

Solid phase microextraction: apparatus, sorbent materials and application

Muhammad Sajid^a, Mazen Khaled Nazal^a, Małgorzata Rutkowska^b, Natalia Szczepańska^b, Jacek Namieśnik^b, Justyna Płotka-Wasyłka^{b,*}

^a Center for Environment and Water, Research Institute, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia.

^b Department of Analytical Chemistry, Faculty of Chemistry, Gdańsk University of Technology, Gdańsk, Poland

*Corresponding author

E-mail: juswasyl@pg.edu.pl; plotkajustyna@gmail.com

Emails of authors:

Muhammad Sajid (msajid@kfupm.edu.sa)

Mazen Khaled Nazal (mazennazal@kfupm.edu.sa)

Małgorzata Rutkowska (malgorzatahelenachmiel@gmail.com)

Natalia Szczepańska (nataliaszczepanska@vp.pl)

Jacek Namieśnik (chemanal@pg.edu.pl)

Justyna Płotka-Wasyłka (juswasyl@pg.edu.pl; plotkajustyna@gmail.com)

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48 **Abstract**

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

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59 **Keywords:**

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

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83 1. Introduction

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

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

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

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

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

120 Fig.1.

121 SPME has been widely used in analysis of environmental [4], food [5], pharmaceutical and
122 biological samples [6]. The search on Scopus revealed that in the past twenty-four years (1992–
123 14 June 2017) 14089 articles have been published in area of SPME. The articles published before
124 1992 did not appear in Scopus search results and it was probably only one article which was
125 published in 1990 [7]. This large volume of publications highlights the research activity going on
126 in area of SPME. It is also supportive to indicate the fact that SPME has gone through numerous

127 advancements. The milestones of SPME is presented in Figure 2, while its classification in
128 Figure 3.

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

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

142 **Fig.2.**

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

149 **Fig.3**

150

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

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

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

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

194 enhanced by using internal cooling, agitation, proper pH adjustment and using salting out
195 strategy.

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

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

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

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

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



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

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

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

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

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

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

280 However, the equilibrium times are much longer in case of SBSE. Stir bar has good mechanical
281 strength than fiber SPME. From the other site, this a small number of commercially available
282 coatings is a limitation in the application of this technique. Moreover, SBSE has other drawbacks
283 including the inability to achieve full automation of the SBSE process and reconstitution in a
284 solvent before chromatographic analysis, where it is possible to contaminate and lose analytes
285 [14].

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

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

302 **Fig.4.**

304 **Tab.1**

306 **3. Advancements in coating supports**

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

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

319 **Tab. 2**

320

321 4. Advancements in coating strategies

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

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

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

339

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

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

360 Molecularly imprinted polymers (MIPs) are also used as coating materials in SPME. They show
361 good selectivity because of their template based synthesis against certain analyte or class of

362 analytes. MIPs are synthesized by one of the following approaches; non-covalent, covalent and
363 semi-covalent imprinting. Their applications have been summarized in a recently published
364 review article [48]. MIP coatings are selective but they arise some issues such as weak
365 performance in aqueous solutions and difficulties in preparation of thick coatings. On the other
366 hand, the coatings prepared by sol-gel technology are rigid and thermally stable but in some
367 cases present poor selectivity. Such issues can be resolved by combining the MIPs with sol-gel
368 and some reports have already published on this combination for preparing SPME fibers [46].
369 Figure 5 shows schematic for preparation of MIP-based SPME fibers for selective analytes [49].

370 **Fig.5.**

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

- 376 (i) Electropolymerization of conducting polymers
- 377 (ii) Electrodeposition of metal oxides
- 378 (iii) Anodizing of metal wires
- 379 (iv) Electrophoretic deposition of carbon nanotubes (CNTs).

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

390 **5. Advancements in coating chemistry**

391 **5.1. Nanomaterials**

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

396

397 **5.1.1. Carbon based nanomaterials**

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

401 First report on the use of multi-walled carbon nanotubes (MWCNTs) as SPME coating was
402 published in 2006 [52]. After that, various forms of CNTs and their carboxylic derivatives are

403 widely tested as SPME coatings. MWCNTs are also used in combination with other materials
404 such as polymers for SPME coatings using sol-gel technology. Polyethylene glycol
405 (PEG)/MWCNTs based coating showed excellent extraction properties along with good thermal
406 stabilities. The results were better than the commercial fibers. Other chemical bonding based
407 approaches for coating involve surface modification of CNTs and solid supports [53].

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

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

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

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

435 **5.1.2. Silica-based nanomaterials**

436 Silica based nanomaterials are good choice for SPME coatings because of their large specific
437 surface area and high thermal stability. They are easy to synthesize and functionalize with
438 different groups on their surface. Silica based materials are less expensive and have good
439 biocompatibility. Nanoporous silica (SBA-15) provides a nice support for its functionalization
440 with different organic groups which can be employed in different extraction applications.
441 Modified SBA-15 can be coated on copper or stainless-steel wires by use of epoxy glue [57].
442 The amino ethyl-functionalized SBA-15 coated fiber showed better performance than
443 commercial PDMS fiber for extraction of polar compounds. This is due to the nature of the
444 functionalized groups. Hence, the functionalized groups can be tuned according to the nature of
445 the analytes to be extracted [58]. The use of methyl or 3-aminopropylsilyl groups enhances the



446 interaction of SBA-15-based coatings for hydrophobic compounds. The performance of SBA-15
447 can be compromised because of its high affinity toward water in headspace. However, its
448 composites with polymers like polypyrrole (PPy) and polyaniline (PANI) can resolve this
449 problem. As SBA-15 has no chemical bonding with the metal or stainless-steel wire, it leads to
450 relatively low thermal stability compared to other fibers. Electrochemical polymerization of
451 silica based material with polymers on solid support can provide them more strength [53].

452 **5.1.3. Metal and metal oxide nanoparticles**

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

460 **5.1.4. Polymeric SPME coatings**

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

469 **5.1.5. Ionic liquids and polymeric ionic liquids**

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

482 ILs are sometimes coated over the pretreated support with other materials such as Nafion for
483 their homogenous loading. Substrate bonded IL coatings provide more thermal and mechanical
484 strength to the fiber. Various strategies have been developed in this regard. IL impregnated
485 SPME coatings have also shown promising applications. PILs are coated using different
486 strategies such as sol-gel, electrochemical deposition, dip coating, substrate bonding etc., and
487 showed good selectivity toward target analytes. The dynamic or static dip-coating are among



488 popular adoptions for loading IL/PILs to the fiber substrate. Despite the simplicity of dip coating
489 method, dynamic dip-coating may give poor IL/PIL loading from fiber-to-fiber while static dip-
490 coating is time-consuming and loading is repeated for several times. Another precaution should
491 be taken while selection solvent as a dispersive media for IL/PIL loading because residual
492 solvent within the sorbent coating can lead to enhanced background and decreased sensitivity.
493 Hence, the solvents with good volatility should be selected. The most important advancement in
494 use of ILs and PILs is associated with their functionalization with polar and/or hydrogen-
495 bonding-capable functional groups because such coatings allow selective extraction of polar
496 analytes from aqueous matrices. In addition, polar cross-linked PILs will allow their use in DI-
497 SPME [65].

498 **5.1.6. Metal organic frameworks**

499 Metal organic frameworks (MOFs) are basically crystalline three-dimensional coordination
500 polymers which are formed by self-assembly of metal clusters or metal centers and organic
501 ligands via coordination bonds. MOFs have permanent porosity and remain crystalline even after
502 removing the guest solvent molecules. They also show good thermal stability ranging from 200
503 to 400 °C. In addition, MOFs are tailorable materials that can be designed with specific pores
504 sizes and pore surface environments. Another interesting fact is that, at least from a theoretical
505 point of view, it is possible to design almost an infinite number of MOFs. There are almost
506 10000 experimentally known MOFs which is much greater number than 300 zeolites (which is a
507 famous class of comparable materials). MOFs are getting considerable attention as sorbent
508 materials in analytical extractions. They can give high selectivity because of specific pore size
509 and pore surface environment which can discriminate analytes based on size as well as
510 interaction with the framework. The selective active sites can also play role in extraction which
511 are accessible through permeable channels. They are easily tunable in terms of polar, non-polar,
512 hydrophobic and hydrophilic properties. MOFs are synthesized using crystalline routes which
513 include slow evaporation, diffusion and hydro/solvothermal methods. A recent review provides
514 comprehensive account on the procedures for MOF coatings on certain supports and their
515 applications in analysis. MOF based coating are mostly used in HS mode. For DI-SPME
516 applications, MOFs with good stability in water are being prepared [66]. The emerging role of
517 MOFs in sample preparation has also been covered in another review article with particular
518 emphasis on dispersive based microextractions [67]. The schematic of solvothermal growth of
519 MOF-5 on porous copper foam is shown in Figure 6 [68].

520 **Fig.6.**

521

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

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

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



- 530 (i) It provides efficient sample clean up as very small volumes of sample are used. Thus,
531 it reduces the amount of interfering compounds that can be co-extracted with the
532 target analytes.
- 533 (ii) It can be good choice for *in vitro* bioanalysis as it requires small sample volume. It
534 does not need any pretreatment.
- 535 (iii) *In vivo* studies give deep insight to dynamic chemical processes occurring in the
536 living systems. SPME, as a syringe like device, can be used for simultaneous
537 sampling and sample preparation.
- 538 (iv) *In vivo* SPME can be used in HS or DI modes. For the analysis of the volatiles and
539 semi-volatiles in the breath or skin emissions, HS mode can be employed.
- 540 (v) For the analysis of polar and non-volatile compounds within the tissues or muscles,
541 DI mode can be used by inserting the fiber inside the tissue. This is the most complex
542 analysis. In such cases, mechanically strong and flexible fibers with small dimensions
543 are needed. Above all other requirement, biocompatible coatings are needed in order
544 to avoid any toxic or adverse effect within the living system. The coatings should also
545 not adsorb any proteins; this may decrease their uptake of target analytes.
- 546 (vi) Biocompatible and affinity materials are being developed for *in vivo* applications.
- 547 (vii) The dimensions of SPME device are important for *in vivo* sampling. In that case, it
548 will be desired that dimensions of SPME device should be as small as possible in
549 order to avoid tissue damaging during insertion and sampling. Thus, coatings with 1
550 and 2 mm have been successfully employed for *in vivo* sampling.
- 551 (viii) The use of such miniaturized devices may have its own shortcomings. Thin coatings
552 will lead to lower extraction. Thus, the analytical instruments with high sensitivity
553 would be required. The other way of improving sensitivity is to use coatings with
554 high distribution constants for target analytes.
- 555 (ix) Inter-fiber reproducibility is also important.
- 556 (x) Along with biocompatibility, the stability of coatings to organic solvents is another
557 desired feature because desorption will be accomplished by the solvents for LC
558 analysis.
- 559 (xi) Several biocompatible materials have shown excellent potential to be employed in
560 SPME coatings. Biocompatible polymers such as PDMS, polyacrylonitrile (PAN),
561 PEG and polypyrrole (PPY) and restricted access materials (RAM) are some of the
562 good candidates. However, some limitations and pitfalls are also associated with such
563 materials. Unmodified PDMS leads to high degree of nonspecific adsorption, PPY
564 have issues of poor inter-fibre reproducibility and displacement effects due to the
565 adsorptive mechanism of extraction. These shortcomings of PPY coatings were
566 resolved by Supelco [69]. New biocompatible SPME devices are now commercially
567 introduced by Supelco for bioanalysis and *in vivo* sampling. These devices are based
568 on C18 bonded porous silica sorbent particles coated on metallic alloy support using
569 non-swelling polymer as a binder.

570 The advancements and applications of *in vivo* SPME can be read in detail [70-72].
571

572 7. Advancements in on-site sampling and sample preparation

573 During analytical determination, 60% of the time and cost is spent on sample preparation [73].
574 The samples may undergo degradation during storage and transportation. On-site sample
575 preparation not only solves the problem of sample degradation but also reduces overall analysis



576 time, cost and labor. On-site sample preparation demands miniaturized, portable and simple to
577 operate extraction devices which utilize very little or no organic solvent at all. SPME is an ideal
578 choice from this perspective, as it combines sampling, extraction and preconcentration into a
579 single step. Moreover, it is solvent free and portable technique. SPME coating sorbent is very
580 critical in on-site sample preparation as it is expected to have good affinity toward target analytes
581 and, stable and compatible with matrix specially under extreme matrix conditions such as high
582 salinity, low or high temperatures, flow rate and volume of sample, suspended materials in the
583 sample etc. Some polymeric coatings have shown good potential for on-site sample preparation.

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

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

591

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

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

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



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

621 **Tab.3.**

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

633 In the environmental field, a manual 96 multi well SPME was used to extract selected
634 organophosphorus pesticides from cucumber. The SPME system included a custom-made PTFE
635 96 multi-well plates with 1.0 cm polydimethylsiloxane (PDMS) located on stainless steel tubing.
636 With 40 minutes equilibrium time, the lower limit of detection was of 8-60 $\mu\text{g}/\text{kg}$ and the
637 precision of the method was lower than 15.4 % [81].

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

643 **9. Coupling of SPME with mass spectrometry**

644 Coupling the SPME with the mass spectrometry (MS) provides a faster and direct analysis of
645 target analytes at very low concentration levels in complex matrices under ambient temperature
646 and pressure. Different approaches for combining the SPME directly to the MS without
647 chromatographic separation have been developed and discussed [82]. In the last two decades,
648 the SPME was coupled with different types of MS i.e. Atmospheric pressure ionization MS
649 (API-MS) [83], Electron ionization MS (ES-MS) [84], Laser desorption/desorption MS (LD-MS)
650 [85], inductively coupled plasma MS (ICP-MS) [86] and Ambient ionization MS (AIMS) [87].
651 In this review the most recent advancements in the strategies for coupling the SPME with MS for
652 quantitative analysis of target analyte in a complex biological matrix has been summarized.

653 Since its development in 2004, the ambient MS has given the opportunity for coupling the SPME
654 with MS instrument by adopting new strategies with higher sensitivity for different applications
655 and more sample analysis throughput. Recently, Mirabelli et. al., [88] reported a new strategy
656 for coupling the SPME technique directly with MS using the dielectric barrier discharge
657 ionization (DBDI) source. The main advantages of this strategy are the following; i) separating
658 the target analyte totally from the ionization source and ii) enhancement the precision of the
659 analysis methods by minimizing the matrix effect and elimination the carry over. The analytical

660 figures of merit for analysis of some pesticides and drugs using that strategy are excellent. The
661 limits of detection were 0.3 pg/mL for diazepam and cocaine, 3pg/mL for parathion and 1.0
662 pg/mL for ametryn. However, the intraday and inter-day precision for analysis of cocaine was
663 3.7% and 2.1% and for diazepam were 2.1% and 2.9% respectively. Pawliszyn's research group
664 coupled a stainless-steel mesh support coated with biocompatible C18-Polyacrylonitrile polymer
665 as SPME part with MS using direct analysis in real time (DART) ionization source [89]. They
666 successfully analyzed the cocaine and diazepam quantitatively at the same time with limits of
667 quantitation (LOQ) of 2 and 5 pg/mL for cocaine and 19 and 479 pg/mL for diazepam in urine
668 and plasma respectively within 3 minutes and with reproducibility < 5 %. More recently,
669 Pawliszyn and coworkers developed a new biocompatible in-tube SPME device coupled with
670 LC-MS/MS instrument or directly to the MS/MS to analyze quantitatively a group of
671 pharmaceutical active ingredients (i.e. riboflavin, caffeine, dexamethasone, pindolol,
672 carbamazepine, diazepam, thiabendazole, testosterone, propranolol, formic acid) in single drop
673 of untreated blood [90]. In this SPME, a nano structured PPY material was used to coat a 2.5cm
674 of commercial medical spinal needle electrochemically. The main advantages of the developed
675 in-tube SPME are its biocompatibility, in situ and *in vivo* sampling and its applicability to be
676 used as an electrospray probe in the MS detector. The limit of detection for analysis of pindolol,
677 propranolol, diazepam in 2 μ L urine using direct coupling the developed in tube SPME to
678 MS/MS were 0.7, 2.0 and 2.0 ng/mL respectively, with accuracy around 101% for all the
679 analyzed compounds. However, the precision of that method was little bit high but less than
680 20%. In 2014, a new SPME configuration was developed to be used for extraction and coupled
681 with electrospray probe working at ambient conditions [19]. This SPME in that new
682 configuration is called coated blade spray, it consists a stainless-steel sheet as blade coated with
683 C18-polyacrylonitrile biocompatible polymer. The coat of the SPME was designed to clean up of
684 matrix and extract the target analyte selectively, therefore the ion suppression or enhancement of
685 signal in the MS detection was decreased. The whole analytical process for extraction and
686 analysis of cocaine in urine or plasma using this configuration was completed within less than 3
687 minutes with lower limit of quantitation 2.0 and 0.5pg/mL and reproducibility 1.8%. The same
688 principle of the miniaturized coated blade spray SPME coupled with MS was employed for fast
689 quantification of quercetin flavonol in 5 μ L homogenized anion sample [91]. A micro tip SPME
690 based on electrochemically coated with biocompatible PPY was developed and coupled to nano-
691 electrospray ionization source with MS detector [92]. This new strategy based on micro tip
692 SPME was used for simultaneous quantitative analysis of carbamazepine, testosterone, pindolol,
693 propranolol and diazepam in very small volume of urine sample (10 μ L) with acceptable
694 analytical figure of merits. In addition, it was employed for qualitative analysis of flavonoids,
695 luteolin and quercetin in single red-onion cell.

696 **10. Recommendations and future prospects**

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

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

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

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

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

- 721 (i) SPME is environment friendly technique compared to conventional LLE and SPE.
722 SPME based methods have potential to replace conventional extraction approaches in
723 routine analysis. With this regard, various SPME methods have been approved by
724 some international organizations.
- 725 (ii) Hundreds of materials have been tested as coatings for SPME in the applications
726 which demonstrate proof of concepts. However, the commercially available coatings
727 are still limited. In future, we can expect some new commercial coatings based on the
728 excellent materials reported in the literature.
- 729 (iii) Based on recent advancements in *in vivo* analysis, SPME can play a significant role
730 food safety and clinical diagnosis.
- 731 (iv) The future of SPME is linked with advancements in analytical instrumentation. It
732 requires compatible GC and HPLC systems that are portable for in field and on-site
733 analysis. Direct coupling with MS will surely benefit in terms of sensitivity and
734 analysis time but MS instruments should also be downsized for portability and in
735 field applications.

736

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