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Recent advances in aptamer-based miniaturized extraction approaches in food analysis

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ABSTRACT

Sample preparation is a relevant step in food analysis to achieve adequate extraction and preconcentration of target analytes before their introduction in the analytical system. Current trends in sample preparation involve moving towards miniaturized extraction devices combined with advanced affinity-based sorbents. Within affinity-based materials, aptamer-based ones have attracted much attention due to their excellent molecular recognition properties, high stability, and the possibility of immobilization onto the surface of different supporting materials, such as nanoparticles, monolithic stationary phases, etc. This review gives an overview of the literature published regarding aptamer-based sorbents and their potential application in the isolation and determination of several compounds such as persistent organic pollutants (POPs), antibiotics, toxins and bacteria in different food matrices. For this purpose, the most relevant improvements achieved in the last five years (from 2016 to 2020) in sample preparation by the integration of these new materials as sorbents in different miniaturized extraction techniques will be reviewed.

1. Introduction

Analytical Chemistry field has recently experimented new several advances by giving out innovative and pioneer micro-extraction techniques, which have been applied in different areas including food science. In particular, food control and safety analysis are critical fields, where the application of extraction techniques is mandatory to selectively determine hazardous compounds at very low concentrations in a great variety of complex food matrices. However, the isolation and determination of analytes of interest still remains a challenging task [1,2]. Consequently, food sample pretreatment should be focused in providing an appropriate analyte preconcentration jointly with interferences' removal prior to instrumental analysis [2].

Until now, solid-phase extraction (SPE) with conventional sorbents combined with mass spectrometry and/or chromatographic techniques, have been the most common methodologies adopted in food analysis area [2]. However, the conventional SPE sorbents can produce the coextraction of other compounds also present in the matrix sample, which difficults the final quantification of analyte/s of interest. Accordingly, there is a real need for one-step sample pretreatment protocols with enough selectivity to efficiently isolate the target analyte/s from other sample components, thus, even allowing the direct detection of the target. To solve this problem, affinity sorbents involving antibodies, molecularly imprinted polymers (MIPs) or aptamers, which promote a selective retention mechanism based on molecular recognition of a target analyte have been developed [3–5]. Antibodies-based sorbents makes use of the high affinity of antibody-antigen interaction towards de analyte of interest, which provides a strong retention of the analyte during sample percolation providing an efficient interferences' removal. However, antibody production is expensive, time-consuming and its synthesis requires the use of mammals. Moreover, antibodies-based sorbents can only be used with analytes that induced an immunogenic response; therefore, their field of application is limited. On the other hand, MIPs are polymeric networks created with specific recognition sites which are complementary in size, shape, and position of the functional groups present in the template analyte. Although their synthesis is easy and quick, a large quantity of the analyte of interest (or one of its

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Abbreviations

AF	aflatoxin
AFB1	aflatoxin B1
AFB2	aflatoxin B2
AFM1	aflatoxin M1
AMC	aptamers magnetic capture
AMPS	2-acrylamido-2-methyl propane sulfonic acid
Apt	aptamer
BDC	benzene-1,4-dicarboxylic acid
BPA	bisphenol A
BSA	bovine serum albumin
CAP	chloramphenicol
CFU	colony forming units
CNBr	cyanogen bromide
CTS	chitosan
DAD	diode array detection
DSPE	dispersive solid-phase extraction
EDC	N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride
EDMA	ethylene glycol dimethacrylate
ELISA	enzyme-linked immunoassay
ENR	enrofloxacin
FAM	carboxyfluorescein
FF	florphenicol
FGO	functionalized graphene oxide
FLD	fluorescence detection
FRET	fluorescence resonance energy transfer
GC	gas chromatography
GMA	glycidyl methacrylate
GO	graphene oxide
HEPES	N-(2-hydroxyethyl)piperazine-N′-(2-ethanesulfonic acid)
HPLC	high performance liquid-chromatography
IgY	immunoglobulin Y
KAN	kanamycin
LAMP	loop-mediated isothermal amplification
LDHM	layered double hydroxide magnetic
LLE	liquid-liquid extraction
LOD	limit of detection
MAA	methacrylic acid
MBA	N,N′-methylene-bis-acrylamide
MIP	molecularly imprinted polymer
MNP	magnetic nanoparticle
MOF	metal-organic framework
MPTMS	mercaptopropyltrimethoxysilane
MS	mass spectrometry
MS/MS	mass spectrometry in tandem mode
MSPE	magnetic solid-phase extraction
NC	nanoclusters
NHS	N-hydroxy-succinimide
NP	nanoparticle
OTA	ochratoxin
PBS	Phosphate buffer solution
PCB	polychlorinated biphenyl
PCD	photochemical derivatization
PCR	polymerase chain reaction
PDDA	diallyldimethylammoniumchloride
PEI	polyethyleneimine
PETMP	polythiolpentaerythritoltetrakis-(3-mercaptopropionate)
POP	persistent organic pollutant
POSS	polyhedral oligomeric silsesquioxane
POSS-MA	Polyhedral oligomeric silsesquioxane methacryl substituted
SBSE	stir bar sorptive extraction
SDM	sulfadimethoxine
SELEX	Systematic Evolution of Ligands by EXponential Enrichment
SLE	solid-liquid extraction
SPE	solid-phase extraction
TAP	thiamphenicol
TC	tetracycline
TCA	Trichloroacetic acid
TCT	2,4,6-trichloro-1,3,5-triazine
TMOS	tetratrimethoxysilane
TRIM	trihydroxymethylpropyl trimethylacrylate
UCNP	upconversion nanoparticle
UHPLC	ultra high performance liquid chromatography
UV−Vis	ultraviolet−visible
ZEN	zearalenone

analogue) is required, which could be a handicap when scarce or expensive analytes should be analyzed. Moreover, analyte removal from the MIP is sometimes time-consuming and tedious depending on the physicochemical properties of both analyte and monomers. To solve these problems, aptamers have emerged as a useful alternative to both antibody-based and MIPs sorbents. Aptamers are single-stranded nucleic acid molecules (DNA and RNA) forming well-defined 3D structures that can bind to specific targets (from single molecules to whole organisms) with high affinity and specificity [3,4,6]. Their main advantages included simple and fast synthesis with high purity, stable reproducibility, relatively low cost, wide target versatility, easily chemical modification, high stability and wide range of applicability, since aptamers can be synthetized for almost any compound [3,4,6]. Moreover, they are produced by an in vitro procedure that does not require the use of animals. Aptamers are selected from a random bank by an in vitro combinatorial selection process called Systematic Evolution of Ligands by EXponential enrichment (SELEX). This method allows the synthesis and screening of complex oligonucleotides for the selection and identification of candidates that exhibit the desired properties according to their ability to recognize a specific target analyte [1,3,4]. Additionally, their controlled synthesis jointly with the possibility of incorporating very different functional groups have made possible to develop different analytical aptamer-based methods [3] including enzyme-linked oligonucleotide assay (a variant of ELISA with aptamers instead of antibodies), biosensors (also called aptasensors), and separation methods, jointly with their use as SPE sorbents, with application in many different scientific fields such as biosensing [3,7], diagnostics [8], therapeutics [8], food safety [4], environmental monitoring [6], affinity chromatography [9] and sample treatment [10,11]. Indeed, excellent reviews (with different emphases) that describe and discuss a wide range of aptamer applications have been published in the last years [2–6,12,13]. Nevertheless, these articles have not specifically evaluated the integration of aptamers combined with other types of nanomaterials and other supporting materials as novel and promising affinity sorbents in microextraction procedures for the particular determination of different analytes in foodstuffs.

Therefore, the current review focuses on the most recent contributions in the development of aptamer-based miniaturized

extraction approaches and their use in food control and safety analysis published in the last 5 years. Firstly, different types of nanomaterials (like magnetic nanoparticles (MNPs), graphene oxide (GO), gold NPs and MOFs) that can be conjugated with aptamers will be described. Also, other supporting materials such as monolithic phases and commercial agarose beads will be mentioned. Then, several binding procedures carried out to immobilize aptamers onto the support surface and the preferred microextraction formats will be briefly described. Finally, the application of these affinity sorbents related to food science will be discussed. For this purpose, the most recent papers have been grouped according to the extracted analyte type: persistent organic pollutants (POPs), antibiotics, toxins and bacteria.

2. Sorbents based on aptamer-modified nanomaterials and other composites

2.1. Types of supporting materials for immobilization of aptamers

Nanomaterials of different types have recently gained increased attention for their application in concert with aptamer-receptors tethered to their surface [14]. Due to the features of these nanostructured materials (*viz.*, high surface-to-volume ratio, flexible interaction chemistries and easy functionalization, among others), their combination with the favourable recognition properties of aptamers can produce affinity sorbents with an enhanced aptamer-density able to increase interaction with the target analyte/s. In recent years, the most common employed nanostructures for aptamer immobilization oriented towards the extraction of several compounds from food samples include MNPs, GO, AuNPs and MOFs.

MNPs based on iron oxides (Fe_3O_4 and γ-Fe_2O_3) have been widely used for extraction purposes [15,16]. Thus, MNPs provide a high surface area-to-volume ratio and a short diffusion route leading to efficient extractions [1]. Concretely, MNPs can be dispersed in the sample and subsequently collected using an external magnet due to their superparamagnetic features [1]. Moreover, the surface of MNPs can be easily modified (using diverse functional groups) to increase their chemical stability and boost selectivity in the extraction [16]. Thus, the resulting aptamer-based affinity magnetic sorbents could lead to materials with enhanced biocompatibility and extremely selectivity for the extraction of a wide range of analytes [17–25].

On the other hand, GO has emerged as a new two-dimensional single-layer carbon material since it offers a large surface area, high flexibility, and good biocompatibility [21,26,27], which make it an excellent support for aptamer immobilization [21]. It offers rich functional groups for the formation of hydrogen bonding or electrostatic interaction with organic compounds containing oxygen- and nitrogen-functional groups [28]. However, the direct use of GO as sorbent into classical SPE cartridges presents several drawbacks such as: i) high pressure under SPE operation and leaking of GO sheets from the SPE cartridge; and ii) the strong interplanar interactions of GO may lead to aggregation phenomena, being the available surface area for retention dramatically reduced. To overcome these problems, the integration with other supporting materials (such as MNP_S) has been reported to fabricate composites for efficient extraction [21,27,28].

Due to their chemical stability, excellent conductivity, unique optical properties and good biocompatibility, AuNPs have received wide attention in many fields, including biosensing, separation techniques and sample treatment [29–31]. It is well-known that AuNPs have a strong affinity towards compounds containing thiol and amine moieties; consequently, these AuNPs constitute ideal substrates for the attachment of aptamers containing these groups [32].

Furthermore, MOFs are a class of highly ordered crystalline) porous materials, constructed from metal ions/clusters and organic ligands, with excellent properties to be used as support to immobilize aptamers [24,33,34]. MOF features that can be highlighted are their high surface area, good thermal stability, chemical resistance, and tunable chemistry, which allows the possibility to fabricate diverse structures that facilitates the introduction of desirable functionalities for concrete requests [33]. Also, their high specific surface area and porosity are convenient to accomplish a higher mass transfer in SPE procedures. As negative aspects, it should be remarked that sometimes an undesired incomplete or irreversible desorption occurred due to the strong retention between MOFs and analytes, which can lead to a poor reusability of the sorbent [35].

Apart from nanomaterials, other materials such as monoliths can be used as suitable substrates to prepare aptamer-based composites for sample treatment [36–41]. Among the countless advantages of monolithic phases, it should be highlighted their high mechanical stability, their easy and reproducible synthesis, as well as their large good permeability (fast mass transfer under dynamic conditions). Moreover, these materials offer particular benefits such as high diversity of surface chemistries, and the possibility of synthesis in a flexible way within the confines of any type of customized mold or support [11]. A large variety of monolithic phases is available for the preparation of different affinity supports, which has been previously reviewed [11]. In this sense, the most popular monolithic phases are silica-based [11,38,39], organic [11] and hybrid organic-silica monoliths [37,40,41]. These composite affinity-based sorbents have demonstrated to display high efficient target separation from sample, thus improving the selectivity and sensitivity of analytical procedures [2,11].

Finally, it has been also included in this section the use of commercially available substrates such as activated Sepharose beads (N-hydroxy-succinimide (NHS)- or cyanogen bromide (CNBr)-activated Sepharose, among others) to immobilize aptamers. The resulting oligosorbents are then placed in conventional SPE cartridges and used as aptamer affinity columns [42–44].

2.2. Immobilization strategies of aptamers in different supports

As mentioned above, the chemical synthesis of aptamers makes possible to introduce modifications at the 5′ or 3’ end of the oligonucleotide sequence to facilitate their posterior immobilization in a wide range of supports. This modification is selected according to the nature of the bonding between the aptamer and the chosen solid support. The most common modifications described in literature consist in the introduction of amino, thiol, biotin moieties and fluorescent labels. The amino modification has often been reported as an immobilization procedure similar to those applied for the random immobilization of antibodies with the benefit that the aptamer sequence is oriented directly toward the analyte [18,24,27,39,42–47]. For example, 5′–NH_2–aptamers have been immobilized onto glutaraldehyde activated supports such as silica- [5] or polymer-based monoliths [48,49]. Although this last immobilization procedure is cost-effective, it could be considered as a time-consuming methodology since exhibits poor efficiency due to limited coverage density of aptamer [24,38,39,50]. Despite the fact that the amino modification has been described as the most common immobilization approach, the aptamer sequence has been also functionalized with thiol moieties [37,38,41]. For example, using the “thiol-ene” click chemistry, thiol-modified aptamers (or 5′–SH–aptamers) have been grafted onto hybrid organic–silica monoliths (containing vinyl groups in their surface), in order to provide “one-pot” sorbents with a high hydrophilic interface and aptamer coverage density [37,41]. Also, as mentioned above, the thiol-modified aptamers can be effectively immobilized onto the

surface of AuNPs taking advantage of this robust and straightforward conjugation, resulting in materials with a high coverage density of aptamers [38,51]. The high affinity of avidin or streptavidin to biotin has been also employed to synthesize aptamer-based sorbents [42]. However, this noncovalent binding process shows some weaknesses in terms of reusability and sorbent lifetime, particularly when organic modifiers are used in the SPE procedures that affect the biotin-streptavidin affinity [3,38]. Moreover, aptamers can be labelled with fluorescent probes (such as carboxyfluorescein (FAM)) to prepare fluorescent aptamer-modified materials [26,37,40]. Additionally, apart from the introduction of the above mentioned moieties, it is possible to modify the aptamers with a spacer arm, which consists in an n-alkyl chain (C6 or C12) that can be introduced to keep the binding properties of the aptamer when it is bounded to a surface [3].

2.3. Extraction formats and modes of aptamer-based sorbents

Until now, aptamer-based sorbents have been prepared and used in different extraction formats and modes such as miniaturized SPE, dispersive SPE (DSPE), magnetic SPE (MSPE), solid-phase microextraction (SPME), and stir-bar sorptive extraction (SBSE), among others. A short discussion of the use of these techniques (including formats and configurations) to carry out microextraction procedures, which overcome the drawbacks of conventional techniques in the sample preparation field is herein described.

SPE in cartridge format has been commonly carried out using aptamer-functionalized Sepharose beads [42–44]. The main advantages of this format are its easy preparation, low-associated cost, short processing times, simplicity and ease of automation that have promoted its use in routine laboratories. To miniaturize these affinity SPE devices, fused-silica capillaries with different internal diameter (75 and 100 μm) have been used to prepare *in situ* monoliths modified with aptamers [37–41]. This approach significantly reduces the analysis cost due to the low price of the extraction material, the easy preparation of the monolith according to the demanding selectivity, and because it can be directly coupled on-line with chromatographic techniques, which facilitates the automation of the whole analytical process.

Also, the isolation of target analytes in food extracts by DSPE using aptamers-modified materials has been reported [36,45]. This approach avoids the difficulties associated to the preparation of the SPE device (including the blocking issues); however, it still shows tedious and time-consuming separation steps, and analytes can experience losses or desorption from the sorbent surface during washing and centrifugation steps. For these reasons, its magnetic-assisted version (MSPE) has been developed to overcome these limitations, being the mode most commonly described in literature for food samples [17–22,24,27,47].

On the other hand, the preparation of aptamer-based affinity sorbents in fibers or rods of different sizes (in SPME) and in stir bars (in SBSE) to develop extraction procedures with higher selectivity and enrichment capacity than the commercial devices have been barely described in food samples [33]. The few contributions in these microextraction techniques is probably related to the challenging preparation of robust coatings for the analysis of complex matrices.

3. Application of aptamer-based miniaturized extraction approaches in food samples

In this section, several applications of aptamer-based sorbents incorporated into the abovementioned supporting materials and formats with sample treatment purposes are discussed below. For this purpose, the most recent papers, published in the last five years, are summarized in Table 1, being classified according to the type of hazardous compound extracted from food samples: POPs, antibiotics, toxins and bacteria. Also, this table shows the substrate materials developed for the immobilization of the aptamers as well as the different microextraction formats used.

3.1. Aptamer-based sorbents for POPs' extraction

POPs are characterized by their high toxicity, long-term stability, poor degradation and bioaccumulation. They can bioaccumulate in fats, and their levels increase in the upper food chains. Polychlorinated biphenyls (PCBs) and bisphenyls, which are the most important POPs found in food samples, have been isolated from food samples using aptamer-based sorbents [17,33]. In an interesting work, Lin et al. [33] developed a SBSE procedure followed by gas chromatography-mass spectrometry (GC-MS) using an aptamer immobilized on $(Zn_4O(BDC)_3$ (known as MOF-5) surface for recognition of PCB72 and PCB106 from fish samples (Fig. 1) [33]. First, MOF-5 was attached to a stainless steel wire by electrodeposition and then the aptamer was assembled. As it can be observed, the aptamer immobilization onto the surface of the MOF was carried out in the presence of a cationic polymer (diallyldimethylammoniumchloride) (PDDA)) via electrodeposition to achieve a large surface area as well as high selective recognition of PCBs. The recoveries were higher than 89% and the obtained limits of detection (LODs) were very low (*ca.* 0.003 ng mL^{-1}). Furthermore, the enrichment factors were compared with available commercial fibers showing better performance (1.2–2 folds). This aptamer-based sorbent could be used until 15 cycles without significant losses of extraction recovery.

In another work, Xu et al. [17] developed an affinity sorbent consisting in a carboxyl-modified bisphenol A (BPA) aptamer attached to Fe_3O_4@SiO_2@MNPs, which was prepared using N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (EDC) and NHS as coupling reagents. Then, the MSPE pretreatment was conducted prior to high performance liquid-chromatography (HPLC) using fluorescence detection (FLD) for the enrichment of BPA from milk samples, achieving satisfactory recoveries (from 78.0 to 113.0%). Nevertheless, the main drawback of this method is that it is not possible to reuse the sorbent since the Apt/BPA composite is lost during the elution step.

3.2. Aptamer-based sorbents for antibiotics' extraction

Antibiotics have been widely used as anti-microbial medicine for veterinary and their residues are present in foodstuffs such as seafood, poultry, milk and honey, among others. They are considered a food contamination that can cause severe negative effects on humans' health such as drug resistance, anaphylactic reactions, liver damage, and gastrointestinal disturbances [18,19]. The most common techniques used for their identification and determination are GC and HPLC coupled to both UV–Vis or MS. However, the LODs of these compounds in cheap and less sophisticated detectors are usually very limited and the matrix interference in food samples is quite relevant [18].

In order to develop effective and convenient pretreatment methods of antibiotics, aptamers have been also used in the fabrication of affinity sorbents. They have been immobilized on MNPs [18,19,21,27], AuNPs [51], or on magnetic mesoporous carbon [52] to selectively isolate diverse antibiotics such as amphenicols [18,27,52], enrofloxacin (ENR) [36], kanamicyn (KAN) [51], tetracycline (TC) [19] and sulfadimethoxine (SDM) [21] from different food matrices (see Table 1). For instance, Huang et al. [18]

Table 1
Applications of aptamer-based miniaturized extraction techniques for isolation of different analytes from food samples.

Analyte (s)	Sample	Sorbent	Sample pretreatment	Extraction format	Technique	LOD (ng mL^{-1})	Recovery (%)	Ref.
POPs								
BPA	Milk	Apt@Fe_3O_4@SiO_2@ MNPs	Dilution with binding buffer (Tris−HCl, SDS, $MgCl_2$, KCl, NaCl)	MSPE	HPLC-FLD	0.05	78.0−113.0	[17]
PCB72 and PCB106	Fish	Apt@$Zn_4O(BDC)_3$, MOF-5	SLE (hexane); extraction with acidic silica gel cartridge. evaporation to dryness, dispersion in PBS	SBSE	GC-MS	0.003−0.004	89.2−97.1	[33]
Antibiotics								
CAP, FF and TAP	Milk	Apt@Fe_3O_4@SiO_2 MNPs	Dilution with mobile phase (MeOH/water)	MSPE	HPLC-DAD	0.12−0.17	78.6−95.9	[18]
ENR	Fish	Apt@UCNPs-MAA-TRIM	SLE (ACN in presence of HCl), washing with hexane, evaporation to dryness	DSPE	FLD	0.04	87.0−96.2	[36]
CAP	Honey and milk	Apt@Fe_3O_4-GO composites	LLE (ACN), washing with hexane and dilution with water	MSPE	HPLC-DAD	0.24	80.5−105.0	[27]
TC	Honey	Apt@Fe_3O_4 MNPs	Protein precipitation and extraction with ACN, evaporation to dryness and dilution with water	MSPE	HPLC-DAD	25000	82.9−107.3	[19]
SDM	Milk	Apt@Fe_3O_4-GO composites	Protein precipitation and extraction with TCA and $CHCl_3$, dilution with water	MSPE	HPLC-DAD	3.3	75.9−92.3	[21]
CAP	Milk powders, fish and chicken	Apt@Mg/Al-LDHM mesoporous carbon	SLE (ethyl acetate), evaporation to dryness, redissolution in MeOH/hexane (60:40 v/v)	MSPE	UHPLC−MS/MS	0.94 pmol L^{-1}	87.0−107	[52]
KAN	Milk and fish	Apt@AuNPs	SLE (ethyl acetate), evaporation to dryness, redissolution with ACN/water (10:90 v/v) containing ammonium acetate	SBSE	Microfluidic chip electrophoresis	0.003	94.0−106	[51]
Toxins								
AFB2	Peanut extracts	Apt@CNBr-activated Sepharose column	SLE (MeOH/water (70:30 v/v) in the presence of NaCl), evaporation to dryness, reconstitution and dilution with binding buffer	1-mL cartridges SPE	HPLC-FLD	0.025	80.9	[42]
AFB1	Lotus seed	Apt@NHS activated Sepharose column	SLE (MeOH/water (70:30 v/v) in presence of NaCl), centrifugation and filtration	1-mL cartridges SPE	HPLC-FLD	0.05	75.4−114.8	[43]
AFB1 and, AFB2	Wheat, maize, peanut and rice	Apt@NHS-activated Sepharose	SLE (MeOH/water (70:30 v/v) in the presence of NaCl), centrifugation and filtration	1-mL cartridges SPE	HPLC-PCD-FLD	0.05 (AFB1) 0.015 (AFB2)	76.1−111.5	[44]
AFB1	Wheat flour	Apt@polymeric dots and cDNA-AgNPs	SLE (MeOH/water (80:20 v/v) in the presence of ammonium acetate), re-extraction with $CHCl_3$, evaporation to dryness, redissolution in MeOH/water (10:90 v/v)	DSPE	FRET	0.003	97.0−105.0	[45]
AFB1 and AFB2	Maize	Apt@Fe_3O_4@SiO_2@Agarose microspheres	SLE (MeOH/water (70:30 v/v) in the presence of NaCl), evaporation to dryness, reconstitution in MeOH/water (70:30 v/v)	MSPE	HPLC-FLD	0.025 (AFB1) 0.01 (AFB2)	83.6−97.8	[20]
OTA	Corn and peanut	Apt@MMIL-101	SLE (ethyl acetate), evaporation to dryness, reconstitution in HEPES buffer	MSPE	UHPLC−MS/MS	0.000067	82.8−108.0	[34]
OTA	Cornmeal	Apt@Fe_3O_4@CTS NPs	SLE (MeOH/Tris (70:30 v/v) in the presence of NaCl)	MSPE	HPLC-FLD	–	91.3−99.1	[22]
OTA	Beer	Apt@POSS-MAA-EDMA monolith	Degassing, filtration and pH adjust	100 μm i.d. capillary SPE	HPLC-FLD	0.025	92.7−101.2	[37]
OTA	Beer and wine	Apt@TMOS-co-MPTMS@AuNPs	Degassing, filtration and pH adjust	75 μm i.d. capillary SPE	HPLC-FLD	0.025	88.2−94.3	[38]
OTA	Beer		Degassing, filtration and pH adjust		HPLC-FLD	0.025	94.9−99.8	[40]

(*continued on next page*)

Table 1 (*continued*)

Analyte (s)	Sample	Sorbent	Sample pretreatment	Extraction format	Technique	LOD (ng mL^{-1})	Recovery (%)	Ref.
		Apt@POSS-MA-co-MBA-co-AMPS monolith		100 μm i.d. capillary SPE				
OTA	Beer	Apt@TCT@POSS-PEI monolith	Degassing, filtration and pH adjust	100 μm i.d. capillary SPE	HPLC-FLD	0.01	94.1–94.6	[39]
ZEN	Rice	Apt@POSS-MA-co-PETMP-co-MBA monolith	SLE (ACN/water (90:10 v/v) in the presence of NaCl)	100 μm i.d. capillary SPE	HPLC-FLD	0.02	98.6–100.8	[41]
ZEN	Beer and wine	FAM-Apt@FGO	Degassing, filtration and pH adjust		FLD	0.5	87.0–96.0	[26]
AFM1	Milk	Apt@Fe_3O_4@ SiO_2 MNPs	Protein precipitation (hexane/MeOH/water containing NaCl)	SPE in glass vial	HPLC-FLD	0.0002	97.0–116.0	[23]
Bacteria								
Salmonella	Milk	Apt@Fe_3O_4@SiO_2@pGMA NPs and Apt@MCM-41	–	MSPE	FLD	1000 CFU mL^{-1}	76.0	[24]
Listeria monocytogenes	Pork	Apt@MNPs and IgY-BSA-AgNCs	SLE (PBS)	MSPE	UV–Vis	10 CFU mL^{-1}	97.4–101.3	[47]
Escherichia coli	Pork	Apt@MNPs-UCNPs	Dissolution and precipitation in alkaline peptone solution (in presence of NaCl)	MSPE	FLD	10 CFU mL^{-1}	97–107	[50]
Listeria monocytogenes	Pork, chicken and fish	Apt@MagneSphere® paramagnetic particles	SLE (PBS)	AMC	LAMP	5 CFU mL^{-1}	–	[25]

developed an aptamer functionalized sorbent to perform a MSPE procedure to selectively extract three amphenicols from milk samples followed by HPLC with diode array detection (DAD) (Fig. 2). For this purpose, Fe_3O_4@SiO_2 microspheres were converted to Fe_3O_4@SiO_2−COOH in order to effectively attach a specific amino-functionalized aptamer (which can recognize the three antibiotics) through adding the EDC/sulfo-NHS coupling reagent. The resulting affinity sorbent (Apt@Fe_3O_4@SiO_2) presented a high surface area and selective recognition towards the target analytes. With this procedure, acceptable LODs (0.12−0.17 ng mL^{-1}) and good extraction efficiency (>78.6%) were achieved. It should be noted that the developed sorbent was reused at least 60 cycles by keeping the recoveries over 80%.

In an another work, Zhang et al. [52] developed an aptamer-modified Mg/Al layered double hydroxide magnetic (LDHM) mesoporous carbon as a novel MSPE sorbent for chloramphenicol (CAP) enrichment from food samples prior to UPLC-MS/MS determination (Fig. 3). The preparation of this aptamer-based sorbent was briefly described as follows. After surface modification with SiO_2−NH_2 of Fe_3O_4 magnetic microspheres, the synthesized Mg/Al-LDH-Orange II microsphere carbon materials were deposited on the modified magnetic microspheres. The resulting magnetic mesoporous carbon materials was coated with streptavidin to posterior capture the biotinylated aptamer. The advantage of this Apt@Mg/Al-LDHM mesoporous carbon material is its acceptable surface area (75.9 m^2/g), good stability and superior adsorption capacity. The significant features of the method were: a wide linear range, low LODs (0.94 pmol L^{-1}), and high recoveries (87.0−107.0%), which makes it a good choice for enrichment of trace amounts of CAP in food samples.

3.3. Aptamer-based sorbents for toxins' extraction

Mycotoxins are toxic metabolites produced by several types of molds, chemically stable and able to survive during food processing being therefore able to grow on a great number of foodstuffs, which can cause certain human diseases. For this reason, the monitoring these analytes in food samples in order to prevent its ingestion is a relevant issue. The most common mycotoxins include aflatoxins (AFs) such as B1, B2, G1, G2 and M1, ochratoxins (A, B and C), patulin and fusarium toxins (like zearalenone (ZEN)) [2]. Several microextraction techniques followed by HPLC-FLD or MS detection have been described for the determination of these compounds [2], although these techniques are not always selective and cost effective enough for their direct analysis in complex food matrices.

Several mycotoxins (AFB1, AFB2, ZEN, ochratoxin A (OTA) and AFM1) have been isolated using aptamers immobilized on different materials such as Sepharose [42,44], monoliths [37,39−41], AgNPs [45], AuNPs [38], MNPs [22,23], and MOFs [34]. Indeed, different extraction formats such as SPE in cartridge [42−44], capillary SPE [37−41], DSPE [45] and MSPE [20,22,34], have been recently reported. For example, an aptamer-based polyhedral oligomeric silsesquioxane (POSS)-containing hybrid affinity monolith able to recognize OTA in beer samples was developed in a 100 μm i.d. fused silica capillary for on-line coupling to HPLC-FLD system [37]. The synthesis of the hybrid affinity monolith and the extraction protocol are depicted schematically in Fig. 4. By using a homogeneous polymerization mixture composed of POSS chemicals, acrylate-based monomers, aptamer (5′−SH−C6-aptamer) aqueous solution and a proper ternary porogenic solvent, a hybrid affinity monolith was directly prepared via a "one-pot" process, in which free radical polymerization and "thiol-ene" click reaction were simultaneously used. It should be highlighted that the hybrid affinity monolith showed a

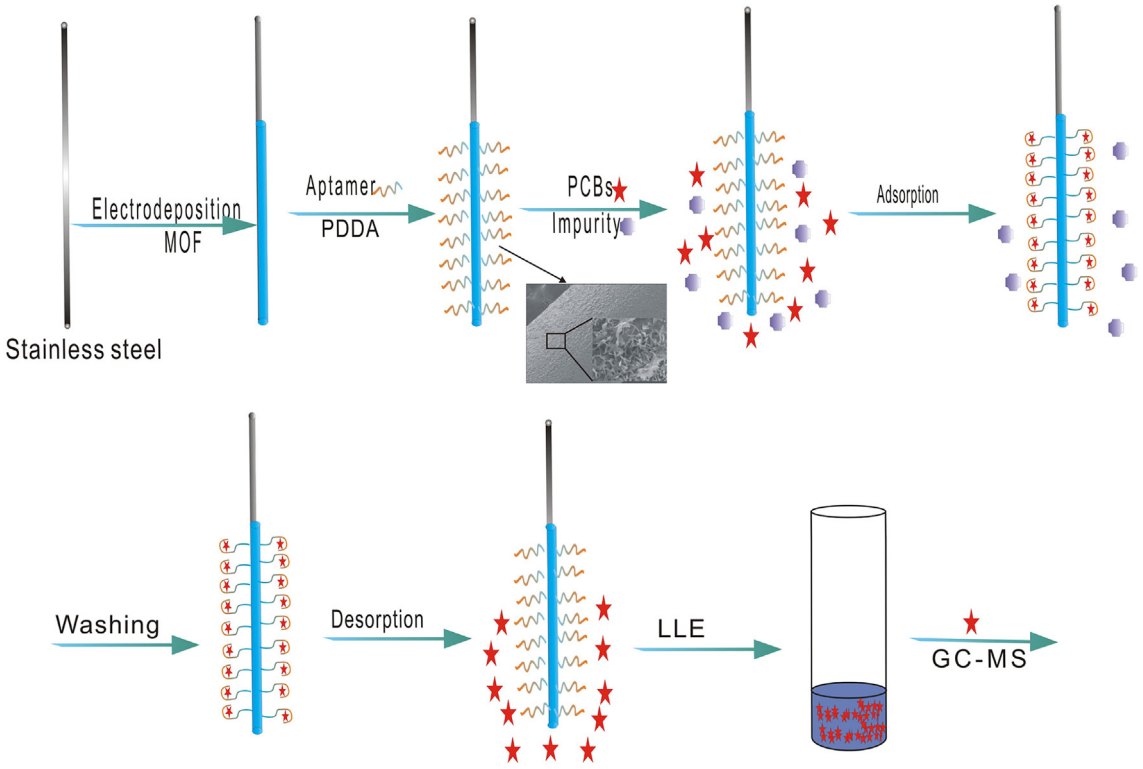

Fig. 1. Schematic overview of the preparation and application of Apt@$Zn_4O(BDC)_3$ (MOF-5) in an stainless steel wire for SBSE of PCB72 and PCB106 from fish samples (reproduced with permission from Ref. [33]).

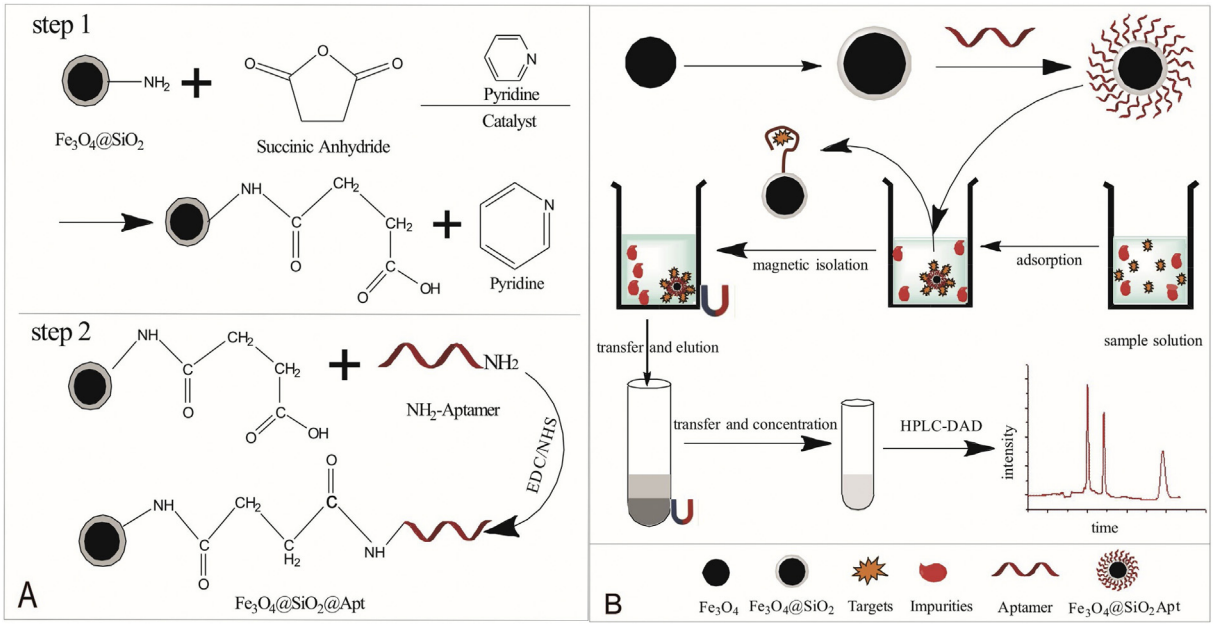

Fig. 2. (A) Scheme of synthesis of Fe_3O_4@SiO_2–COOH and Apt@Fe_3O_4@SiO_2. (B) Scheme of the MSPE process developed to extract amphenicols antibiotics (reproduced with permission from Ref. [18]).

good mechanical stability and repeatability, since it could be continuously used up to 42 h without apparent loss of performance. In addition, the developed method showed acceptable selectivity and LODs (0.025 ng mL^{-1}), as well as high recoveries (>92.7%).

3.4. Aptamer-based sorbents for bacteria extraction

Bacteria are responsible of infectious diseases and human death in severe cases even at low concentrations [50]. As a consequence, many methods have been developed to identify

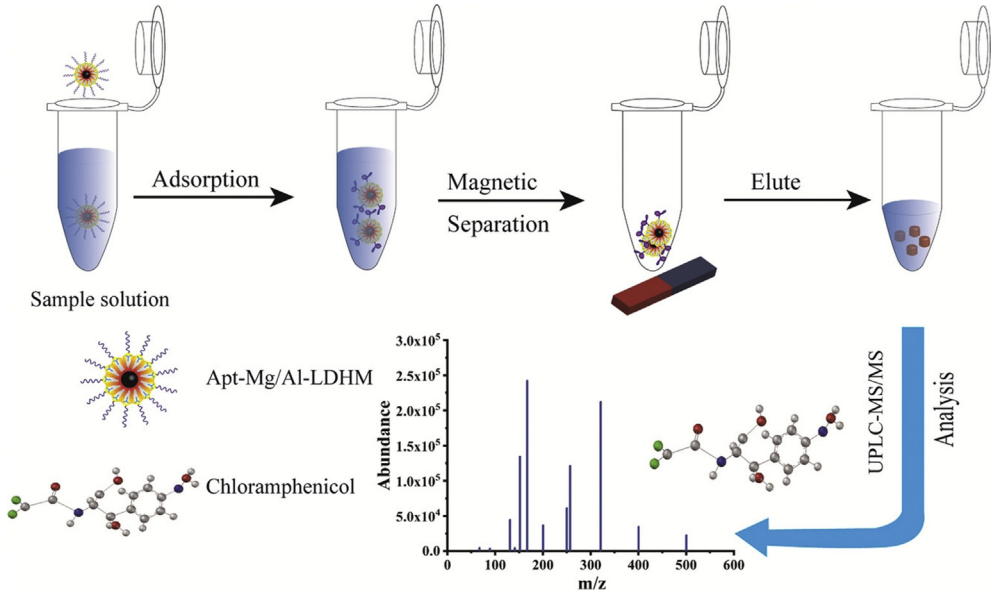

Fig. 3. Schematic procedure for the enrichment of CAP from milk powders, fish and chicken samples using MSPE (reproduced with permission from Ref. [52]).

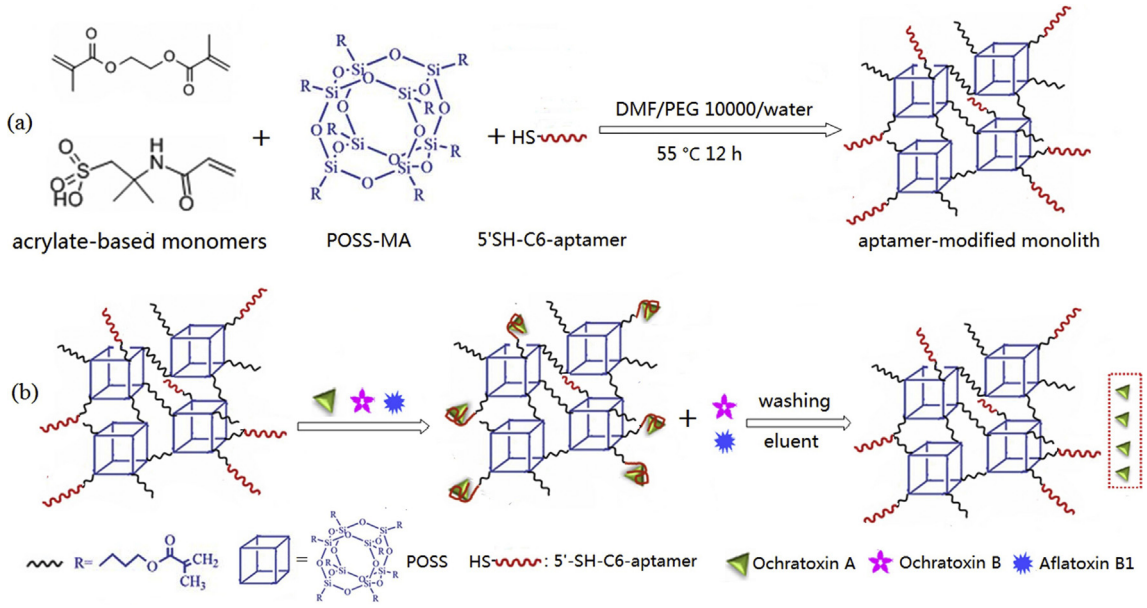

Fig. 4. (A) "One-pot" polymerization of aptamer-based POSS-containing hybrid affinity monolith. (B) Scheme of the affinity recognition of OTA (reproduced with permission from Ref. [37]).

these bacteria, such as conventional bacterial culture, immunofluorescence, and polymerase chain reactions (PCRs). However, these techniques are often time-consuming, and do not always provide a quantitative response. To solve these problems, aptamer-based affinity magnetic sorbents have been proposed to isolate bacteria from food matrices such as milk [24], meat [25,47,50] and fish [25]. Particularly remarkable is the article published by Bayramoglu et al. [24], who had developed a simple two-step procedure to directly detect *Salmonella* in milk samples (Fig. 5). Concretely, in the first step, magnetic silica NPs grafted with glycidyl methacrylate (GMA) (Fe_3O_4@SiO_2@pGMA) were functionalized with *Salmonella* specific aptamers to capture *Salmonella* cells from milk samples. These NPs are composed by a flexible polymer that provides high density of aptamer immobilization and fast specific mass transfer efficiency. Next, in the second step, the captured cells were eluted and mixed with aptamer-gated MCM-41 silica NPs loaded with fluorescein. This fluorescent molecule was released in the presence of *Salmonella* cells, thus providing their specific and sensitive detection. The developed protocol was able to extract

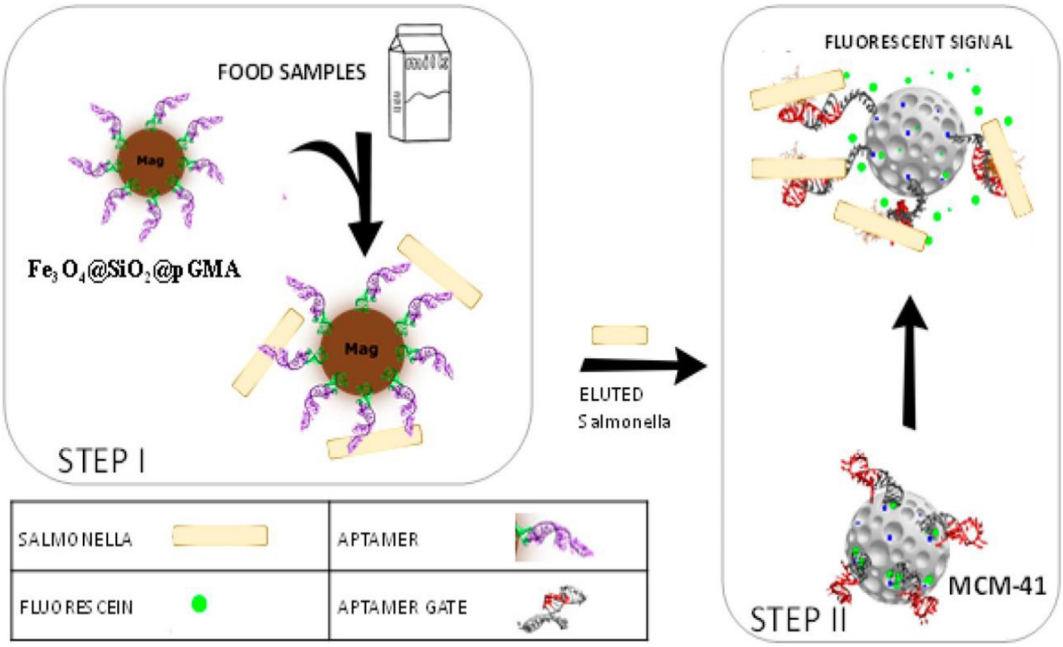

Fig. 5. Scheme of the two-step protocol develop to determine *Salmonella* in milk samples (reproduced from Ref. [24]).

Salmonella cells from milk samples with high selectivity, satisfactory LODs and recovery values (1000 CFU mL^{-1} and 76.0%, respectively). Moreover, this protocol does not require any sophisticated instrument and the analysis time is less than 30 min, thus allowing the possibility to monitor *Salmonella* contaminations directly into milk samples.

4. Conclusions and perspectives

Along this review, it has been showed that the integration of affinity-based materials using aptamers as sorbents in microextraction techniques constitutes a powerful tool to develop efficient, selective and sustainable food sample preparation procedures. The key of their success lies in their advantages such as high affinity and specificity and easy modification as well as their ability to be immobilized on different supporting materials in a wide variety of formats (cartridges, capillaries, fibers, etc). In the future, it is expected that the identification of novel aptamer sequences of enough affinity for relevant analytes continues to allow the development of affinity-based sorbents with high retention ability and selectivity. Also, the possibility to prepare versatile aptamer-based materials to perform efficient and selective multicomponent extraction would be highly desirable. Moreover, efforts must be made in the future to improve the sorbent-based microextraction part including novel immobilization approaches or innovative supports based on 3D printing technology. All these considerations can be a valuable resource to develop sensitive and sustainable analytical strategies able to improve not only quality control and food safety area but also other fields such as biological, clinical and environmental analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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