Recent advances in applications of nanomaterials for sample preparation

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ABSTRACT

Sample preparation is a key step for qualitative and quantitative analysis of trace analytes in complicated matrix. Along with the rapid development of nanotechnology in material science, numerous nanomaterials have been developed with particularly useful applications in analytical chemistry. Benefitting from their high specific areas, increased surface activities, and unprecedented physical/chemical properties, the potentials of nanomaterials for rapid and efficient sample preparation have been exploited extensively. In this review, recent progress of novel nanomaterials applied in sample preparation has been summarized and discussed. Both nanoparticles and nanoporous materials are evaluated for their unusual performance in sample preparation. Various compositions and functionalizations extended the applications of nanomaterials in sample preparations, and distinct size and shape selectivity was generated from the diversified pore structures of nanoporous materials. Such great variety make nanomaterials a kind of versatile tools in sample preparation for almost all categories of analytes.

Contents

1. Introduction

Sample preparation plays a vital role in both qualitative and quantitative analysis of various analytes. During sample preparation, (1) target molecules in low abundance are preconcentrated to increase their amounts/concentrations for subsequent analysis, (2) interfering substances from sample matrix are excluded or eliminated in case of disturbing analysis of target species, and (3) target molecules that are hardly subjected to direct instrument analysis are transformed to forms that can provide more satisfactory analytical results. All these performances help enhancing both accuracy and sensitivity for the analysis of target analytes. Along with the demand of new energy resources and materials, novel nanomaterials have become the star materials in recent

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years and various kinds of nanomaterials have been reported, which provides a large field and potentials for sample preparation.

Nanomaterials refer to a special kind of materials with nanometric scales in at least one dimension of their particles or pore structures, typically in the range of 1–100 nm. Compared with conventional materials with micrometric or larger sizes, such limited scales endow nanomaterials with some exceptional and unprecedented properties in many aspects. Among them, the ultrahigh specific areas [1] and increasing surface activities [2] facilitate the application of nanomaterials in sample preparation. In addition, tunable compositions, various morphologies and flexible functionalization offer a great number of opportunities in the development of novel nanomaterials for more efficient and versatile sample preparation.

Applications of nanomaterials in sample preparation can be classified from several aspects, such as chemical compositions of nanomaterials, molecular species of target analytes, and the specific separation modes or formats. In this review, recent progresses of different types of novel nanomaterials and their applications in sample preparation are summarized and evaluated. Nanoparticles and nanoporous materials are discussed separately, considering their different origins of nanometric scales. In the section of nanoparticles, nanoparticles with different chemical compositions and their respective applications are emphasized; while in the section of nanoporous materials, we focus on the porous structures with distinct properties (Fig. 1).

2. Sample preparation based on nanoparticles

In this section, nanoparticles with various chemical compositions, including carbon nanoparticles, metal/metal oxide nanoparticles, silicon/silica nanoparticles and polymer nanoparticles, and their respective applications in sample preparation are discussed. Those composites hybridized by different nanoparticles are classified based on the components that provided direct interactions towards target molecules.

2.1. Carbon nanoparticles

Carbon nanoparticles (CNPs) with various allotropes, such as fullerene, carbon nanotube, graphene, and carbon nanohorn, have become an important category of nanomaterials applied in sample preparation (Fig. 2). The earliest discovery of CNPs could be traced back to 1985 when C_{60} was firstly prepared by Smalley et al. [3]. And to the best of our knowledge, the preconcentration of lead traces on fullerene mini column reported by Valcarcel et al. [4] in 1994 was the first application of CNPs in sample preparation.
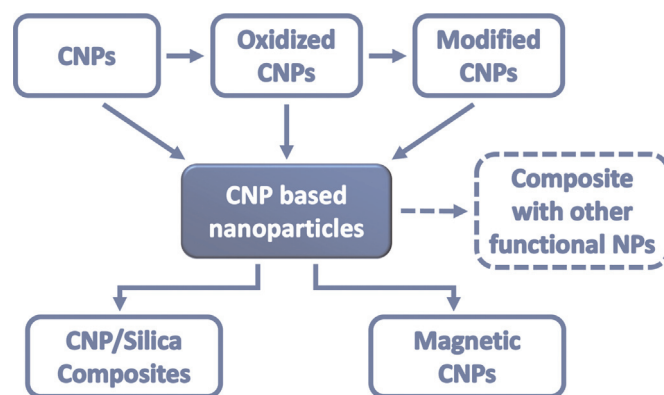

Fig. 2. CNP based nanoparticles in sample preparation.

Despite the earliest discovery and application of fullerene for sample preparation, carbon nanotubes (CNTs) and graphene (G) have become the most popular two kinds of CNPs used for sample preparation in recent years because of their easy preparation, functionalization and operation.

Most pristine carbon nanomaterials have significant similarities in structures and properties because of the existence of continuous six-membered rings and delocalized π-electrons. Such structural characters endow these carbon nanomaterials with strong affinity towards target molecules through hydrophobic interaction and π–π stacking. For many kinds of organic pollutants and additives, such as polycyclic aromatic hydrocarbons (PAHs) [5], organophosphorus pesticides (OPPs) [6,7], and phthalic acid esters (PAEs) [8,9], their aromatic residues and hydrophobicity facilitate their adsorption on carbon nanomaterials. So both pristine graphene and CNTs have been widely used for extraction of organic pollutants or additives with enhancement of sensitivity of subsequent analysis. For large biomolecules such as nucleic acids [10] and hydrophobic proteins/peptides [11], their extraction and enrichment on pristine CNPs have also been realized. Because of the ability to absorb and transfer laser energy by conjugated surfaces of CNPs, large biomolecules extracted by CNPs through weak π–π stacking interaction could be directly desorbed and analyzed by laser desorption ionization (LDI) mass spectrometry [10]. The simple and less selective adsorption mechanisms, however, limit direct use of pristine CNPs for sample preparation to a great extent. In addition, because of their hydrophobicity, spontaneous aggregation of pristine CNPs in aqueous solution is inevitable, which may complicate the experimental procedure [12].

In order to improve the availability of CNP and make them a versatile tool in sample preparation, various modification and functionalization have been employed. Oxidation of CNPs, which is
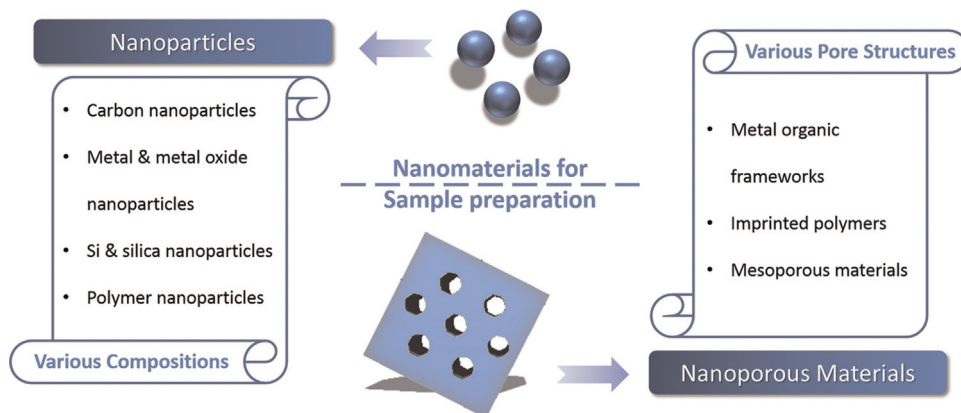

Fig. 1. Nanomaterials used for sample preparation.

the easiest way to equip CNPs with hydrophilic groups such as carboxyl groups, hydroxyl groups and epoxy groups, improves dispersity of CNPs in aqueous solution and brings new types of adsorption mechanisms such as ion exchange, hydrogen bonds, and electrostatic interaction. Such distinct adsorption mechanisms have been adopted for extraction of metal ions such as Pb^{2+}, Cd^{2+}, Sb^{3+}, Bi^{3+} [13–15] and some hydrophilic target molecules [16,17]. Although oxidation is not an effective way to provide sufficient specificity towards certain analytes, it does open a way to functionalization of CNPs with more selective and specific functional groups through further modification of the active oxygen-containing groups on oxidized CNPs.

Modification of CNPs with specific groups or functional agents has been adopted for sample preparation in the analysis of various categories of analytes. For metal ion analysis, multiple chelating reagents or thiolation reagents such as bis(5-bromosalicylidene)-1,3-propandiamine [18], diphenylcarbazide [19], dimethyl acetylenedicarboxylate [20] and (3-mercaptopropyl) silanetriolate [21] were coupled to the surfaces of CNPs to extract metal ions with improved selectivity. In addition, to eliminate interferences originated from sample matrix in metal ion analysis, CNPs could also be modified with matrix-excluded coatings such as restricted access carbon nanotubes (RACNTs) [22]. The external layer of BSA modified on CNTs could exclude proteins through electrostatic repulsion when sample pH was higher than the pI of both BSA and serum proteins, while setting no restriction on the access of positively charged cadmium ions, with which the interference of serum proteins in cadmium analysis was eliminated. With the aid of protein elimination by RACNTs, a lower limit of detection (LOD) of 0.24 $\mu g\,L^{-1}$ for cadmium in blood was obtained compared with the results from other pretreatment methods, such as cloud point extraction (2.0 $\mu g\,L^{-1}$) [23] and acid extraction (14.0 $\mu g\,L^{-1}$) [24]. In the analysis of organic pollutants in real samples, functionalized CNPs could be utilized to realize either target extraction [25] or matrix clean-up [26]. Relying on the strong hydrogen bonds formed between methylamino and carboxylic acid groups, Ma et al. [26] prepared methylamino modified graphene as clean-up adsorbent in the reversed-dispersive solid phase extraction (r-DSPE) to eliminate fatty acid interference for the analysis of pesticide residues in oil crops. In the proteome analysis, interactions between functional groups on CNPs and certain residues on proteins/peptides facilitated the enrichment of proteins/peptides with specific post-translation modification (PTM). By virtue of special affinity between guanidyl groups and phosphate groups, our group developed guanidyl functionalized graphene for selective enrichment of global phosphopeptides and multiphosphopeptides with consecutive phosphorylated residues [27]. Ju et al. [28] modified CNTs with aminophenylboronic acid (APBA) for glycopeptide enrichment via the reversible covalent bonding between glycans and boronic acids. In addition to specific enrichment, immobilization of protease on CNPs has also been developed for fast protein digestion in proteome analysis [29].

Direct use of pristine or chemically modified CNPs, however, often becomes troublesome because of some intrinsic properties of CNPs. When CNPs are packed in columns or catridges, their flexibility in the particle shapes and liability to entanglement may cause undue backpressure and reduction of both effective surface area and adsorption efficiency. On the other hand, in dispersive format, low density, smaller particle sizes, and excellent dispersity after chemical modification make the separation of CNPs from aqueous solution problematic and incompletable. To deal with that, combination of CNPs with other kinds of materials has been adopted to solve these problems and improve the performance of CNPs for sample preparation. For the packed-column method, CNPs could be covalently modified on silica supports to fix their positions in packed column [30]. To facilitate their separation in dispersive format, CNPs were combined with magnetic nanoparticles (MNPs) through different approaches, including spontaneous aggregation between CNPs and MNPs [31], in-situ or indirect growth of MNPs on the surface of CNPs [32,33], and grafting or wrapping CNPs to the surface of MNPs [34]. Zou et al. [35] prepared magnetic oxidized carbon nanotubes oMWCNT@Fe$_3$O$_4$ for extraction of nucleic acid associated proteins (NAaPs) from cell lysates via the affinity between oMWCNT and nucleic acids, and NAaPs adsorbed could be easily separated by an external magnetic field. Compared with a previous method based on chemical cross-linking of DNA-protein and subsequent co-precipitation by organic solvents [36], more NAaPs could be identified with more than 2-fold increase in this work. Because of good biocompatibility and easy ingestion by cells, such oMWCNT@Fe$_3$O$_4$ was further developed as an intracellular probe for NAaP extraction. A larger number of NAaPs were identified compared with that in the in vitro method [37]. Despite the convenience from introduction of magnetism, there may also be some undesirable problems such as dissolution of magnetic particles or non-specific adsorption on the exposed surface of magnetic particles, and more careful optimizations of experimental conditions or protecting shields insulating the MNPs are often required as a result.

Recent applications of CNPs in sample preparation have been summarized in Table 1.

2.2. Metal and metal oxide nanoparticles

Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) are two main metal nanomaterials for bioseparation and bioanalysis due to their excellent physical and chemical properties, providing tunable surface for recognizing target molecules. The interaction between biomolecules containing sulfur groups and AuNPs plays a significant role in biomolecule recognition via Au–S bonds. Generally, this method is limited particularly to compounds with sulfur groups. However, surface functionalization based on Au-S bonds provides a more widely used platform for specific and versatile bioanalysis. Au/γ–Fe$_2$O$_3$ nanoparticles synthesized with gamma-rays or ultrasonics were functionalized with thiol-modified oligonucleotides [38]. Then the target oligonucleotides could be hybridized to the complementary probes connected onto the Au/γ–Fe$_2$O$_3$ composite nanoparticles and magnetically separated without non-specific adsorption. A simple and sensitive method was established by Pourghazi et al. for extraction, preconcentration and determination of progesterone and testosterone from biological fluids (human plasma and urine) using AuNPs grafted thiol modified magnetic nanoparticles [39]. A wide dynamic range of 0.1–200 $ng\,mL^{-1}$ was obtained with 3 orders of magnitude more than the results from some other pretreatment methods such as liquid–liquid extraction (LLE) [40], reversed-phase solid phase extraction (RP-SPE) [41] and reversed-phase solid phase disk extraction (RP-SPDE) [42]. The LODs for progesterone and testosterone were 0.05 and 0.07 $ng\,mL^{-1}$, which were lower than or comparable with the results from methods mentioned above with the same (HPLC–UV) [40] or more sensitive (LC–MS/MS) [41,42] detection techniques. Citrate-modified AuNPs were capable of binding DNA bases [43,44]. Through various surface science tools, it was found that thiolated DNA could interact with gold not only via the thiol groups but also through the DNA bases [43]. Subsequently, rationally designed nucleobases and nucleotides coordinated AuNPs were formed for selective DNA adsorption [45]. Comparing with traditional methods for DNA adsorption employing electrostatic attraction, hydrophobic interaction, or π−π stacking, the bases in the coordinated materials formed base pairs with the DNA to achieve sequence specificity.

In addition to the above mentioned applications, the applied enrichment and detection based on AuNPs could be extended to

Table 1
Recent applications of carbon nanoparticles in sample preparation.

Carbon material	Modification	Operation mode	Analyte	Matrix	Detection technique	Ref.
Graphene	–	SPDE	PAHs	Environmental water	GC–MS	[5]
MWCNT	–	dSPE	OPPs	Cereal-based food	GC–NPD	[6]
MWCNT	–	dSPE	OPPs	Environmental water tap water/drink sample environmental water water plasma	GC–NPD	[7]
Graphene	–	SPE cartridge	PAEs	Tap water/drink sample	HPLC–UV	[8]
Graphene	–	dSPE	PAEs	Environmental water	GC–MS	[9]
Graphene	–	dSPE	ssDNA	Water	SELDI–ToF–MS	[10]
MWCNT	–	dSPE	Peptides	Plasma	2D-nano-LC–MS/MS	[11]
MWCNT	–	dSPE	Triazine herbicides	Environmental water	UPLC–UV	[12]
oMWCNT	Oxidation	On-line SPE	Cd^{2+}	Serum proteins	ETAAS	[13]
oMWCNT	Oxidation	dSPE	Cd^{2+}, Pb^{2+}	Environmental water	TXRF	[14]
GO	Oxidation	dSPE	Cd^{2+}, Pb^{2+}	Water	ICP-OES, AFS	[15]
oMWCNT	Oxidation	dSPE	Quinolone antibiotics	Water	CE–DAD	[16]
GO	Oxidation	SPE cartridge	Chlorophenoxy acid herbicides	Environmental water	CE–UV	[17]
MWCNT	bis(5-Bromosalicylidene)-1,3-propandiamine	SPE column	Pb^{2+}	Vegetables	FAAS	[18]
MWCNT	Diphenylcarbazide	SPE column	Cd^{2+}	Water, food	FAAS	[19]
MWCNT	3-Mercaptopropyl silanetriolate	SPE cartridge	Cu^{2+}, Ag^+, Cd^{2+}, Pb^{2+}, Zn^{2+}, Mn^{2+}	Rosemary, spinach, thymus	FAAS	[21]
MWCNT	BSA	On-line SPE	Cd^{2+}	Human serum	FAAS	[22]
Graphene	Acrylamide	On-line SPE	Heterocyclic amine	Food	HPLC–UV	[25]
Graphene	Amine	r-DSPE for fatty acid clean-up	Pesticides	Oil crops	LC–MS/MS	[26]
Graphene	Guanidyl	dSPE	Phosphopeptides	Milk digest	MALDI–ToF–MS	[27]
CNT	Boronic acid/ MNP	Magnetic SPE	Glycopeptides	Water	MALDI–ToF–MS	[28]
GO	Trypsin	In situ digestion	Proteins	Human lens Tissue	MALDI–IMS	[29]
Graphene	Supported on silica	SPE cartridge	Chlorophenol	Water	HPLC–UV	[30]
GO	Supported on silica	SPE cartridge	OH-PBDE	Hexane	HPLC–MS/MS	[30]
CNT	MNP/ amino or carboxyl	Magnetic SPE	Estrogens	Milk	HPLC–UV	[31]
MWCNT	Fabricated with MNPs	Magnetic SPE	PAEs	Urine	GC–MS	[32]
Graphene	$Fe_3O_4@SiO_2$	Magnetic SPE	Proteins/peptides	Water	MALDI–ToF–MS	[34]
oMWCNT	Fabricated with MNPs	Magnetic SPE	NAaP	Cell lysates	LC–MS/MS	[35]
oMWCNT	Fabricated with MNPs	Magnetic SPE	NAaP	Living cells	LC–MS/MS	[37]

SPDE is the solid phase disk extraction; *dSPE* dispersive solid phase extraction; *SELDI* surface enhanced laser desorption ionization; *ETAAS* electrothermal atomization atomic absorption spectrometry; *TFXS* total-reflection X-ray fluorescence spectrometry; *ICP-OES* inductively coupled plasma optical emission spectrometer; *AFS* atomic fluorescence spectrometer; *IMS* imaging mass spectrometry; and *OH-PBDE* hydroxylated polybrominated diphenyl ethers.

detection of protein biomarkers, lipids and chiral molecules. AuNPs modified with thermally responsive polymers (*e.g.*, poly(*N*-isopropylacrylamide), pNIPAm) could be used as separation/enrichment media [46]. A linear diblock copolymer with a thermally responsive pNIPAm segment and a gold-binding block composed of NIPAm-co-*N*,*N*-dimethylaminoethylacrylamide was used to functionalize AuNPs and subsequently co-decorated with streptavidin. After successful modification of the AuNPs with polymer and streptavidin, the modified AuNPs efficiently conjugated biotinylated antibody for the capture of target biomarkers. With the thermal stimulus and an external magnetic field, coaggregation of AuNP half-sandwiches with the PNIPAm-coated iron oxide nanoparticles created large aggregates. In this way, biomarkers captured by immobilized antibody could be extracted from a spiked pooled plasma. Oxidized low-density lipoproteins (OxLDLs) take part in pathophysiological processes. The novel AuNPs-conjugated anti-OxLDL antibody platform made it a reality to trap OxLDL applying the specific affinity of anti-OxLDL antibodies [47]. After methanol extraction and centrifugation, the extracted oxidized lipids from OxLPL in the supernatant could be directly subjected to LC–MS analysis, showing good compatibility of this method. Enrichment of generated glycosphingolipids aldehydes by chemical ligation using an aminooxy-functionalized AuNPs was reported [48]. As AuNPs were employed, with the reconstruction of the self-assembled microdomain model involving multivalent glycosphingolipids, it could further be used for direct analysis of carbohydrate–carbohydrate interaction by means of SPR. An efficient

way to achieve chiral recognition is to adsorb chiral molecules. As *N*-acetyl-L-cysteine (NALC) could be adsorbed onto the surface of AuNPs, such NALC modified AuNPs had the ability to achieve colorimetric recognition and enrichment of L-tyrosine (L-Tyr), thus providing a potential application for chiral separation of amino acids [49].

Various ions could also be extracted by functionalized metal nanoparticles. Taking advantage of Hg^{2+} selective coordination to thymine (T) bases, 33 thymine nucleotides functionalized silver nanoparticles (T33-AgNPs) were employed to specifically capture Hg^{2+} from aqueous solution [50]. The LOD of Hg^{2+} was 3 pM under the optimal conditions. A dithiol-protected $Ag_7(DMSA)_4$ (DMSA: meso-2,3-dimercaptosuccinic acid) quantum cluster was used for adsorption of cationic dyes [51]. Clusters exhibited higher surface area and reactivity due to smaller size, and the selectivity of such clusters toward cationic dyes probably arose from favorable electrostatic interactions.

Metal oxide nanoparticle has become one of the most promising materials for the enrichment of biological molecules containing specific groups or binding sites. Through the chelating bidentate bonds between the phosphate groups and the material, metal oxide has been widely used for the enrichment of analytes with phosphate groups. A kind of titania-coated silica (TiO_2/SiO_2) core–shell composites acted as the sorbent for selective extraction phospholipids from shrimp waste [52]. A series of metal oxides have been utilized for phosphopeptide enrichment, such as TiO_2 [53], ZrO_2 [54], SnO_2 [55], Fe_2O_3 [56], etc., as well as some binary

[57] and ternary [58] metal oxide materials. In addition to global phosphopeptide analysis, metal oxide adsorbents, which have adsorption priority for peptides with mono- or multi- phosphorylation sites, have been developed for selective enrichment of mono-phosphopeptides or multi-phosphopeptides [57,58]. Based on traditional analysis methods, materials with high efficiency for on-target enrichment have been put forward. Hernandez et al. [59] sintered TiO_2 onto a conductive glass surface for subsequent on-target phosphopeptide enrichment. The total amount of detected phosphopeptides was down to 3 fmol. Photocatalytically patterned TiO_2 arrays provided an alternative way for direct enrichment and analysis on target [60]. On-target enrichment extremely simplified the operation steps and improved the efficiency. However, the modified MALDI target was restricted to a certain function and difficult to recycle, thus it is necessary to develop a more convenient method for target modification to extend applications of on-target enrichment and improve recycling performance.

Metal oxide based magnetic nanoparticles have been widely used in nanomaterials based sample preparation, as their magnetism facilitated rapid collection and convenient recycling of nanomaterials. Applications of magnetic metal oxide in sample preparation could be divided into three different formats. (1) Magnetic metal oxides played roles of both sources of magnetism and affinity towards target species, such as the application of magnetic γ-Fe_2O_3 nanocrystal clusters for enrichment of phosphopeptides [56]. (2) Magnetic metal oxides were co-crystalized with other non-magnetic metal oxides. In these cases, magnetic components provided magnetism for adsorbent collection, while non-magnetic components functioned for capture of target analytes, such as the monodispersed $CuFe_2O_4$ magnetic nanocrystal clusters employed for specific separation of histidine-rich proteins from samples containing other proteins [61]. (3) Magnetic metal oxide nanoparticles were coated or grafted with other functional groups or materials for selective adsorption of target molecules. Because of the variety of different functional groups and materials for the capture of diverse analytes with different properties, most applications of magnetic metal oxides in sample preparation were in this format. Such applications were discussed detailedly in other sections, considering the specific components for analyte capture.

A summary of recent applications of metal and metal oxide nanoparticles in sample preparation is present in Table 2.

2.3. Si and silica based nanoparticles

Silica nanoparticles are easy to synthesize and modify by various functional groups on their surface. *In vivo* bioanalysis has become a research hotspot, and it usually requires more stringent stability of the nanomaterials in physiological conditions. Compared with other materials, Si and silica based materials provided good biocompatibility. Airaksinen et al. [62] reported ^{18}F-labeled fungal hydrophobin coated Si nanoparticles and their pronounced enhancement in adsorption of plasma protein due to the altered hydrophobicity of Si nanoparticles. ^{18}F-radiolabeling enabled the sensitive and easy quantification of nanoparticles in tissues using radiometric methods and allowed imaging of the nanoparticle biodistribution with positron emission tomography. To investigate the effect of the bio-functionalization on nanoparticles *in vivo*, such ^{18}F-labeled hydrophobin coated Si nanoparticles were further intravenously administered to rats, resulting in significant accumulation in the liver and spleen with the potential of targeted drug delivery. The quality and the safety of water source is a key concern of the daily life of human being. Nano-silica fabricated with AgNPs has been reported as an efficient adsorbent for the dye contaminants in water [63]. Similarly, pure and Ag-doped SiO_2 present reliable property in the adsorption of chlorinated compounds in water [64].

Jung et al. [65] attached thymidine receptor residues to the inner side wall of silica nanotubes (SNTs) covalently. The composite material T-SNTs exhibited excellent selectivity both in recognition and separation of adenosine and adenosine-based oligonucleotides through the formation of complementary intermolecular hydrogen bonds. It has been demonstrated that silica surface structure is important for specific binding of peptides and proteins which present different affinities towards different surface properties or functionalization. The adsorption mechanisms are dual actions of ion pairing and hydrogen bonds between peptides and the surface, complemented by ion–dipole, dipole–dipole, and van-der-Waals interactions [66]. For instance, positively charged peptides are strongly attracted to anionic silica surface by ion pairing of protonated N-termini, Lys side chains, and Arg side chains with negatively charged silanol groups. Duan and coworkers [67] prepared Fe_3O_4@SiO_2@NiAl-LDH (layered double hydroxide) with flower like morphology for His-tagged protein

Table 2
Recent applications of metal and metal oxide NPs in sample preparation.

Metal/metal oxide	Modification	Analytes	Matrix	Detection technique	Ref.
AuNPs	Grafted on TMSPT–MNP	Progesterone, testosterone	Plasma, urine	HPLC-UV	[39]
AuNPs	Antibody, pNIPAm (thermally responsive polymer)	Pan-aldolase, PfHRP2	Plasma	immunoassay	[46]
AuNPs	Antibody	OxLDLs	Plasma	LC–MS/MS	[47]
AuNPs	Aminooxy	Glycosphingolipids	Cell	SPR, MALDI–ToF-MS	[48]
AuNPs	*N*-acetyl-L-cysteine	L-tyrosine	Racemate of tyrosine	naked eyes	[49]
AgNPs	Oligonucleotide of 33 thymine	Hg^{2+}	Water	FIA with FLD (after fluorescent dye labeling)	[50]
TiO_2	Composited SiO_2	Phospholipids	Shrimp waste	HILIC-MS	[52]
TiO_2 nanocrystal clusters	–	Phosphopeptides	Milk digest	MALDI–ToF–MS	[53]
ZrO_2 shell	Coated on MNPs	Phosphopeptides	Saliva	MALDI–ToF-MS LC–MS/MS	[54]
Mesoporous SnO_2 nanospheres	–	Phosphopeptides	Milk digest	MALDI–ToF-MS	[55]
Magnetic γ-Fe_2O_3 nanocrystal clusters	–	Phosphopeptides	Milk digest	MALDI–ToF-MS	[56]
SnO_2-$ZnSn(OH)_6$	–	Multi-phosphopeptides	Milk digest	MALDI–ToF-MS	[57]
$NiZnFe_2O_4$	–	Multi-phosphopeptides	Zebrafish egg	MALDI–ToF-MS/MS	[58]
TiO_2	Modified on MALDI target plate	Phosphopeptides	Protein digest mixture	MALDI–ToF-MS	[59]
TiO_2	Modified on MALDI target plate	Phosphopeptides	Casein digest	MALDI–ToF-MS	[60]
$CuFe_2O_4$ nanocrystal clusters	–	Histidine-rich proteins	Human blood	SDS-PAGE	[61]

TMSPT is the 3-(trimethoxysilyl)-1-propanethiol; *PfHRP2* Plasmodium falciparum histidine-rich protein 2; and *FIA* flow injection analysis.

separation and purification. By virtue of the layer-by-layer deposition of LDH, such material had a large surface area (83 m^2 g^{-1}) and higher binding capacity (239 µg mg^{-1}) than that of the traditionally used nickel-nitrilotriacetic acid (Ni^{2+}–NTA) agarose ($\sim$10 µg mg^{-1}). In addition, more satisfactory recyclability was observed owing to the better stability of NiAl–LDH, whereas the Ni^{2+} bleeding problem was often encountered when using Ni^{2+}–NTA agarose.

2.4. Polymer nanoparticles

Driven by the advantages of polymer nanoparticles (PNPs), such as tunable composition of monomer, good flexibility, structure diversity, facile functionalization at room temperature and relatively low cost, it is more flexible to design various PNPs according to different molecular recognition mechanisms. It should be emphasized that the properties of polymer nanoparticles depend not only on the monomers but also on the morphological and interfacial characteristics [68]. In order to achieve fast mass transfer rates and ensure high temporal resolution of equilibrium extraction, core–sheath nanofibers were prepared, in which polystyrene (PS) was used as the core and poly(N-isopropylacrylamide) (PNIPAAm) as the sheath [69]. It is well known that PNIPAAm is biocompatible and protein-resistant and PS is a kind of widely used extractive material. The integrity of the nanofiber guaranteed the complete and fast expansion in aqueous solution, resulting in fast equilibrium micro-extraction of free drugs from biological fluids. Wang and coworkers [70] reported attapulgite/poly(acrylic acid) nanocomposite (ATP/PAA) hydrogels for selective adsorption of the Pb(II) ion. In the composite nanostructure, the attapulgite nanorods acted as cross-linkers and structural strengthening agents and acrylic acid grafted onto ATP to form 3D cross-linking network of the nanocomposite hydrogels. These hydrogels had good adsorption capacity and reusability. Similarly, magnetic attapulgite/fly ash/poly(acrylic acid) ternary nanocomposite hydrogels were reported for the selective adsorption of the Pb (II) ions [71]. The adsorbed ions could be completely desorbed with hydrochloride aqueous solution and the extraction time is significantly shortened through magnetic separation. Besides Pb(II) ions, poly(MMA-co-MA)/modified-Fe$_3$O$_4$ magnetic nanocomposite has been employed as the adsorbent for Co(II), Cr(III), Zn(II) and Cd(II) ions [72]. However, in aqueous environment these nanopolymers are prone to fouling, such as organic fouling, colloidal fouling and biofouling, which may result in structural damage, pore size and surface roughness, and blockage of surface functional groups. So more efforts are still required to solve these problems.

Hybrid inorganic–organic nanocomposites with improved properties combine the advantages of inorganic particles and organic polymers. A high performance hybrid nanocomposite carboxymethyl tamarind-g-poly(acrylamide)/silica has been reported as efficient adsorbent of methylene blue dye in contaminated water [68]. Because of their super large surface area and flat structure, graphene and graphene derivatives have become significant parts in composite materials. Wen et al. [73] reported reduced graphene oxide/poly(acrylamide) nanocomposite for Pb

(II) and methylene blue adsorption with capacities of 1000 and 1530 mg/g for Pb(II) and methylene blue, respectively, which were higher than those of pristine graphene [74], GO [75], unmodified reduced graphene oxide (RGO) [73] and EDTA modified GO/RGO [76].

Interestingly, polymer nanoparticles can achieve chiral recognition as well. Poly(9,9-dioctylfluorene-alt-benzothiadiazole) was reported to achieve selective extraction of larger-diameter semiconducting single-walled carbon nanotubes(SWCNTs) [77]. Although the detailed mechanism for selective extraction has not yet been clarified, it revealed that the energy level matching between SWCNTs and fluorene-based polymers was one of the reasons for selective extraction of SWCNTs with specific chiral indices through spectroscopic analysis. Different from chiral recognition and separation of compounds with chiral groups, the selectivity mechanism of this material should be further clarified for the research in chiral recognition and separation.

Table 3 shows examples of applications of polymer based NPs in sample preparation.

3. Sample preparation based on nanoporous materials

In this section, we focus on nanoporous materials with various porous structures. Metal organic frameworks (MOFs), imprinted polymers, and mesoporous materials are evaluated for their application in sample preparation (Fig. 3). It is noteworthy that some nanoporous materials are also nanoparticles in terms of their particle sizes. However, the properties originating from their distinct porous structures, which are not present in their solid counterparts, are emphasized in this section.

3.1. Metal–organic frameworks

Metal–organic frameworks (MOFs) are a class of hybrid organic–inorganic materials, which were first reported in 1995 [81]. They are usually constructed by strong coordination bonds between metal ions as nodes and organic linkers as rods, so they are endowed with both the stability of inorganic materials and the modifiability of polymer materials [82]. Super large surface area (typically range from 1000 to 10,000 m^2/g [83]) is one of their great advantages, which makes MOFs promising for sample preparation. Moreover, their pore apertures vary substantially, so the analytes can be not only as small as metal ions [84], but also as large as protein [85]. Here, we summarize the utilization of MOFs in sample preparation and hope to provide useful guideline in selecting proper MOFs for new applications.

The first utilization of MOFs for solid-phase microextraction (SPME) was reported by Yan et al. [86] The SPME fiber was fabricated by in situ hydrothermal growth of MOF-199 films on the surface of etched stainless steel wire. This device showed large enrichment factors from 19,613 (benzene) to 110,860 (p-xylene), which were ascribed to following three effects: the large surface area of the MOF-199, the π–π interactions between the aromatic rings of the analytes and the aromatic molecules in the framework, and the π-complexation of the electron-rich analytes to the

Table 3
Applications of polymer based NPs in sample preparation.

Polymer	Functionalization	Analytes	Matrix	Detection Technique	Ref.
Core–sheath PS/PNIPAAm nanofiber	–	Small molecule drugs	Proteins, cells	HPLC–MS/MS	[69]
Poly(acrylic acid)	Composited with attapulgite	Pb^{2+}	Water	FAAS	[70]
Poly(acrylic acid)	Composited with attapulgite and magnetic fly ash	Pb^{2+}	Water	FAAS	[71]
poly(MMA-co-MA)	Immobilized on Fe$_3$O$_4$ NPs	Co^{2+}, Cr^{3+}, Zn^{2+}, Cd^{2+}	Water	AAS	[72]
Poly(acrylamide)	Grafted on RGO	Methylene blue, Pb^{2+}	Water	UV–vis	[73]
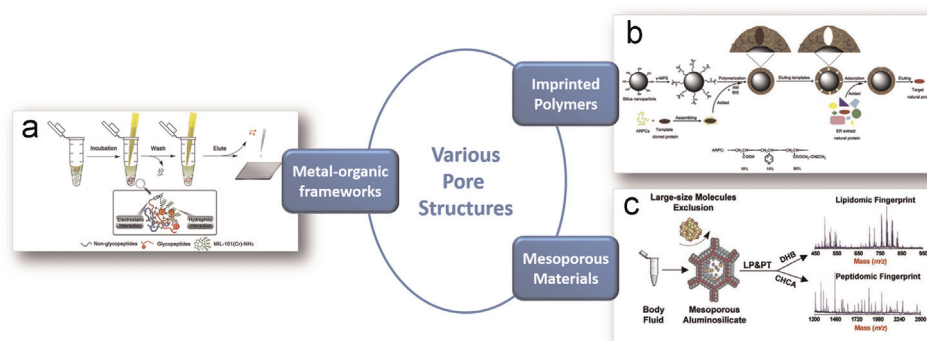
Fig. 3. Representative applications of nanoporous materials with various pore structures in sample preparation. (a) SiO₂@MIP for enrichment of natural low-abundance proteins (Reprinted with permission from [78]. Copyright © 2013, Elsevier). (b) MIL-101(Cr)–NH₂ for enrichment of glycopeptides (Reproduced with permission from [79]. Copyright © 2014, Royal Society of Chemistry). (c) Mesoporous aluminosilicate for size-selective extraction of lipids and peptides (Reprinted with permission from [80]. Copyright © 2012 WILEY-VCH Verlag GmbH & Co. KGaA,Weinheim).

Lewis acid sites in the pores of MOF-199. The strong interactions were confirmed between following MOFs and PAHs: ZIF-8 [87], MIL-53 [88], MOF-5 [89] and MAF-X8 [90]. Furthermore, these MOFs also showed high efficiency even in water samples. Introduction of magnetic component is an effective way to facilitate fast separation from aqueous solution and recycle use of MOFs. Yan and coworkers [91] developed a physical strategy: facile magnetization was realized by the simply mixing MIL-101 and silica-coated Fe_3O_4 particles under sonication by virtue of their electrostatic interaction. Li et al. [92] developed a chemical strategy: Fe_3O_4 magnetic particles were attached to MOF-5 via chemical bonding. Both strategies showed efficient extraction of PAHs. In addition to PAHs, other aromatic compounds, such as polychlorinated biphenyls (PCBs) [93], could also be extracted by MOFs through π–π interactions.

π–π interaction played an important role in the extraction of aromatic compounds, while "molecular sieving effect" had great effect for nonpolar aliphatic compounds. Due to the regular shaped channel, MOFs showed different affinity to target molecules according to their diameter and degree of branching [94]. Therefore, every MOF could selectively absorb molecules in a specific range of scale. Yan et al. [95] fabricated MOF-coated SPME fibers by a layer-by-layer deposition method and GC columns by dynamic coating method to setup a dual platform for micro-extraction and separation. As a result, n-alkanes were selectively extracted and separated on ZIF-8 based platform from complex matrixes such as petroleum-based fuel and biological fluids. Li et al. [96] hybridized MOF-199 with multi-walled carbon nanotubes (MWCNTs) to enrich ethylene, which was an important plant hormone. The MWCNTs provided hydrophobic "shield" to prevent the open metal sites of MOF-199 from being occupied by water molecules, and this nanoporous material was successfully applied to the extraction of ethylene from fruit samples including grape, wampee, blueberry, and durian husk.

Molecular sieving effect and π–π interaction arise from organic rods in MOFs, while the metal nodes can also provide strong interaction from their coordinative unsaturated sites (CUS), which have strong affinity to polar molecules. Our group used MIL-101 to concentrate herbicides residues in water sample [97]. Coordination between unsaturated Cr(III) sites and nitrogen atoms facilitate adsorption of triazine herbicides on MIL-101. Li et al. [98] coated MOF-199/GO hybrid material on fibers to extract organochlorine

Table 4
Application of MOFs in sample preparation.

MOFs	Metal element in MOFs	Analyte	Matrix	Detection technique	Ref.
MIL-101(Cr)–NH₂	Cr	Glycopeptides	Human serum	MALDI–ToF–MS	[79]
Fe₃O₄/IRMOF-3	Zn	Copper	Water	AAS	[84]
IRMOF-74	Zn, Mg	Protein	–	UV–vis	[85]
MOF-199	Cu	Benzene homologs	Air	GC–FID	[86]
ZIF-8	Zn	PAHs	Environmental water	GC–MS	[87]
MIL-53	Al	PAHs	water	GC–MS	[88]
MOF-5	Zn	PAHs	Environmental water	HPLC–FLD	[89]
MAX-F8	Zn	VOCs	Water	GC–MS	[90]
Fe₃O₄@SiO₂-MIL-101	Cr	PAHs	Environmental water	HPLC–UV	[91]
Fe₃O₄/MOF-5	Zn	PAHs	Water	GC–MS	[92]
MIL-88B	Fe	PCBs	River water	GC–MS	[93]
ZIF-8	Zn	Alkanes	Human serum	GC–MS	[95]
MOF-199/CNTs	Cu	Ethylene	Fruit samples	GC–FID	[96]
MIL-101	Cr	Triazine herbicides	Water	DART–MS	[97]
MOF-199/GO	Cu	Pesticides	River water, soil, water convolvulus and longan	GC–ECD	[98]
ZIF-8	Zn	Benzotriazoles	Water	HPLC–UV	[99]
ZIF-8	Zn	Acidic drugs	Environmental water	GC–MS	[100]
UIO-66	Zr	Phenols	Water	GC–FIS	[101]
Fe₃O₄@SiO₂-MOF-177	Zn	Phenols	Environmental water	GC–MS	[102]
UIO-68	Zr	Uranium	Water	ICP–MS	[103]
Fe₃O₄/Cu₃(BTC)₂–H₂Dz	Cu	Lead	Stream sediment, milk powder, water	ETAAS	[104]
MIL-53, MIL-100, MIL-101	Al, Cr	BSA digest	Human plasma	MALDI–ToF–MS	[105]
[Er₂(PDA)₃(H₂O)]·2H₂O	Er	Phosphorylated peptides	Egg white protein	MALDI–ToF–MS	[106]
GO–La(BTC)(H₂O)₆	La	Hemoglobin	Human whole blood	SDS–PAGE	[107]

PDA is the 1,4-phenylenediacetate and *BTC* benzenetricarboxylic acid.

pesticides. Compared with individual MOF or GO and commercial polydimethylsiloxane (PDMS) or polydimethylsiloxane/divinylbenzene (PDMS/DVB) fiber, this hybrid material showed better adsorption affinity.

As mentioned before, many molecular interactions may influence the extraction efficiency together. ZIF-8 showed strong affinity to benzotriazoles due to hydrophobic interaction, π–π interaction and coordination interaction [99], while as to ibuprofen, naproxen and ketoprofen, acid-base interaction could not be ignored [100]. Hydrogen bonding interaction and π–π interaction helped UIO-66 [101] and MOF-177 [102] to extract phenols from water samples.

According to the recent literatures about MOFs in sample preparation, most of the attention was paid to small organic molecules, while few researches have made efforts on metal ions and biological macromolecules. For the extraction of heavy metal ions, Lin et al. [103] used UIO-68 to extract uranium from aqueous media, Hu et al. [104] used $Fe_3O_4/Cu_3(BTC)_2$–H_2Dz to enrich lead and IRMOF-3 was applied to extract copper [84]. These extractions were all based on chelation mechanism. In other words, these MOFs all had strong coordination groups like amino group or dithizone group.

The pore sizes of MOFs varies significantly, so different MOFs can selectively adsorb or exclude large biomolecules. Yan et al. [105] used MIL-53, MIL-100 and MIL-101 to enrich BSA tryptic digest and found that larger pore sizes gave favorable enrichment of peptides with larger molecular weights. Selective enrichment of phosphorylated peptides was realized by Rainer and coworkers [106] by virtue of the CUS of Er(III) ions on the surface. Meanwhile, glycopeptides were firstly highly specifically enriched by MIL-101(Cr)–NH_2 based on the hydrophilic interactions [79]. As for much larger proteins, graphene oxide–$La(BTC)(H_2O)_6$ composite material was successfully applied to selective isolation of hemoglobin [107]. The driven forces of adsorption were strong hydrophobic interaction and π–π interaction, while the inner channels did not affect this adsorption.

Table 4 summarizes recent applications of MOFs in sample preparation. The large surface area and nanoscale channels makes MOFs a promising sorbent candidate for sample preparation and arising attention to MOFs confirms this point. However, the enrichment selectivity is not satisfactory because of the non-specific adsorption, which may be ascribed to the complicated interactions towards both analytes and undesired species arisen from the multiple components in MOFs. Specifically designed or functionalized MOFs may open new channels for these issues.

3.2. Imprinted polymers

Imprinted polymers (IPs) are a special kind of polymers by introduction of templates that serves as a mold for formation of a binding site. Due to their high selectivity, IPs become good adsorbent for sample preparation. From the pioneer work of Sellergren [108] to now, numerous papers on applications of IPs in sample preparation have been published. Herein, we focus on two aspects of the most recent progresses: multiple kinds of templates and hybrid MIPs.

For the template of IPs, in addition to the general neutral organic molecules, ionic templates and epitope templates have also been employed for the development of novel IPs. And corresponding ion imprinted polymer (IIP) and epitope imprinted polymer (EIP) have been prepared. Say and coworkers [109] did the influential work to extract Ni(II) ions. In this work, Ni(II)–methacryloylhistidinedihydrate (MAH/Ni(II)) complex monomer was synthesized and polymerized with cross-linker ethyleneglycoldimethacrylate (EGDMA) to obtain poly(EGDMA-MAH/Ni(II)). Compared with ions with similar radii, such as Cu(II), Zn(II) and Co (II), this polymer showed satisfactory relative selectivity coefficients. By virtue of the success of the early works, more and more transition metal ions were used as templates [110,111]. In preparation of metal ion imprinted polymers, the strength of interaction between metal ions and coordinative monomer is important. Strong interaction would result in insufficient templates removal and serious templates bleeding in the following extraction, while weak interaction would decrease the extraction efficiency and specificity. In addition to metal ions, ionized organic species have also been extracted by IPs. Alizadeh et al. [112] used negative benzoate ion as template to prepare conducting imprinted polypyrrole film which exhibited excellent selectivity in the presence of interference anions including salicylate, sorbate, citrate, phosphate, acetate and chloride ions.

Up to now, only a few proteins have been successfully imprinted for their high-cost and poor stability in organic solvent and polymerization condition. To conquer this problem, Minoura and coworkers [113] developed epitope imprinting technique. In this process, a fragment exposed on the epitope of the target macromolecular was used as template, which was usually more robust and low cost. Chen et al. [114] used pentadecapeptide as template and coated EIP on a quartz crystal microbalance (QCM) chip for the detection of dengue virus NS1 protein. This new method offered several advantages over traditional MIP methods: (1) Embedding and bleeding of the target protein were avoided. (2) Nonspecific interaction between the MIP and target protein was minimized. (3) Analyte washout was quicker and efficient

Table 5
Applications of imprinted polymer in sample preparation.

Template	Functionalization	Analyte	Matrix	Dectection Techinique	Ref.
BiP	–	BiP	ER extract	SDS-PAGE	[78]
Ni(II)	–	Ni(II)	sea water	FAAS	[109]
Au(III) in$Au(a-bipy)_2Cl_3$	Incorporated with Fe_3O_4 NPs	Au(III)	Cationic interferences	FAAS	[110]
UO_2^{2+}	Coated on $Fe_3O_4@SiO_2$	UO_2^{2+}	Water	FAAS	[111]
Benzoate ion	–	Benzoate ion	Beverage	Electrochemical method	[112]
Pentadecapeptide	–	Dengue virus NS1 protein	Serum	QCM (antibody proofreading)	[114]
Synthetic peptide	–	HIV-1 related protein	Human urine	QCM	[115]
Emodin	Polymerized on MWCNTs	Emodin	Kiwi fruit root	HPLC–UV	[116]
Dopamine	Polymerized on GO	Dopamine	Human serum	HPLC–UV	[117]
Ractopamine	Coated on CdTe/ZnS QDs	Ractopamine	Feeding stuffs, pork samples	HPLC–FLD	[118]
Estradiol	Supported on $Fe_3O_4@ZIF-8$	Estrogens	Fish, pork	HPLC–UV	[119]
Thiabendazole and Cu(II)	–	Thiabendazole	Citrus, soil	HPLC–UV	[120]
Quercetin	Al(III) inserted	Quercetin	*Ginkgo biloba* L	HPLC–UV	[121]
Caffeine	–	Caffeine	Water	HPLC–DAD	[122]

a-bipy is the N-Allyl-N-(pyridin-2-yl)pyridin-2-amine; ER endoplasmic reticulum; and BiP Immunoglobulin heavy chain binding protein.

allowing the maximum reusability. Following the same strategy, Yang et al. [115] prepared a new EIP for the detection of HIV related protein, which provided a possibility for the disease detection.

Besides the extended templates, many functional materials have been tried on the preparation of MIP composites. Carbon nanomaterials with unique mechanical properties and extremely large surface area can be an excellent support materials of MIPs. Combination of MIPs with both CNTs and graphene has been reported for their applications in solid phase extraction [116,117]. Wang et al. [118] reported the dual-function MIP-coated QDs, which realized highly selective extraction and sensitive determination of ractopamine (RAC) through spectrofluorometry. As mentioned before, MOFs were promising adsorbents and ZIF-8 had already been used in many reports. Pan et al. [119] prepared Fe_3O_4@ZIF–8@MIP for extraction of estrogens in fish and pork samples. This composite material showed combined advantages: good thermal and chemical stability from MOFs and good selectivity from MIPs. Metal ions could coordinate with some ligands and this interaction found applications in MIP recognition. Li et al. [120] prepared metal ion mediated complex imprinted SPME fiber for the selective recognition of thiabendazole in citrus and soil samples. Dias et al. [121] prepared Al(III)–molecularly imprinted silica (MIS) for solid phase extraction of quercetin in *Ginkgo biloba L.* The recognition and enrichment properties of the Al(III)–MIS in water were significantly improved based on the metal ion co-ordination interaction rather than hydrogen bonding interactions that were commonly applied for the molecularly imprinting techniques.

Ionic liquids (ILs) could act as not only templates and porogens, but also functional monomer in the synthesis of MIPs. Water-compatible MIPs containing 1-(α-methyl acrylate)-3-methylimidazolium bromide were successfully prepared by Luo et al. [122]. The adsorption capacity and relative separation factor of MIPs for caffeine were significantly enhanced by the π–π stacking and hydrogen-bonding interactions from ILs. By introducing the ionic templates or monomers, the extra static electric interaction may help to enhance selectivity.

Table 5 lists some applications of IPs in sample preparation. MIPs is a very selective method for the designed sites, and the choice of templates extended greatly. However, MIPs may be of limited value because of their high-cost, low yields of specific binding sites and the subsequent low sample-load capacity in some cases.

3.3. Mesoporous materials

Mesoporous nanomaterials are a special kind of nanoporous materials defined by their pore sizes. Diameters of the pores in mesoporous materials, according to International Union of Pure and Applied Chemistry (IUPAC), fall in the range of 2–50 nm. Like other kinds of nanoporous materials, high specific area of mesoporous materials originating from the existence of nanopore structure facilitates their application in sample preparation. A large number of mesoporous materials with various components and morphologies have been developed for extraction and pre-concentration of metal ions [123], small organic molecules [124,125] and peptides/proteins [56,126], as well as fast digestion for proteome analysis through immobilization of protease on pore surface [127].

Despite their versatile applications in sample preparation for various kinds of analytes, the most distinct merit of mesoporous materials is their size-selective effect on low molecular weight (LMW) target analytes in the presence of high molecular weight (HMW) interference species (Fig. 4). Endogenous LMW peptides have drawn great attention in recent years because of their
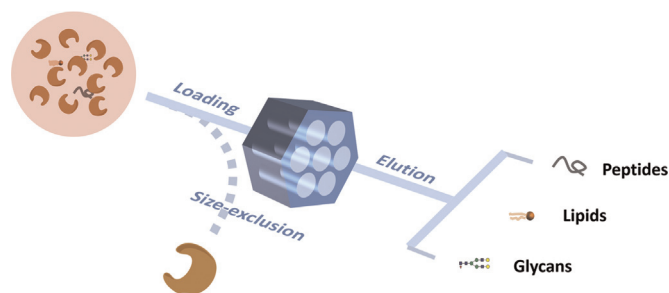

Fig. 4. Applications of size-selective effect of mesoporous materials for sample preparation for the analysis of LMW species in the presence of HMW proteins.

potentials as biomarkers. However, direct analysis of endogenous LMW peptides in biological samples by mass spectrometry is often hampered by high concentration HMW proteins and salts. The existence of HMW proteins would severely suppress the desorption and ionization of target LMW peptides [128], thus reducing detection sensitivity, especially for those in low abundance. The differences in molecular sizes between endogenous peptides and HMW proteins allow mesoporous materials, mostly with pore diameters between 2 and 5 nm, to be applied for their separation. Endogenous peptides have access to the inner space of mesopores and can be adsorbed on the interior surface, while HMW proteins cannot owing to size-exclusive effect on molecules with diameters larger than the pore sizes. Venuta et al. firstly reported selective enrichment of LMW proteome from human plasma by mesoporous silica [129]. It was found that, however, mesoporous silica had poor extraction efficiency for acidic peptides because of the electrostatic repulsion between both negatively charged acid peptides and surface of silica with deprotonated silanol groups [130], while basic peptides could hardly be eluted from mesoporous silica with MS compatible elution buffer because of the strong electrostatic attraction [131]. To overcome these problems, mesoporous materials with neutral and hydrophobic surface have been adopted for more comprehensive endogenous LMW proteome enrichment, such as mesoporous carbon [130,132] and mesoporous silica with hydrophobic surface modification by vinyl [131] or octyl [133]. Such mesoporous materials with hydrophobic surface provided hydrophobic affinity towards both acidic and basic peptides, and peptides adsorbed could be easily eluted by high organic solvent containing elution buffer, both enhancing adsorption and elution efficiency. With mesoporous carbon, elimination of HMW proteins and salts could be realized in one step, saving the trouble and sample losses from an additional SPE step for desalting when performing commonly used centrifugal ultrafiltration (UF) method. Such advantage may contribute to the more LMW peptide identification with smaller volume of sample compared with the UF-SPE method [130,134]. In addition to global endogenous proteome analysis, mesoporous materials with proper surface modification have also been applied for specific LMW peptides extraction and purification, such as endogenous phosphopeptide enrichment by Ti^{4+} or Zr^{4+} immobilized mesoporous materials [135,136].

Besides endogenous peptidome analysis, size-exclusive effect of mesoporous materials was also employed for selective extraction of other LMW species, including glycans [137–139] and lipids [80], in the presence of interference HMW proteins. Zou et al. [137] prepared oxidized mesoporous carbon for selective enrichment of N-linked glycans after PNGase F cleavage in the presence of residual proteins, and 5 N-linked glycans were identified as potential biomarkers of liver cancer. The oxidized mesoporous carbon was replaced by mesoporous silica–carbon composite nanoparticles NP-MCM-C with mesoporous silica support and carbon modified inner surface to obtain uniform particle shape and better

Table 6
Applications of mesoporous materials in sample preparation.

Mesoporous materials	Pore size (nm)	Analytes	Matrix	Detection technique	Ref.
Py–Fe$_3$O$_4$@MCM-41	2–3	Pb^{2+}, Cu^{2+}	Fuel product	FAAS	[123]
Magnetic-graphene@mSiO$_2$–C18	3.3	PAEs	Environmental water	GC–MS	[124]
Au–NH$_2$–MCM-41	2.2	PAHs	Seawater	GC–FID	[125]
Magnetic γ-Fe$_2$O$_3$ nanocrystal clusters	9.7	Phosphopeptides	Milk digest	MALDI–ToF–MS	[56]
SBA-15 AAPTES (trypsin immobilized)	4.3	Proteins (for fast digestion)	–	MALDI–ToF–MS	[127]
Ordered mesoporous carbon	4.8	Endogenous peptides	Human serum	2D LC–MS/MS	[130]
Alkyl diol-vinyl-SiO$_2$	2	LMW proteins and peptides	HMW proteins	MALDI–ToF–MS	[131]
Yolk–shell magnetic Mesoporous carbon	3.4	Endogenous peptides		2D LC–MS/MS	[132]
C8-modified graphene@mSiO$_2$	2.8	Endogenous peptides	Mouse brain tissue	MALDI–ToF–MS nanoLC–MS/MS	[133]
Ga^{3+}/Ti^{4+}/Zr^{4+} modified mesoporous silica chip	4	LMW phospho-proteins/peptides	Human serum	MALDI–ToF–MS	[135]
Ti^{4+}–magnetic graphene@mSiO$_2$	2.17	Endogenous phosphopeptides	Human serum/ human salica	MALDI–ToF–MS	[136]
Oxidized mesoporous carbon (O-CMK-3)	3.4	Glycans from glycoproteins	Residue proteins	MALDI–ToF–MS	[137]
NP-MCM-C	2.8	Glycans from glycoproteins	Residue proteins	MALDI–ToF–MS	[138]
C-graphene@mSiO$_2$	2.8	Glycans from glycoproteins	Residue proteins	MALDI–ToF–MS	[139]
Mesoporous aluminosilicate	3	Peptides, lipids	Body fluids	MALDI–ToF–MS	[80]

AAPTES is the *N*-(2-Aminoethyl)-3-aminopropyl and *NP-MCM-C* ordered mesoporous silica carbon composite nanoparticles.

dispersity, and a more sensitive and comprehensive glycan enrichment was accomplished [138].

Reports of application of mesoporous materials in sample preparation are summarized in Table 6. A contradiction exists between the efficiency and specificity in the application of mesoporous materials for size-selective separation with respect to their particle sizes. Larger particle sizes limit the accessibility of central parts of the pore channels and reduce both adsorption and elution efficiency. On the other hand, although smaller particle sizes benefit higher-efficiency exploitation of its high specific area, it may cause more undesired adsorption of HMW species due to the increase of outer surface area. Modification of outer surface with restricted access materials to reduce adsorption on outer surface and functionalization of inner surface by groups with more specific affinity can be helpful to solve this problem. The latter approach may be more promising because of its potential for more versatile applications of mesoporous materials in sample preparation. Considering the possibility of uncertain decrease in pore sizes due to surface modification, more accurate control in a wide range of pore diameters should be critical for development and application of novel mesoporous materials for sample preparation.

4. Conclusion and perspectives

A great number of novel nanomaterials with various chemical compositions and morphologies have been exploited in sample preparation, relying on intrinsically chemical properties of their components and exceptional shape- or size-selective effects in nanoporous materials. In addition, surface functionalization or hybridization of different nanomaterials facilitate the development of versatile approaches for efficient analysis of various analytes.

Further researches of novel nanomaterials for sample preparation may focus on the following aspects: (1) Because of the high complexity of both analytes and sample matrix, design and development of new nanomaterials with better specificity and selectivity are still in urgent demands. (2) Compatibility of nanomaterials with subsequent analytical methods, such as capability of on-particle analysis, should be highlighted for easier and more effective sample preparation. (3) Automation of sample preparation based on nanomaterials and its on-line coupling with subsequent analysis will attract more attention for improvement of both throughput of analysis and reliability of results.

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