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Thin film microextraction: towards faster and more sensitive microextraction

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Abstract

Thin film microextraction (TFME) is an analytical tool that has been proven to be suitable for integrated sampling and sample preparation of a wide variety of routine and on-site applications. Compared to the traditional microextraction techniques, the most important advantage of TFME is its enhanced sensitivity due to the relatively larger extractive phase spread over a larger surface area. The technique, in this way, facilitates fast extraction kinetics and high extractive capacity. Moreover, TFME offers high versatility for device development over classical SPME technologies due to the plethora of available extractive phases, coating methods and geometry options. The goal of this review is to provide a comprehensive summary of the contemporary advances in this exciting field covering novel extractive phases, technological and methodological developments, and relevant cutting-edge applications. Finally, a critical discussion of the future trends on TFME is also presented.

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1 Introduction and theory

Thin film microextraction (TFME) is a combined sampling and sample preparation technique initially introduced in 2001 [1]. The primary difference between this novel technique and traditional solid phase microextraction (SPME) is that a larger volume of extractive phase with a larger surface area is used. This achieves the ultimate goal of improving sensitivity without surrendering the sampling time [2]. The enhanced sensitivity of the TFME technique can be realized by applying the fundamental mass balance to SPME at equilibrium conditions. Equation 1, derived from the mass balance under equilibrium conditions, illustrates the intrinsic correlation between the amount of analyte (number of moles) extracted into the extractive phase at equilibrium (n_e^{eq}) and its original concentration (C_s^0) in the sample. In this equation, K_{es} denotes the distribution constant of the analyte for the extractive phase and sample matrix, with V_s and V_e indicating the volume of sample and extractive phase, respectively. Ultimately, this equation mathematically derives that an increase in the volume of extractive phase will result in improved analytical sensitivity.

$$n_e^{eq} = \frac{K_{es}V_sV_e}{K_{es}V_e + V_s}C_s^0$$
(Eq. 1)

In the abovementioned scenario, the equilibrium extraction time (t_e), defined as the time required to extract 95% of the equilibrium amount, can be calculated by Eq. 2; where, D_s, b and δ refer to diffusion coefficient of analyte in the sample, the thickness of the extractive phase and the thickness of the boundary layer, respectively. This equation illustrates that for a given amount and type of

extractive phase, a faster extraction equilibrium can be achieved when a thin layer of extractive phase is used.

$$t_e = 3\delta K_{es}(b)/D_s \qquad \text{(Eq. 2)}$$

Moreover, Eq. 3 implies that the initial extraction rate denoted as extracted amount (dn) per given time (dt) is directly proportional to the surface area of the extractive phase (A). Therefore, if a relatively large volume of extractive phase is spread over an ultra-thin layer, there will be a larger interface between the sample and the extractive phase, resulting in faster extraction kinetics.

$$\frac{dn}{dt} = \left(\frac{D_S A}{\delta} \right) C_0 \qquad \text{(Eq. 3)}$$

Using the mathematically derived equations above, it has been proven that TFME has improved sensitivity and extraction kinetics when compared to conventional SPME. For this reason, it has become a widely used tool for the trace and multi-residue analyses in food [3-5], environmental [6, 7], clinical and bioanalytical [8-12] applications. Although TFME approaches have been in use for a considerable amount of time, there are still various new developments, with a particular focus on towards more specific, analytically challenging or practical needs. In this manuscript, we intend to review the recent trends in TFME developments, primarily focusing on research works that have been published in the last two years. More retroactive review articles summarising the applications [13] and various coating technologies [14] can be found in the literature.

2 New developments in coating technologies and applications

In terms of their compatibility with different instrumental platforms, TFME can be divided into two main categories: thermally desorbed TFME which is compatible with instruments allowing gas phase introduction of the analytes, and, solvent desorbed TFME devices, which can be used in combination with any kind of analytical instrumentation amenable with liquid samples [13, 15]. In terms of their synthesis, there is a plethora of thin film preparation methods and extractive materials. The most commonly used coating approaches and a comparison of their key features are illustrated in Figure 1. Of the aforementioned methods, dip coating is the most widely used approach where the support is dipped in a mixture (commonly referred to as a slurry) containing an extractive phase that is dissolved or dispersed in an appropriate solvent or glue [15]. In this method, the thickness of the extractive phase can be controlled primarily by the withdrawal speed of the device from the slurry. Using a particular extractive phase and withdrawal speed, the coating thickness can be reproducibly increased by applying multiple homogenous layers (i.e. dipping the same device multiple times). The convenience and practicality of dip coating has led this method to be frequently used for the

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production of biocompatible TFME devices where extractive particles are immobilized in polyacrylonitrile (PAN). Recently, ultra-thin extractive phases have become increasingly prevalent and in-demand for the most sensitive applications, such as direct coupling to mass spectrometry where fast desorption kinetics are absolutely critical [16-18]. In these types of applications, dip coating is one of the most advantageous coating approaches for the preparation of smooth-surface coatings with coating thicknesses as thin as several micrometers. In the majority of the dip coating approaches, the coating is obtained by a physical accumulation of the extractive phase without any chemical bond formation to the surface. However, based on the nature of the coating, a chemical bonding step may be necessary. In this case, the supporting surface must be activated or pre-functionalized to facilitate the formation of functional moieties which readily react with the extractive phase. This differs from the physical deposition approach mentioned above because usually it results in a thinner layer of extractive phase, primarily due to the fact that most of the surface active groups on the support are occupied in the first immersion. Furthermore, since the coating deposition with surface activation or pre-functionalization requires the formation of chemical bonds to the surface, it is more laborious and tedious to design and optimize the extractive phase. Fabric phase TFME, which has been prepared using a sol-gel approach and aptamer immobilized paper spray devices are examples for TFME prepared by chemical modification [19-21] A different coating methodology is known as spin coating, whereby a liquid extractive phase is placed on a disk which is then spread on its surface as a thin film by spinning the disc at a high speed. Spin coating can be used to produce TFME on a supporting surface and if the extractive phase is sufficiently self-supportive (e.g. PDMS) it can be used without a support. This method also permits the deposition of multiple layers of extractive phases, and produces coatings with different chemistries in each layer. One of the main limitations of this method is that it may affect the inter-device reproducibility due to variation in the thickness between the central part and outer part of the prepared bulk extractive phase. Similar to the spin coating, the bar coating method can be used to prepare TFME devices with and without a supportive core [6, 22, 23]. In this approach, the liquid extractive phase is placed on the stage of a bar coater after which the bar is moved over the stage by spreading the extractive phase in a thin layer. The coating thickness of TFME is controlled by the size of the gap between the bar and the surface. The first thermally stable TFME coatings originated from the same extractive phases employed in commercial SPME fibers (e.g. polydimethylsiloxane, PDMS) were produced using a bar coater or a spin coater. Electrospinning has gained popularity in recent years as one of the emerging methods for preparation of various polymeric TFME devices. Since the targeted polymeric solution can be converted to a mechanically stable membrane with nonwoven nanofibrous structure, this approach does not need to use a binder or support to keep the extractive phase attached to the surface. In this method, the coating thickness can be tuned by controlling the electrospinning time.

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The last method that is covered in this review is spray coating, which can be considered as one of the simplest approaches for the preparation of TFME devices. In this method, a mixture containing the extractive phase is dissolved or dispersed in an appropriate solvent or glue inside a spraying flask [8-10]. The slurry is then sprayed directly on the surface of the support in the form of fine droplets that are formed with the aid of an inert gas that has been pressurized inside the flask. It is worth noting that the difficulty of this method lies in the inability to reliably obtain homogeneous coatings due to challenge of spraying an even amount of extractive phase on the support. The coating homogeneity problem is partially solved by the application of multiple layers of extractive phase which eventually results in coatings with millimeter thickness. Therefore, in most cases, exhaustive extractions are achieved by devices produced using this method and they can be considered as open bed SPE rather than TFME devices. The recent progress in terms of new developments of TFME devices and their applications is summarized in the subsequent section.
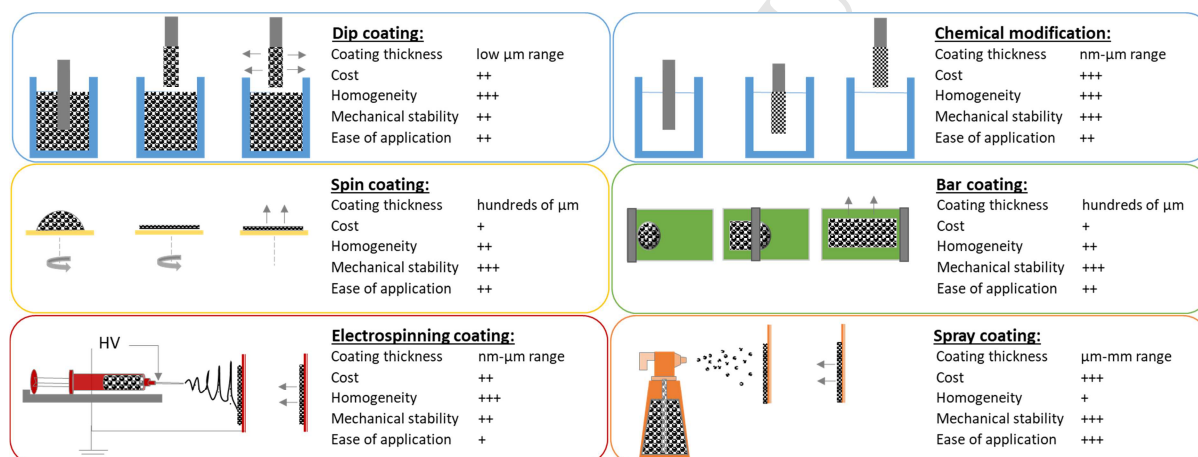
Figure 1. Summary of techniques used for preparation of TFME devices and comparisons of their key features (Cost: +++ economic, + expensive; Homogeneity: +++ homogeneous, + poorly homogeneous; Mechanical stability: +++ stable, + unstable; Ease of application: +++ easy, + difficult, ++ moderate in all cases)

2.1 TFME with thermal desorption

Thin films that are made from thermally stable extractive materials can be coupled to a temperature programmable large volume thermal desorption unit or a Curie point injector and thermally desorbed directly to GC systems or desorbed in a head-space sampler unit and then injected to the GC. As the number of thermally stable extractive phases is limited, and large volume thermal desorption units are not readily available in every laboratory, there are relatively few developments and applications in this area. For instance, polydimethylsiloxane/divinylbenzene (PDMS/DVB) and

PDMS/DVB-carbon mesh supported membranes were used in an intra-laboratory validation study for extraction of pesticides from aqueous samples [6]. Comparison of the results of two types of membranes against the results obtained by a reference method (liquid-liquid extraction) showed similarities in accuracies while both TFME devices provided better sensitivities. Thus, for collected laboratory samples, TFME devices not only present better quantitation sensitivity at ultra-trace levels but also offer less labour-intensive workflow and a major decrease in the amount of organic solvents used – a must for any "green" technology. The TFME devices can also be deployed directly on-site due to their simplicity and robust design. Alcudia-León et al. chemically bound poly(dimethyldiphenylsiloxane) (PDMDPS) to silica fiber-glass fabric using the sol-gel approach [21]. The coated fabric was then placed in a homemade holder connected to a pump which was used in the field as an active on-site air sampler, specifically targeting sexual pheromones (i.e. *tutaabsoluta*) from insects. Following the TFME field sampling, the holder was placed directly into a head-space desorption unit and the analytes desorbed from the sampler were immediately transferred into the GC-MS for further separation and detection. Such a practical field sampler could be useful for many other on-site applications, particularly as a complement to existing sample preparation methods that may be more cumbersome and impractical. In another study, Hijazi and Bottaro have developed molecularly imprinted polymeric (MIP) thin films for selective extraction of semi-volatile thiophenes from sea water [16]. After sampling with the MIP-TFME devices, the extracted analytes were again desorbed using a head-space desorption unit and quantified by a GC-sulfur chemiluminescence detector. Importantly, the authors identified that the use of MIPs as an extractive phase might require particular care during the direct thermal desorption to avoid temperatures that would potentially result in the decomposition of the MIP phase. Consequently, the decomposition of the MIP extractive phase could generate other interferences during the analysis, ultimately affecting the accuracy of the analysis. In this study, the authors also concluded that the desorption from such a coating required the application of a few microliters of acetonitrile, which acts as a phase transfer mediator and decreases the response variability due to incomplete desorption. Sub-ppb detection limits and low matrix effects were obtained for selected analytes in sea water samples, validating that the method would be a valuable analytical tool for determination of thiophenes in environmental emerging circumstances such as a hazard analysis after an oil spill.

It is worth to highlight that, the thermally stable TFME devices can be also used with solvent desorption applications; however, this has not been extensively reported in literature. Therefore, they are not exclusive to GC based applications.

2.2 TFME with solvent desorption

Compared to thermal desorption, solvent desorption from TFME is more challenging. One of the main difficulties is related to the lack of conventional interfaces for on-line coupling of TFME device to the workflow of the analytical instrument. This would facilitate the direct introduction of the extracted analytes into the analytical instrument. Furthermore, the relatively large TFME device also requires a larger volume of eluent during the desorption process. Considering that after solvent desorption only a small portion of the solution is introduced to the instrument, this does not take full advantage of the large extractive phase, unless additional evaporation and reconstitution steps are employed to generate a smaller, more concentrated sample volume to account for the extra dilution. Moreover, compared to gas phase, the diffusion kinetics are slower in liquid phase, resulting in relatively longer desorption times. Despite these limitations, the prevailing advantages such as easy automation of the sampling step and the wide variety of available or potentially viable extractive phases and supports continue to drive new advances in this field. New developments for TFME devices that employ solvent desorption are summarized in the following sections.

2.2.1 Paper based supports

A variety of low-cost and readily available cellulose-based supporting materials have been employed to improve the properties of extractive thin films. Likewise, as it is described in Section 4, the paper-based substrates are commonly used for fast analyses in conjunction with a mass spectrometer. This readily available natural polymer provides flexibility and sufficient resistance to TFME devices even under acidic and basic conditions. Initially, it would appear that the cellulose-based materials do not seem suitable for use as robust supports in very complex matrices, layering the extractive phase to the cellulose usually enhances the overall stability of the final device. For instance, polydopamine (PDA) modified cellulose membranes were employed for extraction of nitrophenols from oil samples prior to detection by HPLC-UV [4]. This extractive phase was produced via in situ polymerization, whereby a piece of paper is fully immersed into a basic dopamine solution. Polydopamine layer not only provided good extraction for selected polar analytes, but also made the thin films amenable for oily samples. As a result, the final method provided limits of detection in low ppb levels for 4-nitrophenol and 2,4-dinitrophenol from common cooking oil. In another study, researchers used paper supported polystyrene thin film membranes for the extraction of methadone from urine samples [24]. In that study, polystyrene was chosen due to its ability to be easily dissolved in organic solvents, allowing it to be easily coated on a paper without the need for extra polymerization or cross linking. Polystyrene coated thin films were simply prepared by several sequential dipping cycles of a small piece of filter paper into the polymeric solution. The coating homogeneity was guaranteed by changing the dipping direction in each submersion. Importantly, the flexibility of the final material

enabled the thin films to be rolled and placed in a confined volume of pipette tips for extraction from small sample volumes (e.g. 200 μL). To obtain adequate interaction between the sample and TFME device, and to ensure fast extraction kinetics, the sample was circulated by 20 withdraw-release cycles. The use of pipette tip as a sample container not only allowed for easy control of the agitation by simply withdraw-release actions, but also facilitated the use of very small volume of eluent in the desorption. These two distinct advantages contributed to a superior analytical sensitivity in GC-MS. Furthermore, cellulose materials also represent an excellent base support for synthesis of various nanoparticles directly on their porous surfaces using in situ functionalization. For instance, zinc oxide nano-rods were synthesized on cellulose paper by soaking the paper in precursor solution under appropriate conditions [25]. This surface was further functionalized with phenyl carbamate and the final TFME device was successfully employed for extraction of linuron, monuron and neburonfrom water samples prior to their HPLC-DAD quantitation. Moreover, as it is described in Section 4, the paper-based substrates are commonly used for fast analyses in conjunction with a mass spectrometer. This format completely omits the chromatographic separation; therefore, highly selective sample preparations are imperative for these types of approaches. Finally, it must be pointed out that despite the practicality of novel reusable devices, in some research areas/industrial fields such as clinical and forensic sciences, the reusability of a particular device is limited due to strict requirements for disposable devices. In such cases, cellulose based TFME devices could be advantageous low-cost alternatives.

Despite all of the advantages described above, it is worth to mention that there are several drawbacks associated with the use of paper-based materials. Firstly, nanoparticles developed on paper usually are physically stabilized in the fibrous structure; therefore, leaching of the extractive phase from the substrate could be a potential issue [26]. Secondly, water can penetrate cellulose structure and destroy the network [4] which may decrease the lifetime of the material and its reusability as a TFME device. Finally, although the cellulose itself is cheap, the modification of its surface brings an extra cost and single use of such materials could make the analyses relatively costly compared to other reusable devices.

2.2.2 Selective extractive phases

Another rapidly growing area of developments with TFME is preparation of novel extractive phases with tuned properties towards specific analytes or group of analytes. In this context, ionic liquids offer endless structural possibilities that have recently become quite appealing as potential extractive phases. Such materials can be used to fine-tune the properties of TFME devices. In a recent study, the researchers modified standard filter paper with 1-dodecylimidazolium, making it

suitable for the determination of amphiphilic compounds like bisphenols [5]. Another approach for the preparation of selective coatings is the implementation of molecular diffusion restrictive frameworks. This approach was used in a recently published work, whereby the inner surface of a glass bottle was coated with a thin hybrid film consisting of a ZSM-5 zeolite loaded directly into PDMS [27]. For this extractive phase, ZSM-5 immobilization was necessary to introduce hydrophilicity to the TFME coating, primarily because PDMS itself is a highly hydrophobic polymer that restricts the absorption of hydrophilic compounds. In addition to this, ZSM-5 has strictly defined pores which are smaller than 2 nm, ensuring molecular weight-based selectivity via molecular sieving action, selective adsorption and difference in diffusion rates to the hybrid material. Using these TFME devices, highly aliphatic (C7-C11) volatile organic compounds (VOCs) showed exhaustive recoveries, while there was a sharp decrease in the recoveries of VOCs with number of carbon atoms smaller than six. Besides the examples given above, TFME devices coated with aptamers or MIPs can also be used to provide very selective extraction which is critical when (i) a non-selective detector is in use, (ii) chromatographic separation is omitted, or (iii) the analyte is affected from potential interfering species [19]. In this note, with a similar purpose, Zargar et al. immobilized methamphetamine aptamer on cellulose paper modified with carbon nanomaterial [19]. The modified TFME devices were successfully implemented for extraction, as well as the solid substrate support for paper spray ionization source for determination of methamphetamine in plasma and saliva samples.

2.2.3 Electrospinning as convenient and relatively novel coating approach

Electrospinning, which is based on drawing charged threads of polymeric solution with electric force to produce polymeric materials, is an excellent method for the preparation of extractive films with ultrafine nano-to-micro sized particles and nonwoven fibrous structures [28]. This method provides an innovative platform for the preparation of new TFME devices. The thin films produced by electrospinning approach have several advantages over the classical coating approaches, specifically in regard to high specific surface areas of coatings and glue free immobilization of the polymeric extractive phase, both of which ensure ultra-fast extraction kinetics. Likewise, fine tuning of the extraction phase properties by addition of various dopants is also possible. Using this approach, several recent studies have been conducted. For instance, metal-organic framework-199 (MOF-199) was used as a dopant in a polystyrene electrospun nanofiber for the determination of lung cancer biomarkers in urine samples [29]. In another work, polystyrene/grapheme electrospun nanofibrous TFME devices were prepared on a filter paper and additionally modified with polydopamine (PDA) [30].The polar layer of the PDA shielding layer not only provided more hydrophilicity, which enables

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maximum wettability, but also ensured that the TFME device was completely biocompatible. These thin films were effectively employed for the extraction of metabolic aldehydes from urine samples.

2.2.4 Biocompatible TFME devices

In recent years, the usage of biocompatible tools has gained great attraction in the bio-analytical field such as *in vivo* sampling and sample preparation of collected bio-specimens. For preparation of biocompatible TFME devices, polyacrylonitrile (PAN) is frequently used as a binding glue to immobilize the extractive phase on the supporting surface. In addition to its biocompatibility (i.e. ensuring the device is nontoxic), if PAN is used as an over-coating, it acts as a molecular cut off filter which further protects the extractive phase from macromolecular bio-fouling. Hydrophilic-lipophilic polymeric particles (HLB), C18, C18 with benzene sulphonic acid moieties (i.e. mixed-mode) and other extractive phases used with PAN-based TFME devices can be found in a recent review which extensively summarizes their applications in clinical, environmental and food analyses [13]. The recent, appealing applications and new developments regarding all TFME coatings developed in the last two years are summarized in Table 1.

It is important to note that the PDMS-based membranes reported in Section 2.1 have high thermal stability and are capable of resisting desorption temperatures typically used in GC (about 250 °C). This intrinsic property is what allows these types of devices to be reused many times. On the other hand, PAN-based devices are not sufficiently stable for direct desorption in GC; therefore, they cannot be reused, and even single use devices may result in a high background due to considerable decomposition products. For these reasons, they have not been reported yet for direct thermal desorption in GC. However, PAN-based devices can handle such temperatures without decomposition of the binder when they are used in combination with DART source where the extractive phase is subjected to high temperatures for shorter times.

Table 1. Recent developments in TFME extractive phases and their applications

Analyte	Sample matrix	Extractive phase	Coating method	Desorption method	Analytical instrument	LOD ng/mL	Note	Reference Pub.Year
Benzoic acid	Carbonated beverages	Silica gel thin film	Ready to use	No desorption	SERS	3600	Prior to detection 10 µL of Au NPs dropped onto TFME surface	[31] 2018
Triazines	Water	Magnetic polybutylene terephthalate	Electrospinning	Solvent	GC-FID and GC-MS	0.02–0.05	Particles can be collected by a magnet	[32] 2017
Sexual pheromones	Air	Various sol gel	Dip coating	Thermal	HS-GC-MS	0.8-1.6 µg	On-side sampling and in lab analyses are performed by an integrating unit	[21] 2017
Codeine and acetamiprid	Standard	Aptamer coated paper	Chemical modification by dipping	Solvent	IMS	3.7 and 1.8	Paper spray ionization	[20] 2017
Endocrine disruptors	Water	Diatomaceous earth	Adhesive tape	Solvent	LC-DAD	1-8	High throughput sampling in 96 blade format	[7] 2017
Volatiles	Grape	PDMS/DVB	Dip coating	Metastable He	DART-MS	0.0019-1100	Possible isobaric interferences	[33] 2017
Organophosphorous pesticides	Water	ZnO nanoparticles doped polyamide	Dip coating	Solvent	GC-FID	0.05 to 0.3	Solvent exchange-based coating on a filter paper	[34] 2018
Semi-volatile thiophenes	Seawater	MIP	Glass deposition	Thermal	GC-SCD	0.24–0.82	Photo-radical polymerisation of solution sandwiched between glass slides	[16] 2018
Various pesticides	Water	PDMS-DVB	Bar coating	Thermal	GC-MS	0.025-0.1	Coating developed on carbon mesh Direct TD to GC-MS via TDU	[6] 2017
Methadone	Urine	Polystyrene	Dip coating	Solvent	GC-MS	3	Polystyrene was obtained from yogurt container	[24] 2017
Nitrophenols	Cooking oil	Polydopamine	Dip coating	Solvent	LC-UV	1.54 and 2.16	In situ polymerization on support	[4] 2016
Selected phelyurea herbicides	Water	ZnOnanorodesmodified with phenyl carbamate	Dip coating	Solvent	LC-DAD	40-130	In situ formation of nanoparticles	[25] 2017
Bisphenol-A	Plant oil	1-dodecylimidazolium	Chemical modification by dipping	Solvent	LC-UV	2.7	Ionic liquid based extractive phase	[5] 2017
Methamphetamine	Plasma and saliva	Aptamer	Chemical modification by dipping	Solvent	GC-MS	0.6 saliva 0.45 plasma	Aptamer immobilized on carbon nanomaterial modified paper	[19] 2018
Various antidepressants	Urine	Single-wall carbon nanohornsuprastructures	Dip coating	Solvent	LC-MS/MS	0.01	Leaching from the TFME	[26] 2018
Nickel	Water	Phosphorus	Dip coating	No desorption	Colorimetry and reflection scanometry	18	Non destructive, further analysis can be performed on TFME device	[35] 2017
VOCs	Soft drink	ZSM-5 zeolite in PDMS	Direct deposition	Solvent	GC-MS	0.0034–0.049	1 g of ZSN-5 in PDMS was placed in a bottle	[27] 2017
Various aldehydes	Urine	MOF-199 in PS	Electrospinning	Solvent	LC	0.0034–0.049	-	[29] 2017
Various aldehydes	Urine	Polydopamine modified polystyrene/graphene	Electrospinning	Solvent	LC-UV	0.17-0.92	Coating developed on paper substrate	[30] 2016
Quetiapine and clozapine	Plasma and urine	Magnetic octadecylsilane	Spraying	Solvent	LC-UV	3-15	Easy collection due to use of superparamagnetic $SiO_2@Fe_3O_4$	[36] 2016
Biocides and UV filters	Water	C18 and HLB	Spraying	Solvent	LC-MS/MS	0.13-0.8 (retracted device) 1×10^{-5}-5×10^{-4} (open bed device	Used as active and passive sampler for TWA and spot analysis on site	[37] 2017

Ivermectin and iohexol		C18 and PS-DVB	Spraying	Solvent	LC-fluorescence LC-MS/MS	0.1 LC-fluoresc. 2 LC-MS/MS	In flow through cell	[17] 2017
Polycyclic aromatic compounds	Water	Cork	Adhesive tape	Solvent	LC-DAD	0.3-5.5	High throughput sampling in 96 blade format	[38] 2018
VOCs	Water	HLB/PDMS	Bar coating	Thermal	GC-MS	Not reported	Extractive phase deposited on carbon mesh	[23] 2018
Various pesticides	Water	PDMS/DVB	Bar coating	Thermal	Bench top and portable GC-MS	0.001-0.03	On-site sampling and analysis	[22]2018

3 Automation of TFME

For high throughput and routine analyses, automation of sampling, sample preparation and sample introduction of the extracted analytes into the analytical system is critical. Unlike the SPME fiber configuration, there is no commercial system available that automates the entire process of TFME and its integration to an analytical instrument [39]. In the case of GC based applications, to the best of our knowledge, there is no investigations reporting automated sample extractions using TFME. However, the automation of the desorption process as well as the injection to the instrument is well-known [6, 13]. As it has been mentioned earlier in Section 2.1, thermally stable TFME devices can be easily coupled to any of the following units: temperature programmable large volume thermal desorption unit, Curie point injector or head-space sampler unit. These automated units also automate the desorption step into the GC, either directly into the instrument or via a headspace sampler unit. The most common automated approach for TFME devices primarily revolves around implementing the thermal desorption of the analytes from the membrane using a thermal desorption unit (TDU). In brief, following the sampling step, the membrane is placed in a glass liner and positioned in the autosampler. Then, a robotic arm transfers this liner from the sample rack into the TDU where a sharp ramp of temperature is generated to facilitate complete thermal desorption of the analytes. The desorbed analytes are carried by the carrier gas of the GC to the head of the column, where the analytes are cryo-focused. Upon total desorption of the target analytes from the TFME membrane, the cryo-focusing temperature is suddenly ramped up and the volatilized analytes are injected in a concentrated plug into the GC system. A study recently published by Piri-Moghadam et al. reported the use of this approach for an inter-laboratory validation of a method based on PDMS/DVB and PDMS/DVB-carbon mesh supported membranes for pesticides determination in water [6]. In this study, the researchers described desorption and analyte introduction from the TFME device directly into the GC-MS, whereby a cooling injection system and a thermal desorption unit (both from GERSTEL, Mülheiman der Ruhr, GE) were employed. Also, for automated injection of membranes, a multipurpose system autosampler (MPS2, GERSTEL) was used. It is important to highlight that there are several companies in the market that have commercialized similar multipurpose sample preparation platforms for GC systems [40-42]. More importantly, these stations can be easily adapted for high-throughput TFME applications using thermal desorption methods. Automation technology for high-throughput analysis for LC or LC-MS applications is also available (Concept-96®, PAS® Technology, Magdala, Germany). This instrument consists of a robotic arm and different stations dedicated for conditioning, extraction, desorption and evaporation with processing capabilities of 96 TFME devices at a time. The design of the 96 TFME allows the total integration of the sampler with a wide variety of 96-well plates commercialized by various life science companies.

In recent years, several LC-MS applications have been developed in a variety of fields such as doping control [8, 9], therapeutic drug monitoring [10, 12], and food research [43]. In spite of the fact that the Concept-96 was primarily developed for LC-based applications, it was adapted by Tascon et al. [35] to perform high-throughput extractions of 96 coated blade spray devices at once. As gathered in Figure 2, this innovative approach for automated direct coupling to MS technology was used to obtain sub-ppb limits of quantification for a large number of prohibited substances in less than 55 seconds per sample. In this context, the automation was optimized for conditioning, extraction and rinsing steps leaving desorption and analysis stages manual (Figure 2). Besides this commercially available instrument, several works have demonstrated the feasibility of high-throughput TFME using semi-automatic in-house setups that can be used not only for routine analytical applications, but also for practical and rapid screening and evaluation of new coatings [7, 38]. Another high throughput sampling approach was proposed by Wohde et al. [17], using a flow-through cell model that allows for 12 simultaneous extraction and desorption experiments in a fully automated manner. This setup enables full control of the flow rate within each cell, making it ideal for surface water extraction simulation experiments. With the proposed device, the authors successfully studied the sorption kinetics and thermodynamics of ivermectin and iohexol in a C_{18}-phase and a PS-DVB-phase, respectively. The automated TFME technologies are important for quantitative purposes in routine laboratories and for research ends such as biomarker discovery, studies concerned about physicochemical properties of compounds, and extraction kinetics in different environments [17, 44, 45].
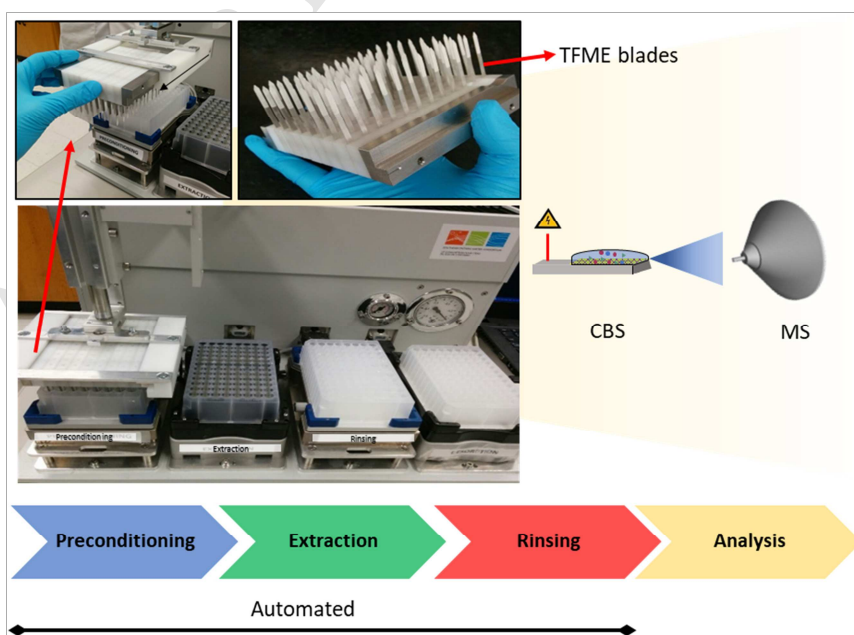

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Figure 2. Integration of high throughput automated sampling with direct coupling to MS technology

4 Direct coupling of TFME to different detection systems

Direct coupling of TFME devices to various detection systems relies on preforming the sample preparation step, followed by introduction of the extracted analytes into the instrument. This approach omits the time consuming chromatographic or capillary electrophoretic separation step, guaranteeing rapid, yet accurate analyses. Any direct coupling approach relies heavily on extremely selective detectors and/or in combination with sophisticated data analysis tools. The main benefits of this approach can be noted by a dramatic reduction in the time of analysis, an increase in sensitivity, a reduction in sample losses as well as elimination of degradation and carry over due to the simplification of the analytical workflow (Figure 3) [13, 46]. In recent years, there has been an explosion of new developments that employ TFME, primarily due to the outstanding advances achieved in ambient mass spectrometry [13, 47]. Since its inception and initial publication in 2012, where TFME was used for waste water sampling before being directly coupled to MS via desorption electrospray ionization (DESI)[48], many new direct coupling technologies have been developed. Among these technologies, coated blade spray (CBS) has grown the most over the last six years. Essentially, CBS is a metal sheet with a sharp tip that is coated with a thin film of an extractive phase (thickness ≈ 10 μm). This thin coating facilitates the extraction and enrichment of the analytes in the extractive phase in a single step. Following the consolidated extraction/enrichment step, the analytes are desorbed in a droplet of solvent and ionized via the application of a high voltage that induces a stable electrospray from the tip of the blade [46]. This simplified and extremely practical workflow makes the CBS technology extremely useful in rapid analysis and multi-residue screenings for a wide variety of analytical fields [49]. In the last two years the feasibility of using CBS for therapeutic drug monitoring of voriconazole from plasma and immunosuppressive drugs from whole blood was demonstrated [50, 51]. In both cases, great precision and accuracy as well as excellent sensitivity and speed of analysis (≤ 2-4 min) were achieved. In addition, the screening of a large number of substances prohibited by the world anti-doping agency (WADA) was also recently reported. The performance of the CBS device was tested both for regular biofluid volumes as small as 0.2-1.5 mL by fully immersing the coated portion of the device into the biofluid. It was also validated for relatively smaller volumes (*i.e.* 10-20 μL) by spotting the biofluid onto the surface of the blade [16, 17]. The results satisfied the stringent WADA requirements in terms of both precision and accuracy. Building off the resounding success of CBS, recent works in paper spray include the deposition of a thin film of an extractive material with the aim of performing a sample clean-up before ionization and introduction to the mass spectrometer. Some relevant examples have reported the implementation of deposited imprinted polymers, polystyrene microspheres and silver nanoparticles [18, 52, 53]. To

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this end, most of the applications of coated paper spray are focused on target clinical analyses and forensic science. Alternatively, Gómez-Ríos et al. have also developed new TFME meshes for direct analysis in real time (DART) ionization in transmission mode coupled to MS [3]. In this publication, high sensitivity and fast analysis for different environmental and food applications was demonstrated. Moreover, the design identified a particular suitability for these TFME devices for on-site analysis in conjunction with the use of portable mass spectrometers [54, 55]. Furthermore, Cai L. et al. [31]demonstrated the effective coupling of TFME to Raman spectroscopy for the fast monitoring of benzoic acid from carbonated beverages. The extractive phase used was typical silica gel but, after the extraction, gold nanoparticles were added onto the surface to promote surface-enhanced Raman spectroscopy (SERS) effect with quantitative results. In another study, Fedick et al. [18] combined Raman and mass spectrometry detection by means of paper spray approach after depositing silver nanoparticles onto the surface of the papers for SERS. Thus, both analyses are simultaneously used to quantitate and confirm the presence of certain analytes. Another interesting approach with paper-based materials is the modification of filter paper with phosphorus by dipping it in phosphoric acid. Those TFME devices were used for extraction of nickel from aqueous samples followed by direct analysis from the surface of the device using colorimetry and reflection scanometry with a scanner [35]. Although there are numerous well-developed nickel determination methods, this study is critical and can be taken as a "proof of the concept" study for rapid non-destructive determinations that can be conducted directly from the surface of TFME device using simple instrumental approaches.

Interestingly, laser desorption ionization (LDI) approaches were exclusively implemented for the direct coupling of SPME fibers to mass spectrometry [56, 57]. Considering the flat and smooth surfaces that are characteristic of TFME, its implementation can improve not only the reproducibility of the determinations but also the simplicity of laser focus in different areas of the coating.
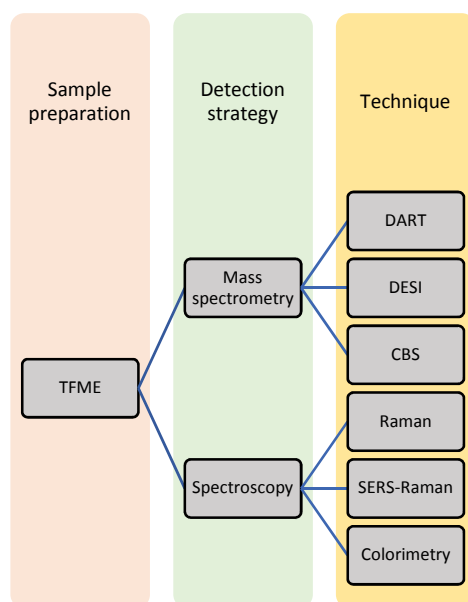
Figure 3. Scheme of the current approaches to direct coupling of TFME to different detection systems.

5 Future directions and concluding remarks

One of the main advantages of TFME over other SPME technologies lies in the fast mass transfer kinetics for both extraction and desorption processes. This key feature results in higher extraction rates for non-equilibrium conditions and shorter equilibration times. Another aspect to note is the high extraction capacity afforded by the TFME devices due to the higher extractive phase volume available. The combination of both features makes TFME the most suitable microextraction technology for applications where fast analyses with high sensitivity are required without significant sample volume restrictions.

Leveraging some of the fundamental aspects of TFME, such as fast mass transfer kinetics and high extraction capacity; the future work is directed towards fast analyses with high sensitivity requirements where sample volume is not the limiting factor. For such applications, the development of technologies for rapid and on-site analysis is strongly encouraged. In this matter, direct coupling of TFME to MS is the main focus due to its selectivity and sensitivity of cutting-edge MS instruments; however, other detection systems such as Raman spectroscopy, laser-induced breakdown spectroscopy (LIBS), X-ray fluorescence (XRF), among other spectroscopic methods, must be explored as well. In spite of the lack of selectivity in comparison to MS, these detectors can provide lower cost per analysis and robust portability. These features will be extremely useful not only in industry but also in clinical laboratories due to their low-cost nature and overall high speed. In order to achieve these goals, "*smart" sorbents* should be investigated further, providing new features such as high

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surface area and enhanced selectivity. Examples of these materials are immunosorbents, metal-organic frameworks, aptamers, nanostructured sorbents, molecularly imprinted polymers, ionic liquids, etc. It is important to note that these advances must work in conjunction with fully automated setups for these approaches in order for widespread adoption by the analytical community. Finally, aiming to solve the most complex applications in analytical chemistry, namely, *in vivo* sampling, single-cell analysis or reduced sample volume analysis, the miniaturization of the TFME devices must be a medium-term objective. Hence, technological advances that can scale down TFME dispositives and, most important, fundamental research that allow the understanding of the physical processes involved in those miniaturized systems are highly valuable for future work in the long term.

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Highlights

- Thin film microextraction provides enhanced sensitivity compared to classical microextraction technologies.

- The automation of thin film microextraction allows for high throughput sample preparation with excellent turnaround times.

- Pushed by state of the art extractive phases, TFME directly coupled to mass spectrometry provides a reliable platform for fast and sensitive analysis.