

# Solid phase microextraction: apparatus, sorbent materials and application

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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  $\pi$ -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  $\pi$ -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  $\pi$ - $\pi$  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  $\pi$ - $\pi$  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 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  $\mu$ 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  $\mu$ 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  $\mu$ 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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