Solid phase microextraction: apparatus, sorbent materials and application

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Abstract

The primary objective of this review article is to strategically screen and highlight the advancements in the area of solid phase microextraction (SPME). The plenty of review articles have been written on different aspects of SPME, this review is dedicated to provide the brief but clear overview of the research footprints so produced from SPME. Some of the key advancements in types and designs, coating materials, coating strategies, *in vivo* sampling and direct coupling of SPME with MS have been critically discussed.

Keywords:

Solid phase microextraction; SPME; Thin film microextraction; biocompatible coatings; Sample preparation; Chromatographic analysis

1. Introduction

Sample preparation is a critical step before the analytical determination of target analytes in different matrices. Sample preparation is carried out to extract or concentrate the analytes from the matrix. This is achieved by

(i) Removal of the interferences related to matrix components which otherwise can interfere the detection ability of the instruments
(ii) Enriching the low-level concentrations of analytes to bring them to detection level of the instruments or to get higher sensitivity by attaining low limits of detection.
(iii) Selective extraction of target analytes by employing certain adsorbents or solvents as extraction media.
(iv) Converting the analytes to a form which is measurable through certain processes such as derivatization.

The conventional sample preparation techniques include liquid–liquid extraction (LLE) and solid phase extraction (SPE). These techniques involve several clean-up steps to remove complex matrix components. Moreover, they are time and labor intensive, require large volumes of organic solvents and result in significant quantity of waste. In this way, they are not considered environmental friendly. To solve the problems associated with conventional LLE and SPE, number of new microextraction techniques have been introduced over the last two and half decades. The research in area of microextractions was started after the introduction of solid phase microextraction (SPME) in 1990 by Pawliszyn and co-worker [1]. The principle objective for the development of SPME and other microextraction techniques is based on minimum or no use of organic solvents, reduction of sample size and shorter extraction times.

SPME is a technique which involves extraction of target analytes from the sample media via adsorption/absorption onto extracting phase coated on silica fiber or some metallic support. This extraction is followed by desorption of the analytes into a suitable instrument by the provision of heat or application of desorption solvent. The choice of the sorbent material for SPME coating is dictated by the nature of target analytes. SPME is coupled with GC in most of the applications. As the analytes are thermally desorbed into the injection port of chromatograph, application of GC is generally limited to volatile and thermally stable compounds. However, such problems in certain applications are solved by derivatization of analytes in the sample matrix, in the injection port and on the fiber derivatization after and/or during SPME.

SPME can also be used to analyze nonvolatile and thermally unstable compounds by coupling it with LC. However, in that case, desorption is carried out using organic solvent or mobile phase instead of thermal desorption. The use of high temperature during such desorption may lead to degradation of the polymer and incomplete desorption of many nonvolatile compounds from the fiber. Theory of SPME is described in detail elsewhere [2]. General scheme for extraction and desorption in SPME is given in Figure 1 [3].

Fig.1.

SPME has been widely used in analysis of environmental [4], food [5], pharmaceutical and biological samples [6]. The search on Scopus revealed that in the past twenty-four years (1992–14 June 2017) 14089 articles have been published in area of SPME. The articles published before 1992 did not appear in Scopus search results and it was probably only one article which was published in 1990 [7]. This large volume of publications highlights the research activity going on in area of SPME. It is also supportive to indicate the fact that SPME has gone through numerous advancements. The milestones of SPME is presented in Figure 2, while its classification in Figure 3.

Over the years, number of review articles have been written on different aspects of SPME. The main objective of this article is to introduce the readers with all the aspects and the variants of SPME in a comprehensive way. For this, we have reviewed both the published review articles and the articles describing recent advancements. The advancements in the following subject areas of SPME have been covered with sufficient detail:

(i) Different geometries
(ii) Coating supports
(iii) Coating strategies
(iv) Coating chemistries
(v) Biological and in vivo analysis
(vi) On-site sampling and sample preparation
(vii) High throughput formats
(viii) Coupling of SPME with mass spectrometry

Fig.2.

It can be noted that most of these review articles focus on one or other aspect of SPME and give comprehensive summaries of SPME applications based on that particular aspect or direction. While the advancements in all major aspects of SPME are critically discussed in this review, we avoid lengthening a single aspect unnecessarily. The readers who will be interested in any specific details of applications/list of publications in a particular direction of SPME, are advised to go through the relevant review articles.

Fig.3

2. Methodological solutions in SPME: different geometries and modes of SPME

SPME technique is characterized by many advantages such as easy of performance, simplicity and solvent-free or requirement of smaller solvent aliquots than other extraction methods, and lowered cost. In addition, it provides linear results for a wide analytes range as well as their concentration. Furthermore, quantitative or semi-quantitative data are supplied even in case of the low concentration of analytes determined and analytes losses that can occur during the stage of sample preparation performed with application traditional sample procedures e.g. extraction, concentration and clean-up steps are mostly avoidable. All of these merits affect the fact that SPME technology is almost universal. In addition, it can be used for a many kinds of samples on different physical states – gas, liquid and solid – mainly with a complex matrix composition, including trace as well as ultra-trace capacity levels for the analytes determination [8]. From the other side, such drawback as a limited number of commercially available stationary phases which mainly roughly cover the polarity of target analytes, is a big problem in general use. In addition, the application range is reduce due to the specificity of stationary phase of the fibers, which can be operated under relatively low temperature (240–280°C). Also another problems exist including stripping of coatings, the instability and swelling in organic solvents, bending of the needle, breakage of the fiber, limited fiber lifetime and relative high costs [9]. Considering both, the advantages and the limitations of SPME, it has come under continuous technical development over the last years. Therefore, several other methodological solutions have appeared and these are described in the following section with the supporting of Figure 4, which presents different methodological solution of SPME.

The most popular SPME is fiber SPME and as far as the design of the fiber SPME is concerned it can be resembled with modified syringe like device that consists of fiber holder with a needle in which fiber is protected. During the extraction, this fiber is exposed to the solution for a defined period of time. After the extraction, fiber is retracted to the needle of the SPME holder. Then, the needle is injected into injection port of the instrument and fiber is again extended through the needle. Here, needle works as protection, fiber is retracted to the needle when not in use. The different forms of fiber SPME devices which were initially developed and went through evolution are covered in a review article published in 2000 in JCA [10]. The commercial SPME device which consist of fiber and fiber holder was introduced in 1993.

Extraction efficiency of SPME can be improved by selecting suitable coating phase and then extraction mode according to the nature of the analytes of interest. SPME is generally operated in direct immersion (DI-SPME) or headspace (HS-SPME) or hollow fiber membrane protected (HF-SPME) modes. In DI-SPME, fiber is directly exposed to sample solution and it is considered as a good choice when analyzing clean and aqueous samples. Although, this mode is applicable to the complex matrices but in that case pretreatment is necessary because the interfering compounds from the matrix can irreversibly bind to the fiber. HS-SPME is also another choice for the complex samples such as sludge, milk, blood, urine but it requires analyte to be volatile in nature or can be volatilized by provision of moderate heat without degradation. Another situation arises when non-volatile and thermally unstable compounds are present in complex matrix, in this situation DI-SPME can be used after protecting the fiber with hollow membrane. This protection basically hinders the diffusion of large molecules from diffusing into the fiber while allowing the mass transfer of analytes [11]. The extraction efficiency can be enhanced by using internal cooling, agitation, proper pH adjustment and using salting out strategy.

In-tube SPME is performed using internally coated tubing. This tube is mounted inside a needle or it can constitute a needle itself. It typically uses GC capillary column which is internally coated with the extraction phase. This approach is easily automated with HPLC [12]. The analytes are extracted by the inner coating of the capillary or tubing and after completion of extraction analytes are desorbed or washed with organic solvents into LC column. It overcomes many disadvantages of coupling fiber SPME with HPLC such as lack of automation and sensitivity of fibers to organic solvents. In tube SPME exhibits higher mechanical strength than fiber SPME. However, the clogging of the inner side of capillary may be a disadvantage of in-tube SPME which can be easily avoided by using samples free from any particles and macromolecules. In some configurations of in-tube SPME, a sorbent can be packed inside the tubing and they are similar to SPE. Detail of theory of in-tube SPME can be read [12]. A recent review gives an overview of chromatographing coupling, coating materials and applications of in-tube SPME [13].

Another mode of SPME, named, in-needle SPME uses a needle instead of a tube for extraction. This approach can be classified as microextraction by packed syringe (MEPS), a solid-phase dynamic extraction (SPDE), and fiber-packed needle microextraction (FNME). The first mode, is actually a miniaturized and automated version of the SPE technique; however, in MEPS, a small aliquots of the SPE sorbent is introduced into a pipette-tip or syringe as a plug secured at both ends. In this technique, the analytes adsorb on the appropriate SPE sorbent after first sampling using a syringe. The sorbent is next washed with suitable solvent, the elution of analytes occur, and then are injected into the chromatograph. In MEPS, a small volume of sorbent, sample as well as organic solvents for elution of the analytes are applied.

In the second approach of in-needle SPME, namely SPDE, a syringe with a stainless steel needle with an inner wall coated by a thin film of 10% activated carbon and PDMS is applied [14]. After the needle is introduced manually or automatically into the sample, the plunger is moved up and down frequently. In that way, the analytes are concentrated onto a thin film. The advantages of this approach are: short time of extraction, good repeatability and high mechanical stability of the SPDE device. Moreover, it is characterized by a larger volume of coating when compared to the SPME method. This results in the concentration capacity increases [15].

The last in-needle approach, FNME is an alternative method applying the fiber instead of particle materials inside the needle. A short capillary made of polyetheretherketone (PEEK), fused-silica or polytetrafluoroethylene (PTFE) is an extraction medium in the FNME device. Into this capillary, a hundreds synthetic polymers filaments are packed.

The in-tip SPME is another of the newest approaches for sample preparation. Here, the pipette tips is filled with solid packing material and the off-line extraction process takes place on the packed bed. In this approach, such sorbents as silica and methacrylate monoliths are used due to the fact that can be prepared with a wide selectivity range and they are stable over a wide pH range. This mode can be in total automated. In addition, it can be used in multi-way what allow to handle of several samples. An optional approach to the in-tip SPME mode is to use fiber instead of particle materials.

The SPME Arrow system is another approach of SPME. This system was created to solve problems related with the combination of large SPME sorbents volumes and GC analysis which can be problematic due to difficulties in the analytes desorption stages. The SPME Arrow system is made from a steel rod coated with more volume of sorbent material than the fiber used in SPME [16]. Due to the dimensions of this system and sharp, closed tip it is still possible to connect SPME Arrow system with the standard desorption mode in GC liner. In comparison to typical SPME fiber, this mode is characterized by better robustness and sensitivity. In addition, it could be used to extract large analytes amounts from samples characterized by complex matrices composition.

Another configuration involves modification of commercial SPME fibers for analysis of complex samples such as food. This configuration eliminates the step of sample pretreatment before extraction. This modification involves creation of thin layer of PDMS or other polymers on original fiber. In this design, fiber becomes compatible with complex matrix while retaining its sensitivity toward target analytes. The PDMS-modified SPME coating was directly applied to grape pulp and it showed good reusability for more than 100 successive DI-SPME cycles [17].

Another configuration of SPME was developed in order to improve analytes release from the interfering phases in complex matrices and it is named an internally cooled coated fiber device (CCF). This device allows for the sample matrix heating while simultaneously cooling the fiber coating. What is very important, in this system the mass transfer is accelerated and a gap of temperature is created between the hot headspace and the internally CCF. This solution allows to significantly increase the distribution coefficient [18]. In general, internally CCF device is helpful for matrices characterized by high viscosity or for volatiles with low partition coefficients [9]. The advantages of this technique are high sensitivity, high sample throughput. However, it need to be mentioned that the loss of selectivity can occur due to the fact that the capacity of the fiber through this CCF increased. In addition, both, the analytes as well as the interferences are exhaustively extracted onto the coating [15]. Nowadays, a miniaturized version of CCF device is applied for direct insertion into the GC injector, maintaining the appropriate septum lifetime.

SPME configuration that can be used as substrate mass spectrometry has also been introduced and named as coated blade SPME. This basically consists of metallic sheet cut as a “gladius sword” and coated with adsorbent. This configuration is an ideal compromise between the use of SPME as sample preparation technique and its direct coupling with mass spectrometry [19].

In addition to the SPME modes mentioned above, there are also non-fiber SPME methodological solutions. Here, two techniques need to be described: the stir bar sorptive extraction (SBSE) and thin-film microextraction (TFME).

SBSE is performed using a stir-bar that is coated with extraction phase. The analytes are extracted from the sample solution by stirring the coated bar for a certain period of time. After extraction, analytes are desorbed thermally or by the aid of suitable solvent [20]. In the case when SBSE is coupled with GC, thermal desorption (TD) of the analytes is caused by introducing the bar into the GC injection port or by adding a few microliters of an appropriate liquid solvent into a small vial where the bar is placed. In the case of SBSE coupled to LC technique, the mobile phase can be added directly to the stir bar. Because of thick coatings, SBSE can provide more sensitive and accurate results than SPME because the extraction of the analytes is proportional to the amount extraction phase, which is very small in case of SPME.

However, the equilibrium times are much longer in case of SBSE. Stir bar has good mechanical strength than fiber SPME. From the other site, this a small number of commercially available coatings is a limitation in the application of this technique. Moreover, SBSE has other drawbacks including the inability to achieve full automation of the SBSE process and reconstitution in a solvent before chromatographic analysis, where it is possible to contaminate and lose analytes [14].

In its most famous format, SPME fiber extracts very small amount of the target analyte because of very minute quantity of the extraction phase deposited over the fiber. This may lead to poor sensitivity in trace analysis. However, deposition or coating of large amount of sorbent (forming a thick film) can increase the amount of extracted analyte but it will also increase extraction equilibrium time. The other way is to use high surface area thin films over the solid support. For instance, PDMS membrane was used as thin film and its performance was better than PDMS SPME fiber. This new configuration has many new opportunities for applications. Different polymeric membranes or polymeric membranes coated with new materials can be utilized in this technique, named thin-film microextraction TFME [21]. This technique is characterized by higher sensitivity, shorter amount of time than in SPME and less thickness of the extraction phase. In TFME, the extraction phase consist of a flat film which is characterized by a high surface area-to-volume ratio [15]. Such formats are commonly used in TFME: directly placing the membrane on/in the sample matrix [22] and coating the flat film on the surface of the vial that contains the sample [23].

All of mentioned in this section methodological solutions of SPME are schematically presented in Figure 4, while its applications are presented in Table 1.

Fig.4.

Tab.1

3. Advancements in coating supports

In its most widespread format, a thin layer of suitable polymer is coated on fused silica fiber. Despite its large number of applications that are still growing, fused silica based SPME lacks mechanical strength. This drawback led to an extensive research activity for exploring new solid supports for coating. The new solid supports include metal wires (stainless steel, gold, platinum, titanium and alloys etc.) which are mechanically stable and unbreakable during operation. Metal-alloy based SPME fibers are now commercially available [44].

For bioanalytical applications, single use samplers based on thin film SPME devices prepared on plastic supports have been recently introduced. Polybutylene terephthalate was employed as a support owing to its recognized features such as good chemical resistance, low cost, and suitability as a material for different medical grade components [45]. Table 2 lists different supports used to manufacture SPME devices. Advantages and disadvantages of these support materials are also mentioned.

Tab. 2

4. Advancements in coating strategies

The coatings of SPME fibers play a major role in extraction of target compounds. The selection of suitable coating material is of prime importance in SPME applications. There are certain features which are desired in SPME coating. The mechanical, thermal and chemical stability make SPME coatings highly applicable for different kinds of analysis. SPME coatings can be prepared using physical or chemical methods which include direct use of hollow fiber membrane, dipping, adhesion, electrochemical deposition, sol-gel synthesis etc.

Physically deposited coatings present some limitations such as low operating temperatures, sensitivity to organic solvents which may deteriorate the coatings and issues related to mechanical stability. The coatings prepared by chemical methods, however, provide more mechanical, chemical and thermal stability because they result from chemical bonding between support and coated material. Sol-gel technology is important from this perspective.

Sol-gel process which is also known as inorganic polymerization, is a wide-ranging approach for synthesis of oxides at room temperature using wet route. This approach provides an effective way for synthesis of inorganic polymers and organic–inorganic hybrids under mild conditions. Sol-gel technology can be used to prepare the products in desired sizes, shapes and formats. This technology is widely used in preparing SPME fibers [46]. It has many advantages over conventional coatings which include:

(i) The simple and single step preparation
(ii) Chemical interaction between the coating and support (fused-silica surface)
(iii) Homogenous morphology of sorbent at molecular level
(iv) Excellent mechanical, thermal and physical stability.
(v) Highly porous structure of hybrid material.
(vi) In addition to that, combination of inorganic and organic material (in the form of hybrid) provides excellent sorption properties to the sorbent which are not possible to achieve using pure organic or inorganic materials.
(vii) Tailoring the coating by incorporation of desired materials into the final product. The materials like crown ethers, CNTs, graphene, ionic liquids and metal nanoparticles have been incorporated into the polymeric network using this approach [47].

For preparation of SPME fibers using sol-gel technology, precursor, coating polymer, catalyst and deactivating agent (non-polar fibers) are needed. The functionality of the solid support is one of the major issues using this technology. Selection of precursor, coating polymer and new modifiers to get desired capacity and capability, defines new research trends in SPME using sol-gel technology [46]. A recently published review article highlighted some of the limitations of sol-gel based SPME coatings. Mainly, they have not been examined/compared with commercial fibers for different analytical applications. Most of the published worked focuses on development of new coatings. These coatings need to be fully validated through inter-laboratory validation, because without that they cannot be commercialized [47].

Molecularly imprinted polymers (MIPs) are also used as coating materials in SPME. They show good selectivity because of their template based synthesis against certain analyte or class of analytes. MIPs are synthesized by one of the following approaches; non-covalent, covalent and semi-covalent imprinting. Their applications have been summarized in a recently published review article [48]. MIP coatings are selective but they arise some issues such as weak performance in aqueous solutions and difficulties in preparation of thick coatings. On the other hand, the coatings prepared by sol-gel technology are rigid and thermally stable but in some cases present poor selectivity. Such issues can be resolved by combining the MIPs with sol-gel and some reports have already published on this combination for preparing SPME fibers [46]. Figure 5 shows schematic for preparation of MIP-based SPME fibers for selective analytes [49].

Fig.5.

Electrochemically prepared coatings utilize unbreakable metal wire as a support for electrochemical deposition of coating material. Moreover, such coatings have relatively more thermal, mechanical and chemical strength. Electrochemical methods can help in controlling the thickness of coating to desired level and overall set up for such coatings is simple, and cost-effective. A recent review classifies electrochemical methods of coatings into four

(i) Electropoymerization of conducting polymers
(ii) Electrodeposition of metal oxides
(iii) Anodizing of metal wires
(iv) Electrophoretic deposition of carbon nanotubes (CNTs).

Conducting polymers have good biocompatibility and porous and π-electron rich structure which make them a good coating material for in-vivo applications. The desired materials can be incorporated into conducting polymers to enhance their extraction efficiency. The low adsorption of organic compounds by electrochemically deposited metal oxides is a drawback of such coatings. However, such fibers can be used as substrate for sol-gel reaction [50]. Although, there are only few polymers that can be used to synthesize electrochemical based SPME coatings, but the properties of the conducting polymers such as porosity and hydrophobicity are amenable to modification by use of suitable counter ions and surfactants [47]. Conductive polymeric ionic liquids can also be electrochemically deposited on macro and micro electrodes which are also useful as SPME coatings [51].

5. Advancements in coating chemistry

5.1. Nanomaterials

Nanomaterial have gained considerable attention as coating materials because of their excellent physical and chemical properties which include but not limited to good capacity, mechanical and thermal strength. Here, we give brief information of some types of nanomaterials which are widely adopted in SPME coatings

5.1.1. Carbon based nanomaterials

Carbon-based nanomaterials are good candidates for SPME coatings because of their cost effectiveness and excellent properties as adsorbents. In this regard, CNTs, fullerenes, graphene and ordered mesoporous carbon are mentionable.

First report on the use of multi-walled carbon nanotubes (MWCNTs) as SPME coating was published in 2006 [52]. After that, various forms of CNTs and their carboxylic derivatives are widely tested as SPME coatings. MWCNTs are also used in combination with other materials such as polymers for SPME coatings using sol-gel technology. Polyethylene glycol (PEG)/MWCNTs based coating showed excellent extraction properties along with good thermal stabilities. The results were better than the commercial fibers. Other chemical bonding based approaches for coating involve surface modification of CNTs and solid supports [53].

CNTs are also combined with other materials to get benefit of the properties of CNTs and other materials simultaneously. The examples include simultaneous electrodeposition of MWCNTs and conductive polymers on the metal wires. Some polymers such as nafion can be used as binders to immobilize CNTs on stainless steel wires. Such fibers are electro conductive and can be used as working electrodes in electro driven SPME. Moreover, CNTs can be made more selective by functionalizing their surfaces and their applications can be extended to extraction of polar compounds [53].

For single walled carbon nanotubes (SWCNT) based coatings, three coating strategies have been reported which include; sol-gel technology, physical agglutinating method and electrophoretic deposition [53]. The conjugate system of π-electrons leads to better extraction efficiency for organic compounds. Other than sol-gel approach, SWCNTs were also coated on stainless-steel wire and fused silica fiber surfaces using organic binders However, such physical binding leads to lower thermal stability, resistance to organic solvents and fiber-to fiber reproducibility. The electrophoretic deposition of SWCNTs employs electric field for deposition of charged nanoparticles from the solution on the solid support. This approach is cost effective and provides a better control of thickness while coating by providing suitable voltage for a certain period of time. In addition to good mechanical, chemical and thermal properties, high conductivity of such coatings allow their applications in electro-enhanced SPME [54].

Graphene is another carbon material which has shown excellent applications in SPME coatings because of its large effective surface area, extraordinary thermal and chemical stability and noble mechanical properties. Hydrophobicity of the graphene and π-π interactions with organic compounds such as polycyclic aromatic hydrocarbons (PAHs) make graphene a good material for extraction applications [55]. Like CNTs, graphene can also be electrochemically polymerized with polymers like pyrrole on stainless steel wire [56].

Fullerenes are also used in SPME coatings but the major hurdle in its utilization as SPME sorbent is poor solubility in solvents. Ordered mesoporous carbons are some other materials which are used in SPME coatings.

5.1.2. Silica-based nanomaterials

Silica based nanomaterials are good choice for SPME coatings because of their large specific surface area and high thermal stability. They are easy to synthesize and functionalize with different groups on their surface. Silica based materials are less expensive and have good biocompatibility. Nanoporous silica (SBA-15) provides a nice support for its functionalization with different organic groups which can be employed in different extraction applications. Modified SBA-15 can be coated on copper or stainless-steel wires by use of epoxy glue [57]. The amino ethyl-functionalized SBA-15 coated fiber showed better performance than commercial PDMS fiber for extraction of polar compounds. This is due to the nature of the functionalized groups. Hence, the functionalized groups can be tuned according to the nature of the analytes to be extracted [58]. The use of methyl or 3-aminopropylsilyl groups enhances the interaction of SBA-15-based coatings for hydrophobic compounds. The performance of SBA-15 can be compromised because of its high affinity toward water in headspace. However, its composites with polymers like polypyrrole (PPy) and polyaniline (PANI) can resolve this problem. As SBA-15 has no chemical bonding with the metal or stainless-steel wire, it leads to relatively low thermal stability compared to other fibers. Electrochemical polymerization of silica based material with polymers on solid support can provide them more strength [53].

5.1.3. Metal and metal oxide nanoparticles

Metal and metal oxide nanoparticles (NPs) have shown promising applications in SPME coatings. In this regard, ZnO based NPs have achieved greater attentions because of their large specific surface area and good sensing capability for gases. Hence, they are used in headspace-SPME of volatiles like BTEX and aldehydes. Similarly, titania and alumina have shown remarkable applications in analysis of volatile organic compounds. Gold NPs which have very good chemical stability, high surface area, and ability to form π-π interactions with analytes, were used for extraction of polyaromatic hydrocarbons [53] and organochlorine pesticides [59].

5.1.4. Polymeric SPME coatings

Polymer based coatings include both conductive and non-conductive polymers. The synthesis of nanostructured conductive polymer by electrodepositing the polymer directly on a metal substrate. Such coatings can be controlled by applied potential, monomer selection and concentration and addition dopant ion. The selectivity of such coatings remains a question, however use of molecular imprinting approach can resolve the issue of selectivity while keeping the sensitivity maintained at desired level [60]. The examples conductive polymer based coatings include PANI, PPy, polythiophene and their derivatives. Non-conductive polymer coatings were prepared by electrospinning.

5.1.5. Ionic liquids and polymeric ionic liquids

Ionic liquids (ILs) are basically salts with melting points at or below 100°C and are consisted of organic cations and organic/inorganic anions. They are unique because of exceptional properties such as high thermal resistance, adjustable viscosities and solvation capabilities, and very low vapor pressures. The main motivation of employing ILs in SPME sorbent coatings comes from their tunable structure which allow to incorporate various different species selective to target analytes. Initially disposable IL coatings were developed for HS applications [61] but later on reusable fibers were introduced [62]. IL monomers are used to synthesize polymeric ionic liquids (PILs). Compared to ILs, PILs have higher viscosity and greater mechanical strength with almost same extraction selectivity. Coatings made of PILs do not flow from SPME support under high temperatures. PILs eliminate the need for recoating after each extraction and desorption cycle [63]. In recent studies, cross-linked PIL based copolymers were also employed as SPME coatings [64].

ILs are sometimes coated over the pretreated support with other materials such as Nafion for their homogenous loading. Substrate bonded IL coatings provide more thermal and mechanical strength to the fiber. Various strategies have been developed in this regard. IL impregnated SPME coatings have also shown promising applications. PILs are coated using different strategies such as sol-gel, electrochemical deposition, dip coating, substrate bonding etc., and showed good selectivity toward target analytes. The dynamic or static dip-coating are among popular adoptions for loading IL/PILs to the fiber substrate. Despite the simplicity of dip coating method, dynamic dip-coating may give poor IL/PIL loading from fiber-to-fiber while static dip-coating is time-consuming and loading is repeated for several times. Another precaution should be taken while selection solvent as a dispersive media for IL/PIL loading because residual solvent within the sorbent coating can lead to enhanced background and decreased sensitivity. Hence, the solvents with good volatility should be selected. The most important advancement in use of ILs and PILs is associated with their functionalization with polar and/or hydrogen-bonding-capable functional groups because such coatings allow selective extraction of polar analytes from aqueous matrices. In addition, polar cross-linked PILs will allow their use in DI-SPME [65].

5.1.6. Metal organic frameworks

Metal organic frameworks (MOFs) are basically crystalline three-dimensional coordination polymers which are formed by self-assembly of metal clusters or metal centers and organic ligands via coordination bonds. MOFs have permanent porosity and remain crystalline even after removing the guest solvent molecules. They also show good thermal stability ranging from 200 to 400 °C. In addition, MOFs are tailorable materials that can be designed with specific pores sizes and pore surface environments. Another interesting fact is that, at least from a theoretical point of view, it is possible to design almost an infinite number of MOFs. There are almost 10000 experimentally known MOFs which is much greater number than 300 zeolites (which is a famous class of comparable materials). MOFs are getting considerable attention as sorbent materials in analytical extractions. They can give high selectivity because of specific pore size and pore surface environment which can discriminate analytes based on size as well as interaction with the framework. The selective active sites can also play role in extraction which are accessible through permeable channels. They are easily tunable in terms of polar, non-polar, hydrophobic and hydrophilic properties. MOFs are synthesized using crystalline routes which include slow evaporation, diffusion and hydro/solvothermal methods. A recent review provides comprehensive account on the procedures for MOF coatings on certain supports and their applications in analysis. MOF based coating are mostly used in HS mode. For DI-SPME applications, MOFs with good stability in water are being prepared [66]. The emerging role of MOFs in sample preparation has also been covered in another review article with particular emphasis on dispersive based microextractions [67]. The schematic of solvothermal growth of MOF-5 on porous copper foam is shown in Figure 6 [68].

Fig.6.

6. Advancements in biological analysis with emphasis on *in vivo* analysis

Biological samples are extremely complex matrices and may contain large amounts of salts, proteins, and other compounds. They pose a special requirement of sample preparation for the analysis of target analytes, even when employing very advanced analytical instrumentation, such as liquid chromatography–tandem mass spectrometry (LC–MS/MS).

SPME can be used in the analysis of biological fluids and even entire living systems because of several excellent and unique features. Here we enlist some of unique features and challenges related to SPME for biological, *in vitro* and *in vivo* sampling and analysis.

(i) It provides efficient sample clean up as very small volumes of sample are used. Thus, it reduces the amount of interfering compounds that can be co-extracted with the target analytes.

(ii) It can be good choice for *in vitro* bioanalysis as it requires small sample volume. It does not need any pretreatment.

(iii) *In vivo* studies give deep insight to dynamic chemical processes occurring in the living systems. SPME, as a syringe like device, can be used for simultaneous sampling and sample preparation.

(iv) *In vivo* SPME can be used in HS or DI modes. For the analysis of the volatiles and semi-volatiles in the breath or skin emissions, HS mode can be employed.

(v) For the analysis of polar and non-volatile compounds within the tissues or muscles, DI mode can be used by inserting the fiber inside the tissue. This is the most complex analysis. In such cases, mechanically strong and flexible fibers with small dimensions are needed. Above all other requirement, biocompatible coatings are needed in order to avoid any toxic or adverse effect within the living system. The coatings should also not adsorb any proteins; this may decrease their uptake of target analytes.

(vi) Biocompatible and affinity materials are being developed for in vivo applications.

(vii) The dimensions of SPME device are important for *in vivo* sampling. In that case, it will be desired that dimensions of SPME device should be as small as possible in order to avoid tissue damaging during insertion and sampling. Thus, coatings with 1 and 2 mm have been successfully employed for in vivo sampling.

(viii) The use of such miniaturized devices may have its own shortcomings. Thin coatings will lead to lower extraction. Thus, the analytical instruments with high sensitivity would be required. The other way of improving sensitivity is to use coatings with high distribution constants for target analytes.

(ix) Inter-fiber reproducibility is also important.

(x) Along with biocompatibility, the stability of coatings to organic solvents is another desired feature because desorption will be accomplished by the solvents for LC analysis.

(xi) Several biocompatible materials have shown excellent potential to be employed in SPME coatings. Biocompatible polymers such as PDMS, polyacrylonitrile (PAN), PEG and polypyrrole (PPY) and restricted access materials (RAM) are some of the good candidates. However, some limitations and pitfalls are also associated with such materials. Unmodified PDMS leads to high degree of nonspecific adsorption, PPY have issues of poor inter-fibre reproducibility and displacement effects due to the adsorptive mechanism of extraction. These shortcomings of PPY coatings were resolved by Supelco [69]. New biocompatible SPME devices are now commercially introduced by Supelco for bioanalysis and *in vivo* sampling. These devices are based on C18 bonded porous silica sorbent particles coated on metallic alloy support using non-swelling polymer as a binder.

The advancements and applications of in vivo SPME can be read in detail [70-72].

7. Advancements in on-site sampling and sample preparation

During analytical determination, 60% of the time and cost is spent on sample preparation [73]. The samples may undergo degradation during storage and transportation. On-site sample preparation not only solves the problem of sample degradation but also reduces overall analysis time, cost and labor. On-site sample preparation demands miniaturized, portable and simple to operate extraction devices which utilize very little or no organic solvent at all. SPME is an ideal choice from this perspective, as it combines sampling, extraction and preconcentration into a single step. Moreover, it is solvent free and portable technique. SPME coating sorbent is very critical in on-site sample preparation as it is expected to have good affinity toward target analytes and, stable and compatible with matrix specially under extreme matrix conditions such as high salinity, low or high temperatures, flow rate and volume of sample, suspended materials in the sample etc. Some polymeric coatings have shown good potential for on-site sample preparation.

Due to complications associated with addition of internal standards and control of agitation of the matrix, new calibration methods are desired for on-site SPME sampling. In this regard, some articles have been dedicated to description of traditional and novel kinetic calibration methods. Passive samplers based on SPME can be a good choice. LDPE based passive samplers have been used in environmental analysis. Certain modifications in the SPME device and sampler can be more helpful for on-site sample preparation [74,75].

8. High throughput multi well SPME format and its advancements.

Employing the SPME in the high throughput analysis offers many advantages such as reducing the solvent usage, decreasing the cost, shortening the analysis time, its ability to extract the target analytes from different complex matrices (i.e blood and plasma) without pretreatment and excellent compatibility with the new analytical instruments. The traditional sample preparation methods such as LLE and SPE have been automated using 96 or 384 multi-well plate format to achieve a high throughput samples analysis [76]. In the last decade, the SPME has been partially automated, whereas the samples are processed sequentially using coated capillary column SPME, configured and coupled on-line to HPLC [12, 77, 78]. The fully automated multi well format of SPME is the most recent and advanced configuration that can provide a high throughput for samples preparation. Three main configurations of automated multi well SPME are: (i) in-tip SPME (ii) fiber SPME and (iii) thin film or blade SPME.

The general procedure for automated multi well SPME includes the following steps [79];

(i) Providing a computerized robotic arm with XYZ coordinates and 96 or 384 fiber device and plates.
(ii) Lowering either the fiber, tip or thin films SPME device for a certain period of time into the multi-well plate contains a preconditioning solvent.
(iii) Automatically dispensing a certain amount of internal standard into the extraction plate using a syringe.
(iv) Relocating the SPME device to the extraction plate and lowering the arm for an enough time into its wells which contain the samples.
(v) Washing the fiber, tip or thin film SPME by moving the arm to another plate contains a rinsing solvent.
(vi) Moving and lowering the fiber, tip or thin film SPME device into a multi-well plate contains a desorption solvent. And
(vii) If necessary, automatically evaporating desorption solvent using nitrogen gas then re-dissolve the multi-well plat contents using a reconstitution solvent.

Generally, the automated multi-well in-tip and fiber SPME share the same rod shape of SPME while the thin film SPME has a blade shape. The main advantages and disadvantages of each automated system are summarized in Table 3.

Tab.3.

The multi well SPME system has been used for different samples extraction in many applications such as pharmaceutical, clinical, food and environmental application. For example, in the field of clinical study, the system was tested, validated and compared with the conventional LLE for the analysis of the target drug analyte in plasma [80]. After a single dose administration of 25 mg target drug, the obtained concentration-time profile using automated multi well SPME was agreed with that obtained using the liquid-liquid extraction technique. The main advantages of the used multi well SPME in this study was its ability to reduce the usage of solvent and eliminate the evaporation and reconstitution steps, therefore its high throughput was higher with lower cost. However, the limitations of using the multi well SPME technique in that study were related to its need for extensive clean up after usage to decrease the carry-over, in addition to the high cost of building the multi well SPME automated device using the commercial fibers.

In the environmental field, a manual 96 multi well SPME was used to extract selected organophosphorus pesticides from cucumber. The SPME system included a custom-made PTFE 96 multi-well plates with 1.0 cm polydimethylsiloxane (PDMS) located on stainless steel tubing. With 40 minutes equilibrium time, the lower limit of detection was of 8-60 μg/kg and the precision of the method was lower than 15.4 % [81].

The main challenge in the automated multi well SPME configurations is to obtain uniform agitation, developing a flexible coating method compatible with different coating materials, the materials able to extract the target analyte and reach the extraction equilibrium quickly as well as increasing the rigidity and robustness of the multi well SPME system to prevent bending the tip, fiber and thin film SPME.

9. Coupling of SPME with mass spectrometry

Coupling the SPME with the mass spectrometry (MS) provides a faster and direct analysis of target analytes at very low concentration levels in complex matrices under ambient temperature and pressure. Different approaches for combining the SPME directly to the MS without chromatographic separation have been developed and discussed [82]. In the last two decades, the SPME was coupled with different types of MS i.e. Atmospheric pressure ionization MS (API-MS) [83], Electron ionization MS (ES-MS) [84], Laser desorption/desorption MS (LD-MS) [85], inductively coupled plasma MS (ICP-MS) [86] and Ambient ionization MS (AIMS) [87]. In this review the most recent advancements in the strategies for coupling the SPME with MS for quantitative analysis of target analyte in a complex biological matrix has been summarized.

Since its development in 2004, the ambient MS has given the opportunity for coupling the SPME with MS instrument by adopting new strategies with higher sensitivity for different applications and more sample analysis throughput. Recently, Mirabelli et. al., [88] reported a new strategy for coupling the SPME technique directly with MS using the dielectric barrier discharge ionization (DBDI) source. The main advantages of this strategy are the following; i) separating the target analyte totally from the ionization source and ii) enhancement the precision of the analysis methods by minimizing the matrix effect and elimination the carry over. The analytical figures of merit for analysis of some pesticides and drugs using that strategy are excellent. The limits of detection were 0.3 pg/mL for diazepam and cocaine, 3pg/mL for parathion and 1.0 pg/mL for ametryn. However, the intraday and inter-day precision for analysis of cocaine was 3.7% and 2.1% and for diazepam were 2.1% and 2.9% respectively. Pawliszyn's research group coupled a stainless-steel mesh support coated with biocompatible C18-Polyacrylonitrile polymer as SPME part with MS using direct analysis in real time (DART) ionization source [89]. They successfully analyzed the cocaine and diazepam quantitatively at the same time with limits of quantitation (LOQ) of 2 and 5 pg/mL for cocaine and 19 and 479 pg/mL for diazepam in urine and plasma respectively within 3 minutes and with reproducibility < 5 %. More recently, Pawliszyn and coworkers developed a new biocompatible in-tube SPME device coupled with LC-MS/MS instrument or directly to the MS/MS to analyze quantitatively a group of pharmaceutical active ingredients (i.e. riboflavin, caffeine, dexamethasone, pindolol, carbamazepine, diazepam, thiabendazole, testosterone, propranolol, formic acid) in single drop of untreated blood [90]. In this SPME, a nano structured PPY material was used to coat a 2.5cm of commercial medical spinal needle electrochemically. The main advantages of the developed in-tube SPME are its biocompatibility, in situ and *in vivo* sampling and its applicability to be used as an electrospray probe in the MS detector. The limit of detection for analysis of pindolol, propranolol, diazepam in 2 μL urine using direct coupling the developed in tube SPME to MS/MS were 0.7, 2.0 and 2.0 ng/mL respectively, with accuracy around 101% for all the analyzed compounds. However, the precision of that method was little bit high but less than 20%. In 2014, a new SPME configuration was developed to be used for extraction and coupled with electrospray probe working at ambient conditions [19]. This SPME in that new configuration is called coated blade spray, it consists a stainless-steel sheet as blade coated with C18-polyacrylonitrile biocompatible polymer. The coat of the SPME was designed to clean up of matrix and extract the target analyte selectively, therefore the ion suppression or enhancement of signal in the MS detection was decreased. The whole analytical process for extraction and analysis of cocaine in urine or plasma using this configuration was completed within less than 3 minutes with lower limit of quantitation 2.0 and 0.5pg/mL and reproducibility 1.8%. The same principle of the miniaturized coated blade spray SPME coupled with MS was employed for fast quantification of quercetin flavonol in 5 μL homogenized anion sample [91]. A micro tip SPME based on electrochemically coated with biocompatible PPY was developed and coupled to nano-electrospray ionization source with MS detector [92]**.** This new strategy based on micro tip SPME was used for simultaneous quantitative analysis of carbamazepine, testosterone, pindolol, propranolol and diazepam in very small volume of urine sample (10 μL) with acceptable analytical figure of merits. In addition, it was employed for qualitative analysis of flavonoids, luteolin and quercetin in single red-onion cell.

10. Recommendations and future prospects

Over the last two and half decades, the area of research in SPME has progressed in a multitude of directions. The literature published in area of SPME indicate the intensity of research activities being carried out in this field. The major developments in SPME technology can be summarized in the following points:

(i) New designs and formats of SPME that solve several problems associated with extraction of complex samples.

(ii) Development of new coating materials that allow SPME to extract the wide range of analytes in wide range of matrices. Biocompatible and matrix compatible coatings represent some major advancements are mention-able from this perspective.
(iii) New supports and coating strategies resulted in mechanically stable SPME fibers.
(iv) Multi-well design of SPME is suitable for extraction of large number of samples thus reducing extraction times significantly.
(v) Coupling of SPME with very powerful mass spectrometers has resulted in fast analysis.
(vi) Advancements in *in vivo* extraction that permits extraction under real and dynamic conditions without affecting the system.
    a. It can benefit in investigating short living species
    b. It can be used to determine inter-animal variation of some species.
    c. Reduction in steps needed for sample handling and analysis
(vii) Miniaturization of SPME devices for in vivo and on-site sampling.

The disadvantages/limitations of commercially available coatings such as poor interaction with polar compounds and incompatibility with complex samples persist but it can be anticipated based on the research activity to handle with such challenges in near future.

Future prospects of SPME technology are depicted in the following directions:

(i) SPME is environment friendly technique compared to conventional LLE and SPE. SPME based methods have potential to replace conventional extraction approaches in routine analysis. With this regard, various SPME methods have been approved by some international organizations.

(ii) Hundreds of materials have been tested as coatings for SPME in the applications which demonstrate proof of concepts. However, the commercially available coatings are still limited. In future, we can expect some new commercial coatings based on the excellent materials reported in the literature.

(iii) Based on recent advancements in *in vivo* analysis, SPME can play a significant role food safety and clinical diagnosis.

(iv) The future of SPME is linked with advancements in analytical instrumentation. It requires compatible GC and HPLC systems that are portable for in field and on-site analysis. Direct coupling with MS will surely benefit in terms of sensitivity and analysis time but MS instruments should also be downsized for portability and in field applications.

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