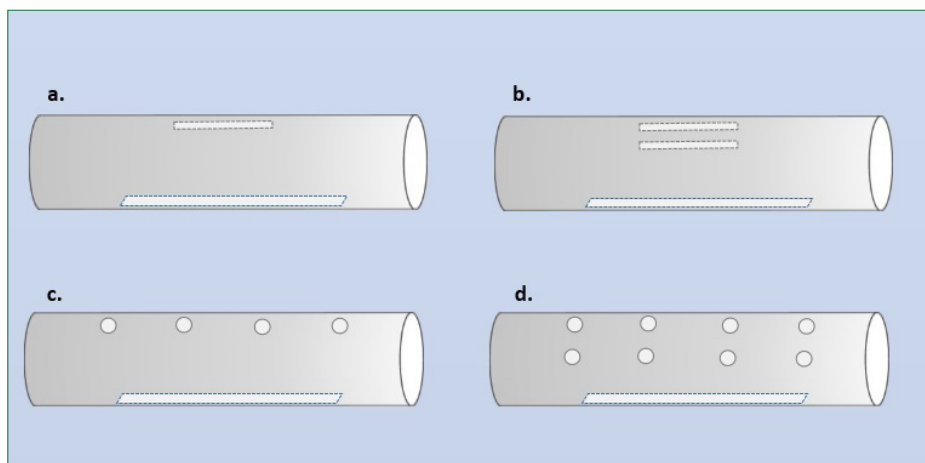. Due to the inverse relation between adsorption and temperature, the flame of the FAAS system in trapping studies is operated under lean conditions (low fuel flow rate) to allow efficient adsorption. Prof. O. Yavuz Ataman (*of blessed memory*) is one of the pioneers of atom trapping studies with his early works reported in the literature. His pioneering works were focused on enhancing the trapping efficiency of atoms by coating the surface of the quartz tubes with elements (e.g. Au, Mo, W and Ta) that have high melting points, and the use of very low volumes of organic solvents to cause the revolatilization of trapped atoms to obtain sharp and transient signals [5].
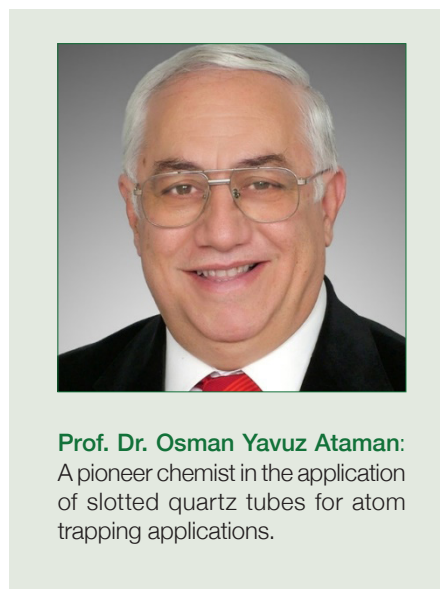
Prof. Dr. Osman Yavuz Ataman: A pioneer chemist in the application of slotted quartz tubes for atom trapping applications.

Despite the high enhancement factors recorded for the trapping studies performed with organic solvents for revolatilization, the rapid flame burst and the organic component of the solvent result in an unstable flame that causes the deuterium signal to fluctuate and consequently lower the signal-to-noise ratio [6]. With the aim of reducing the deuterium signal in trapping studies, hydrogen gas was proposed as an alternative to the organic solvents because it provides a stable reducing environment for the release of trapped atoms from the inner surface of the quartz tube. The SQTs used in hydrogen gas mediated atom trap studies are T-shaped in design (T-SQT), with the narrow T component serving as channel for rapid delivery of the gas to the flame housed quartz tube, as depicted in Figure 2. In the study reported by Kasa et al., the absorbance value recorded for molybdenum coated T-SQT was about 75% higher than the uncoated duplicate, and the enhancement factor recorded for cadmium determination was remarkably 1202 folds [6].

MICROEXTRACTION came into prominence in the early 1990s after the introduction of SPME by Arthur and Pawliszyn, but this was preceded by two separate studies that were reported in the late 1970s. Karlberg and Thelander (1978) reported the extraction of caffeine with microliter volumes of chloroform before the determination by a UV spectrophotometer, and Murray (1979) reported the extraction of selected pesticides, phthalates and organic solvents with hexane for determination by gas chromatography electron capture detector and flame ionization detector [7, 8]. However, the SPME method gained popularity because thermal desorption of the analytes adsorbed onto the modified fused silica fibers implied a solvent-free system that mitigated blank effects [9], and this opened the door for subsequent miniaturization and automation with instrumental systems. Automation of SPME is very common for chromatographic systems, with gas chromatography being the most suitable system for integration due to the configuration of the fiber sorbent being
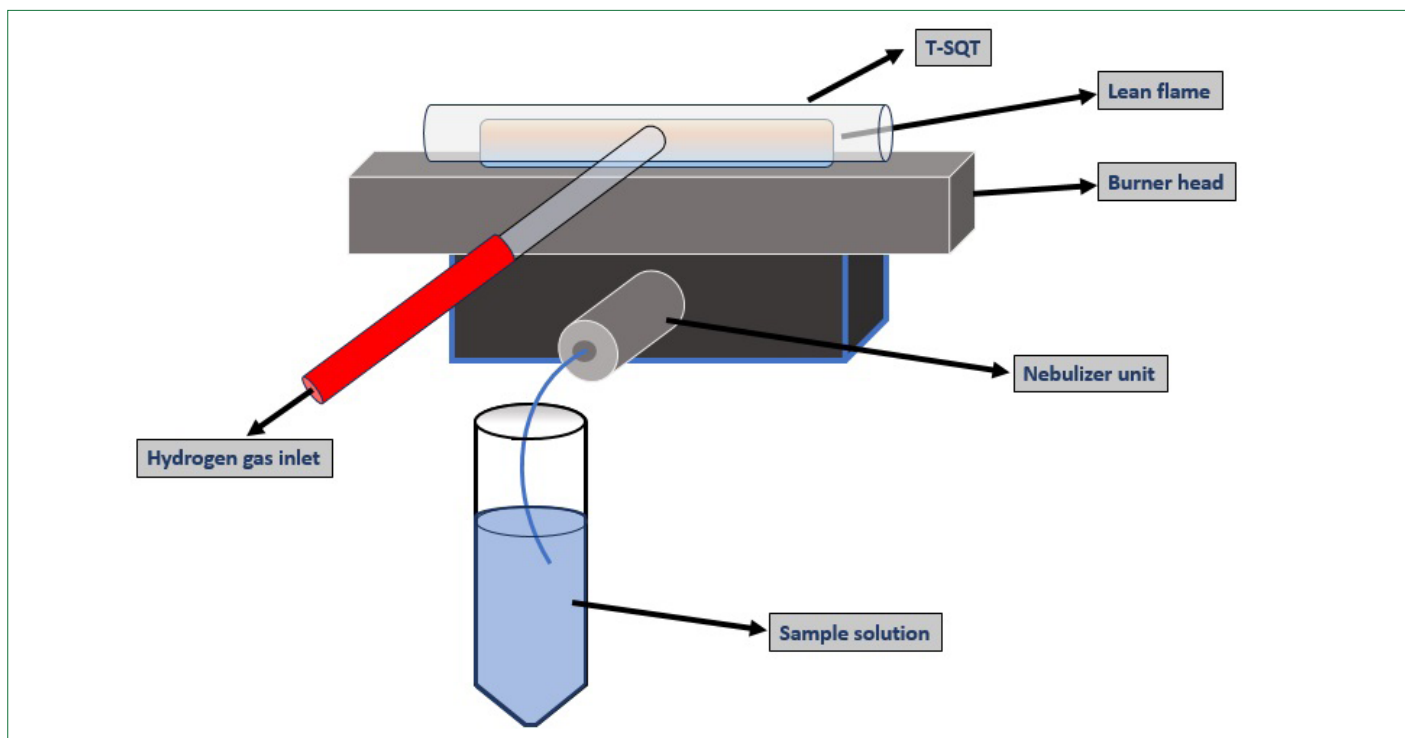

Figure 1. Slotted quartz tubes with the same entry slot length but different exit slots: (a) standard single line exit slot, (b) double line exit slots, (c) four equivalent exit holes and (d) eight equivalent exit holes.

Figure 2. T shaped slotted quartz tube with narrow channel for hydrogen gas introduction into the flame to release trapped atoms.

similar to the conventional microsyringe used for GC injections. Thus, microsyringes are easily modified to obtain an automated SPME-GC system [10].

Conventionally, SPME is performed in three working modes depending on the position of the fiber in the extraction vessel.

The first working mode is headspace SPME, where the fiber is placed above the sample matrix without contact, making it ideal for volatile and semi-volatile organic compounds. The second working mode is direct immersion SPME, where the fiber is placed in the sample matrix for direct contact. The third working mode (membrane protected

SPME) stems from the need to prevent large molecules or particulate matter from adsorbing onto the fiber, and this is achieved by using porous membranes that only allow analytes to pass through [11]. The efficiency of SPME is enhanced by coating thin layers of different sorbent materials onto the fiber. Advancements in nanoparticles and their
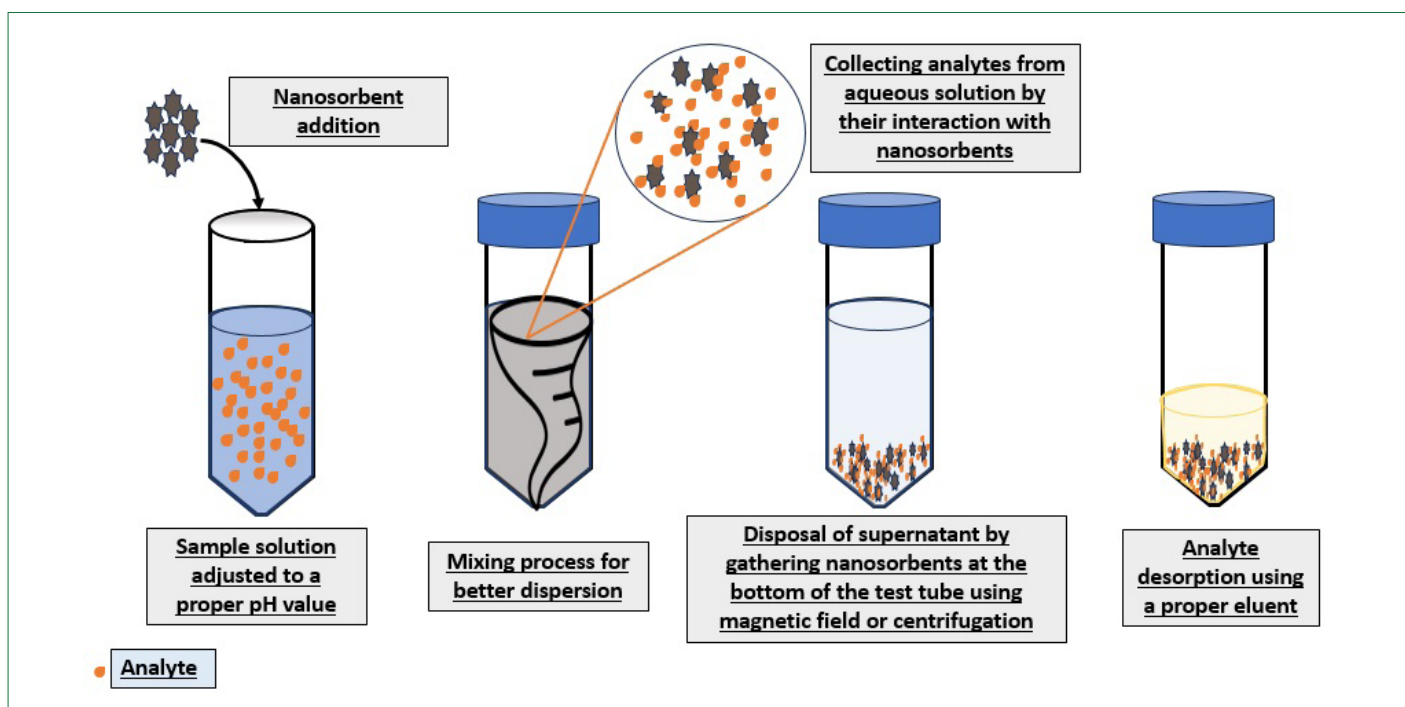

Figure 3. DSPME experimental procedure to separate/preconcentrate analyte(s) by using different nanosorbents.
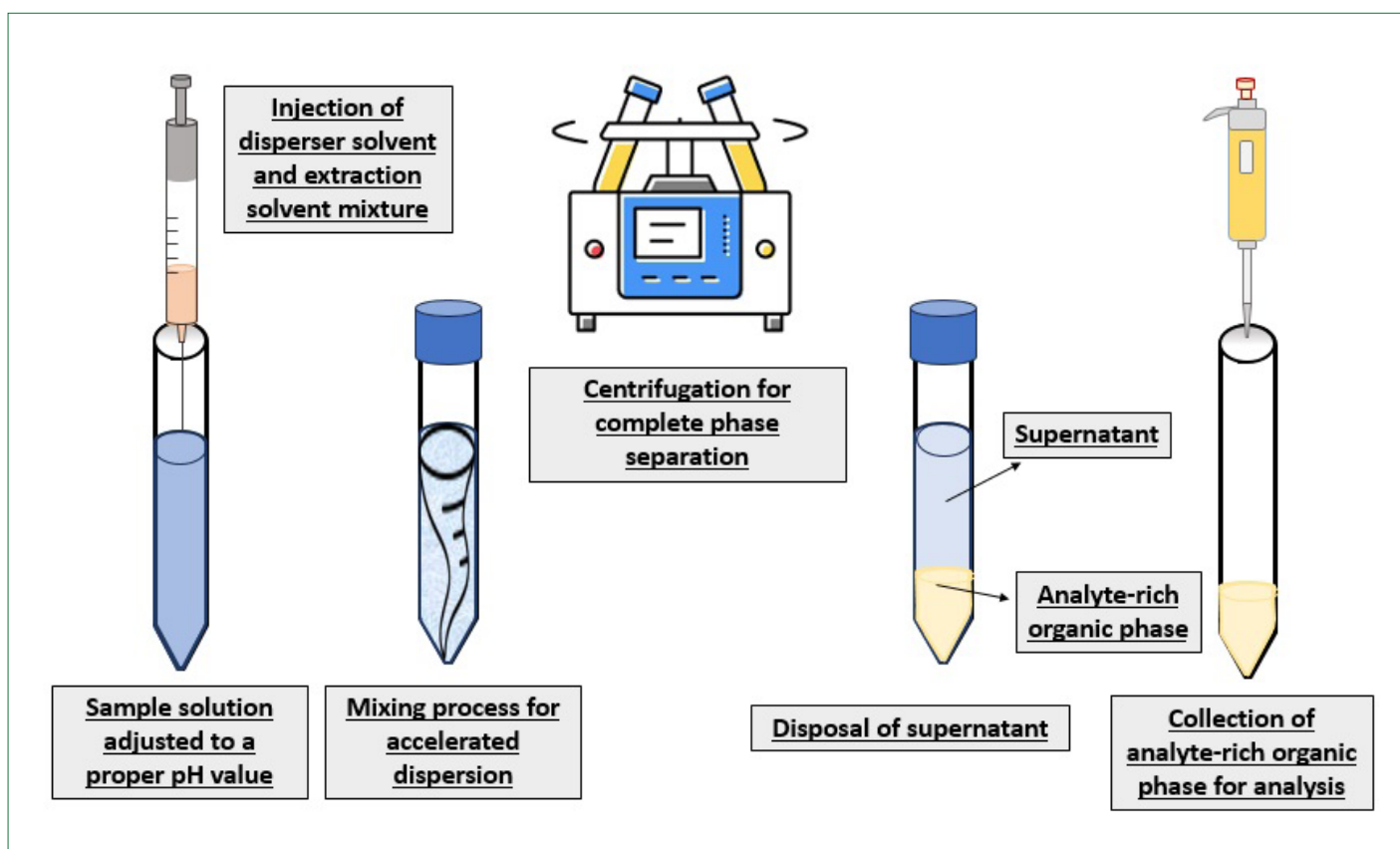
Figure 4. Experimental steps for the conventional DLLME procedure.

unique features (e.g. nanoscale size, large surface area, physicochemical and biological activities) make them suitable coating materials for fibers that are used in SPME applications. Sample stir (fiber SPME) and sample flow through (in-tube SPME, in-needle SPME and in-tip SPME) are two broad SPME techniques reported in the literature, where the sorbent materials are kept stable as the sample solution is stirred and kept stable as the sample is passed through, respectively [2]. Direct dispersion of sorbent materials in sample solutions without being immobilized on a stationary fiber support has gained popularity in recent years, and nanoparticles with magnetic properties suit this technique due to ease of separation using an external magnetic material (Figure 3). Dispersion forms the basis for this technique and studies in the literature use different terms such as *dispersive solid phase microextraction* (DSPME), *dispersive solid phase extraction* (DSPE) and *dispersive micro solid phase extraction* (D-µSPE) to describe the approach [12].

Desorption of adsorbed analytes with very low volumes of appropriate solvents is very common in SPME applications but thermal desorption is more suitable for automated SPME methods and laser desorption is a less common approach reported in the literature [13]. The feasibility of solventless extraction

and the use of very low solvent volumes in SPME results in very high enhancement factors, leading to very low detection limits such as 0.001 – 0.052 ng/mL as reported by Cai et al. for eleven pesticides [14]. In addition to recording very high preconcentration factors for analytes, the sorbents used in SPME can be further explored as effective sorbents for the removal or remediation of contaminants from wastewater, serving a dual role for analytical chemists and environmental scientists.

Single drop microextraction (SDME) was first reported in the literature in 1995 by Liu and Dasgupta, and it involved the use of a liquid droplet of sulfuric acid to trap gaseous ammonia for determination by a spectrophotometric detector at parts per billion levels [15]. In the ensuing year (1996), Jeannot and Cantwell performed the first direct immersion SDME method, where a drop of *n*-octane, suspended at the tip of a Teflon rod was used to preconcentrate the flavoring agent 4-methylacetophenone from an aqueous solution under constant stirring [16]. The concept of using microsyringes to develop the microdrop for SDME was introduced by He and Lee in 1997. In that study, a microdrop of toluene (<2.0 µL) was used to extract chlorobenzenes under static (without mixing) and dynamic (repeated movement of syringe plunger) conditions, where the

former condition yielded a relatively low enrichment factor but high precision, and the latter condition yielded a relatively high enrichment factor but with lower precision [17]. Several advancements have been made to the SDME method and its application to different compounds yields high enrichment factors reaching up to 1700-folds [18].

Maintaining the integrity or stability of a microdrop is the greatest challenge in SDME applications. In 1999, Pedersen-Bjergaard and Rasmussen introduced ***hollow fiber liquid phase microextraction*** (HF-LPME), an effective method capable of facilitating mass transfer of analytes into extractants without losing the integrity of the extractant [19]. The hollow fiber used in this method acts as a porous barrier that allows analytes to migrate from the sample solution into the extractant while preventing direct contact with particles or larger molecules that could interfere with instrumental determination of analytes. Two working principles are available in the application of HF-LPME. The two phase system consists of the immobilized acceptor phase (extractant) in the hollow fiber, which is immersed in the donor aqueous phase (sample solution). The walls of the fiber used in the two phase system is soaked in the same acceptor phase solvent before immersion in the sample solution to facilitate the permeation of analytes through

the pores into the immobilized acceptor phase. The three phase system consists of an aqueous solution as the donor phase, an organic solvent incorporated into the pores of the fiber to serve as a supported liquid membrane, and an organic/aqueous solution as the acceptor phase. In this system, analytes move from the donor phase through the intermediate phase into the acceptor phase [20]. Several advancements have been made to the HF-LPME method and its application to different compounds yields very high enrichment factors reaching up to about 4000-folds [20].

Rezaee et al. introduced a very effective LPME method in 2006 and it has probably become the most utilized LPME method in the literature. ***Dispersive liquid-liquid microextraction*** (DLLME) introduced the unique feature of extractant dispersion in solution, using very basic apparatus and a rapid procedure (Figure 4).

In the first reported study, acetone was used to disperse tetrachloroethylene in aqueous samples to preconcentrate polycyclic aromatic hydrocarbons, which were determined by GC flame ionization detector [21]. Sample agitation is a very important step in both SPME and LPME methods, as it ensures the movement and interaction of analytes with extractants/sorbents for high extraction efficiency. However, the high efficiency observed in the DLLME method by reason of extractant dispersion makes sample agitation an auxiliary step that is not the primary contributor to the enrichment factor of the method. Disperser solvents serve as

bridges between extraction solvents and aqueous samples, ensuring homogenous mixing that is visualized as a cloudy solution. Most DLLME methods utilize syringes to introduce the mixture of extraction solvent and disperser solvent into aqueous sample solutions, and the air-assisted pressurized injection further enhances the extraction efficiency and rapidity of the entire process [22]. Low density and high density solvents are both employed in DLLME applications but the latter is more preferred because they settle below aqueous solution, where they are clearly distinguished at the base of tapered tubes and are not susceptible to evaporative loss. Several studies reported in the literature validate DLLME as a very efficient microextraction method and with its versatility, it has been combined with other extraction methods such as SPE to record extremely high enrichment factors up to approximately 18,000-folds [23].

In the use of low density solvents that settle above aqueous solution in the DLLME method, irregular evaporation of the solvent could result in high uncertainties between replicate extractions, and very low volumes might not be easily distinguished from the bulk solution. In attempt to mitigate evaporative loss of low density solvents and enhance the collection of low extract volumes, Khalili Zanjani et al. in 2007 introduced an LPME method that worked on the principle of freezing low density solvent into a solid that is easily collected for instrumental determination. The method was named ***solidified floating organic drop microextraction*** (SFODME) and it was first

reported for the preconcentration of polycyclic aromatic hydrocarbons from water samples for determination by GC flame ionization detector [24]. Solvents used in the SFODME method satisfy two critical criteria: the solvent should have a density lower than the density of water (1.0 g/mL) to allow it settle above the solution, and should be readily frozen when placed in a cold environment. After the extraction process, the floating solid should readily melt into its original liquid form to allow further processing or direct instrumental measurement, thus, the melting point should range between 10 and 30 °C. A couple of organic solvents satisfy the peculiar criteria for the SFODME method and these include long chain alcohols such as dodecanol and undecanol [22]. A disperser solvent can be used to enhance the extraction efficiency of the SFODME method and some typical enhancement factors reported in the literature for organic and inorganic analytes using this method go as high as about 1500-folds [25].

GREEN SOLVENTS have received considerable attention in the past decade due to greater awareness and priority being placed on *Green Chemistry*. Despite the use of very low volumes of conventional organic solvents in the microextraction methods discussed above, routine analysis that involve multiple samples would eventually produce wastes with elevated volumes of solvents such as chlorinated organic solvents, which are major concerns for the environment. The high volatility of some conventional solvents pose significant risks to analysts that utilize them in day to day extraction processes. In
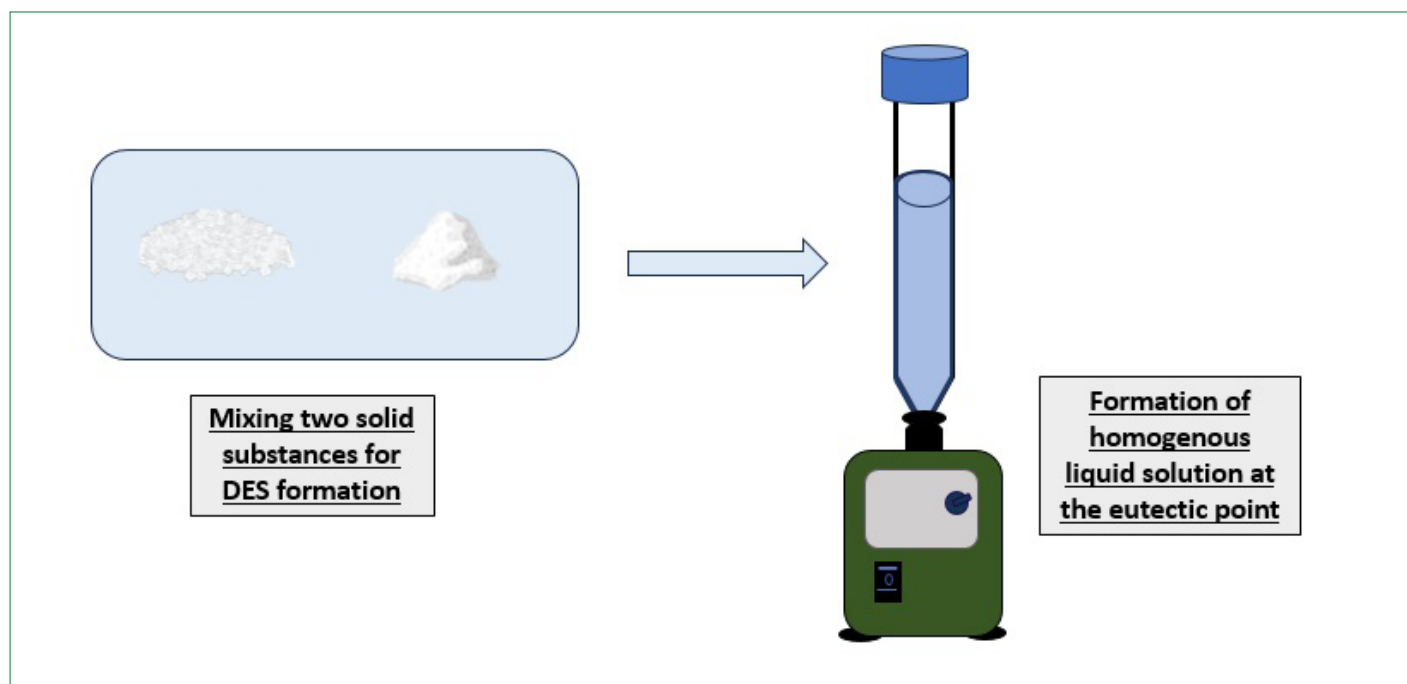

Figure 5. DES formation with the aid of mixing at room temperature.

the last two decades, three peculiar solvents have stood out as green solvents that mitigate the negative effects associated with the conventional solvents, and equally present very high extraction efficiencies for both organic and inorganic analytes.

Ionic liquid was reported for the first time in the literature by Paul Waldin in the early years of the twentieth century (1914) but its active utilization as an extraction solvent started about a century later [26]. Ionic liquids are comprised solely of ionic or charged organic salts that easily melt below 100 °C and remain liquid at/close to room temperature. Ionic liquids are also referred to as "designer solvents" in the literature due to the flexibility of tuning their physical and chemical properties (e.g. compatibility with aqueous and organic solutions, density, viscosity, melting point, acidity, conductivity, stability) to suit the designated purpose [27]. By fine-tuning the physicochemical properties of ionic liquids, they can be used as extraction solvents or coating of sorbents in DLLME, HF-LPME, SDME and SPME applications to preconcentrate both organic and inorganic analytes and achieve very high enrichment factors that correspond to low detection limits [28].

Deep eutectic solvents (DESs) are composed of two solid components that mix to become liquid at a melting point that is significantly lower than the respective melting points of the starting materials (Figure 5). The concept of deep eutectic solvents was reported for the first time in the literature by Abbott et al., where the mixture of different quaternary ammonium salts with urea resulted in liquids that showed distinct properties [29].

For the two components that are used in preparing deep eutectic solvents, one serves as a hydrogen bond donor and the other acts as a hydrogen bond acceptor. Similar to ionic liquids, DESs have unique and tunable properties (density, viscosity, nonflammability, nonvolatility, thermal stability, varying polarity, surface tension) that make them suitable for both LPME and SPME applications. Based on polarity, deep eutectic solvents can be classified into hydrophobic and hydrophilic DESs. When used in LPME methods, hydrophobic DESs are readily separated from aqueous solution for instrumental measurement. For the hydrophilic analogue, a trigger agent is required to disrupt the interaction between water molecules and the DES molecules, resulting in emulsification and self-aggregation of the DES [30]. Aprotic solvents such as 1,4-dioxane, tetrahydrofuran and acetone are some common trigger agents, with tetrahydrofuran

being the most commonly utilized one in the literature. As modifiers for solid sorbents in SPME and as extraction solvents in LPME, DESs have been reported to be very effective in preconcentrating a broad variety of analytes for determination by different analytical instruments at ultra-trace levels [31].

Switchable polarity solvent, also referred to as switchable hydrophilicity solvent was first reported by Jessop et al. in 2005 as a smart solvent due to its unique property of switching from one polarity state to the other in a single step [32]. With the single step switchability of these solvents, chemical processes can do without extra experimental steps and excess solvents, and this makes them suitable for applications in catalysis, purification, synthesis and chemical separations. Switchable solvents are simply prepared by mixing a non-polar secondary/tertiary amine with an equivalent volume of water, and stirring the mixture with a periodic supply of dry ice (solid carbon dioxide) or its gaseous form until a homogenous polar solution is obtained. The addition of carbon dioxide to water produces carbonic acid, which in turn protonates the lone-pair electrons of the amine to facilitate its solubility in water as the first switch step. The second switch step, which converts the switchable solvent into its original state requires a trigger agent that causes deprotonation, and some common agents include inert gases (argon and nitrogen) and sodium dioxide [22]. This simple conversion and reversion of switchable solvents is particularly useful in extraction applications because the solvent with complete solubility in water interacts efficiently to extract analytes of interest, and is separated into a low volume non-polar phase after the deprotonation step. The use of switchable solvents in LPME methods is widely preferred not only for its simplicity and rapidity, but also because of their high extraction output and high analyte recovery [33].

COMBINATION OF TWO SUPERIOR ANALYTICAL TECHNIQUES. It is well known that lower detection limits are susceptible to high interferences that could significantly impact the accuracy and precision of an analytical determination. The microextraction methods discussed above offer very high enrichment factors for analytes, but replicate extraction procedures may suffer low repeatability that may arise from variations in procedural steps and operation of apparatuses. Another major source of error in analytical determinations is the measurement step, where irregular injections or sample introduction, and sudden fluctuations in electricity could alter

the analysis output. Internal standards are commonly used to resolve these issues to enhance the precision of replicate extractions and measurements but the internal standard method is still limited. Isotope dilution mass spectrometry (IDMS) is an advanced version of the internal standard method, with exceptional accuracy and precision that makes it the preferred technique for the validation of certified reference materials [34]. The IDMS technique works on the fundamental principle of spiking the unknown amount of an analyte in a sample with a known amount of its isotopically enriched or labelled standard. The IDMS technique differs significantly from the internal standard method by reason of the formation of an isotopic equilibrium, a condition that ensures that the ratio of the analyte and its isotopic analogue remain constant throughout the sample preparation procedures and instrumental measurement. This accounts for the high precision and accuracy of the technique, mitigating uncertainties to almost negligible levels.

Different IDMS techniques including single, double, triple and quadruple IDMS techniques (IDMS, ID^{2}MS, ID^{3}MS and ID^{4}MS) have been developed to offset the uncertainties in the mathematical expressions of the technique [35]. Despite the superiority of the isotope dilution technique, it is only executed at trace levels using highly sensitive and sophisticated analytical instruments such as inductively coupled plasma mass spectrometry (ICP-MS), liquid chromatography-quadrupole time of flight-tandem mass spectrometry (LC-QTOF-MS/MS), liquid chromatography tandem mass spectrometry (LC-MS/MS) and liquid chromatography orbitrap high resolution mass spectrometry (LC-Orbitrap-HRMS). These instruments are very expensive and not available in most laboratories, limiting the number of applications reported in the literature. To overcome this limitation, the Bakirdere research group reported the coupling of both LPME and SPME methods with ID^{4}MS, facilitating the determination of organic analytes at trace levels by GC-MS with unrivalled accuracy and precision. The ID^{4}MS technique was selected because it eliminates some variables of the IDMS mathematical equations, making it more compatible with the GC-MS system [36]. Chormey et al. reported the first combination of DLLME and ID^{4}MS for the determination of the organophosphorus pesticide parathion methyl in water samples by GC-MS. Whereas direct ID^{4}MS was performed at approximately 4.0 mg/kg with major concern on the signal to noise ratios of the analyte and its isotopic analogue, the DLLME-ID4MS method was performed at 0.04 mg/kg with a very high signal to noise

ratio that could permit determinations at much lower concentrations. The combined method recorded 99.9% accuracy with a very low percent relative standard deviation value of 0.3% [37]. After the successful combination of these two superior techniques, the research group has reported the combination of ID[4]MS with different microextraction methods including switchable solvent liquid phase microextraction [35], spraying based fine droplet formation liquid phase microextraction [38], binary solvent liquid phase microextraction [39] and dispersive magnetic solid phase extraction [36]. In all the combination studies, approximately 100% accuracy was recorded for the determination irrespective of the very complex nature of the sample matrices including wastewater, human serum, urine and saliva.

Conclusions

The road to lower detection limits has been clearly demarcated by pioneer scientists and this road is being trodden by other scientists, who are fine-tuning and expanding the access routes for the larger scientific community. The advantages of microextraction methods for the determination of pollutants at trace levels and isotope dilution techniques for enhanced accuracy and precision are being actively explored for a broad range of organic and inorganic compounds. It is without doubt that major advancements have been made to contemporary analytical methods but it has become imperative to introduce green components and approaches that will significantly reduce the negative impacts of the procedures and wastes generated from the methods. With what past experiences have taught humanity, contaminant levels that are accepted today might be reviewed and further lowered in the future, and this makes the road to lower detection limits a perennially important place for scientists.

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