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REVIEW ARTICLE

Synthesis and analytical applications of molecularly imprinted polymers on the surface of carbon nanotubes: a review

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Abstract This review (with 142 references) summarize the state of the art in molecularly imprinting technology as applied to the surface of carbon nanotubes (CNTs) which result in so-called CNTs@MIPs. These nanomaterials offer a remedy to the flaws of traditional MIPs, such as poor site accessibility for templates, slow mass transfer and template leakage. They also are flexible in that different materials can be integrated with CNTs. Given the advantages of using CNT@MIPs, this technology has experienced rapid expansion, not the least because CNT@MIPs can be produced at low cost and by a variety of synthetic approaches. We summarize methods of, and recent advances in the synthesis of CNT@MIPs, and then highlight some representative applications. We also comment on their potential future developments and research directions.

Keywords Multi-walled carbon nanotubes · Molecularly imprinted polymers · Synthesis · Nanoparticles · Solid-phase extraction · Chemical sensor

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Abbreviations

2 or 4-VP	2-or 4-vinylpyridine
AA	Acrylic acid
AEP	(p-acryloylaminophenyl)-{(4-aminophenyl)-diethyl ammonium}-ethylphosphate
AIBN	Azo-bisisobutyronitrile
APS	Ammonium persulfate
APTMS	Aminopropyltrimethoxysilane
β-CD	Beta-cyclodextrin
BDC	N,N-diethyldithiocarbamate
BSA	Bovine serum albumin
CLRP	Controlled/living free radical polymerization
CNTs	Carbon nanotubes
CNTs@MIPs	Molecularly imprinted polymers on the surface of carbon nanotubes
CS	Chitosan
CSDT	Chitosan derivative
DMAc	Dimethyl acetamide
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DVB	Divinylbenzene
ECL	Electrochemiluminescence
EE	Ethoxyethanol
EGDMA or EDMA	Ethylene glycol dimethacrylate
FQs	Fluoroquinolones
Ga(III)	Gallium(III)
MAA	Methacrylic acid
MIM	Molecularly imprinted membrane
MIPPy	Molecular imprinted polypyrrole
MIPs	Molecularly imprinted polymers
MIT	Molecular imprinting technology
MTMOS	Methyltrimethoxysilane
MWNTs	Multiwalled carbon nanotubes
NNMBA	N,N-methylenebisacrylamide
NPA	4-nitrophenyl acrylate

OTA	Ochratoxin A
PAMAM	Polyamide amine
PEG	Polyethylene glycol
PETRA	Pentaerythritol triacrylate
PPy	Polypyrrole
PTMOS	phenyltrimethoxysilane
SPE	Solid-phase extraction
SPME	Solid phase micro extraction
SWNTs	Single-walled carbon nanotubes
TCP	2,4,6-Trichlorophenol
TEOS	Tetraethylorthosilicate
THF	Tetrahydrofuran
μ-SPP	Micro-solid phase preconcentration

Introduction

The omnipresence of molecular recognition process indicates its essential role in nature, this exquisite process is exploited in enzymatic catalysis, antibody-antigen recognition, cell communication and some other biological processes [1]. Via biomolecular recognition process, numerous purposes have been achieved such as immunoassay and enzyme catalysis. But the usage has been greatly circumscribed due to the biomolecule's restricted availability, intolerance towards rigid chemical conditions and inferior performance compared to intracellular functioning. To circumvent the limitations above, much research has been carried out to obtain equivalents to biological recognition system.

Mimicking the mechanism of biomolecular recognition, but with high stability, ease of preparation and low cost, molecularly imprinted polymers (MIPs) have been demonstrated itself as the most promising synthetic materials bearing selective molecular recognition sites [2]. In the 1970's, molecular imprinting technology (MIT) was first introduced by Wulff et al. using covalent approach [3]. This technique has been advanced and soon developed [4] since the emerging of non-covalent approach which is marked by the synthesis of an acrylic-based imprinted polymer by Mosbach in 1981 [5].

According to Nicholls [6], "molecular imprinting is a technique which involves the formation of binding sites in a synthetic polymer matrix that are of complementary functional and structural character to its 'substrate' molecule". The monomers were first compounded with the analytes (or templates) and then polymerized. There are cavities created in the polymers, which are sterically and chemically complementary to the templates. Upon removal of the templates, the specific binding cavities are able to discriminate the templates from their analogs.

According to the mechanism of interaction between the monomers and templates, the molecular imprinting methods can be divided in to four categories: pre-organized approach (covalent bonding), self-assembly approach (non-covalent interactions), hybrid molecularly imprinting method and metal chelating method [7]. Attributed to the specific bonding, covalent imprinting polymers show high selectivity and homogeneous binding sites distribution. Nevertheless, they were confined to a narrow range of use because of the restrictive choices of templates [8]. On the other hand, profited from less restricted binding sites, MIPs resulting from self-assembly approach have been frequently developed and could be applied for a wider scope [4]. Some comprehensive reviews collecting and comparing different synthesizing methods and approaches of MIPs are recommended for reading [8–10].

Although conventionally prepared bulk MIPs exhibit high selectivity, some inherent defects are suffered from coarse post-treatment (as grounding and sieving of MIP [11]). These post-treatments reduce the polymer yield and produce irregular polymer fragments which narrow the usage in chromatography or solid-phase extraction. As another main congenital imperfection of bulk MIPs, limited mass transfer efficiency become the main issue in the macromolecule imprinting or biosensor field [12]. Different polymerization methodologies are shown in Fig. 1.

To solve the above-mentioned problems, surface imprinting technology was developed. Because the imprinting sites are located on or near the surface of the substrates, polymers synthesized by surface imprinting method show high mass transfer efficiency, high sensitivity and short response time. Furthermore, new properties (e.g. electrical, magnetic and optical [13, 14]) could be incorporated into the materials by changing or modifying the solid supports. In recent years, many new solid supports have been studied, such as monodispersed polystyrene [15], chitosan [16–19], silica beads [20–29], Fe_3O_4 nanoparticles [30], graphene [31–34], halloysite nanotubes [35–37] and quantum dots [38–45], some of which suffer disadvantages like lacking in mechanical strength and small specific surface area.

Belonging to the fullerene family, first described by Iijima [46], carbon nanotubes (CNTs) had been then expanded into multiwalled carbon nanotubes (MWNTs) and single-walled carbon nanotubes (SWNTs). Multiwalled carbon nanotubes are ideal support materials because of high strength, stability under acidic conditions, lack of swelling and large surface areas [47]. Taking these advantages, CNTs@MIPs should be superior, in some aspects, to other similar materials. Schematic protocol for the preparation of CNTs@MIPs is given in Fig. 2.

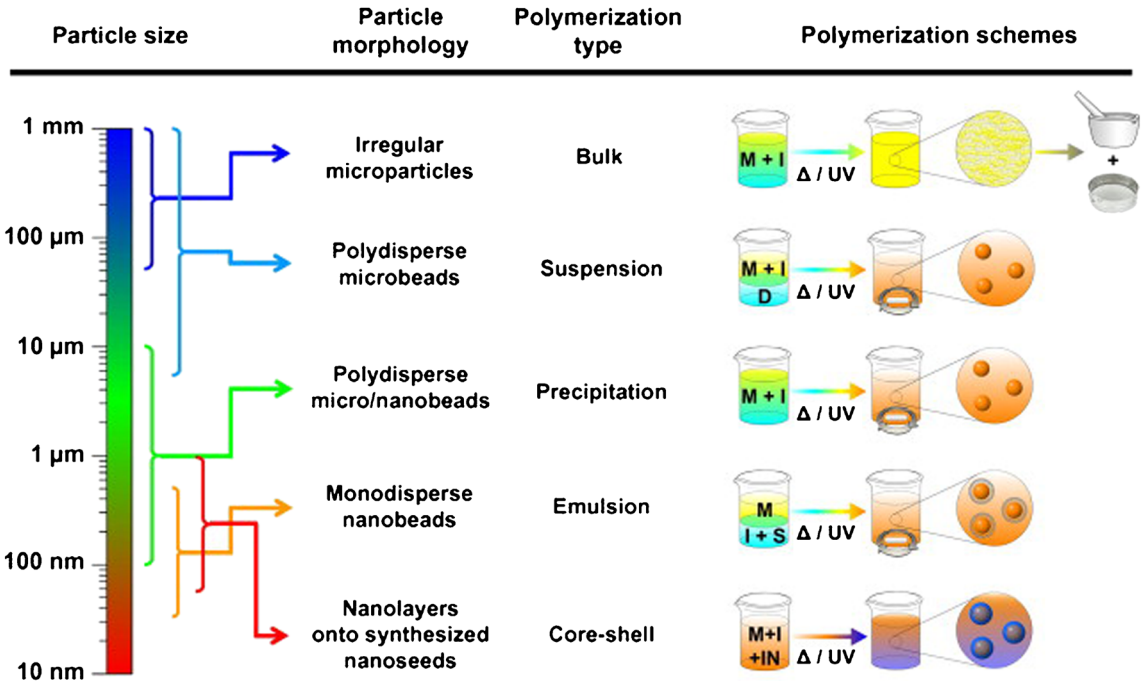

Fig. 1 Polymerization methodologies. *M* Monomers; *I* Initiator; *D* Dispersing phase; *S* Surfactant, *IN* Insoluble nanoseeds [10]

This review reports the principle of synthesizing CNTs@MIPs. Different particulars in the syntheses were also discussed. Applications in the field of SPE and sensor are highlighted. In the closing paragraph, we attempt to explore the potential development of CNTs@MIPs.

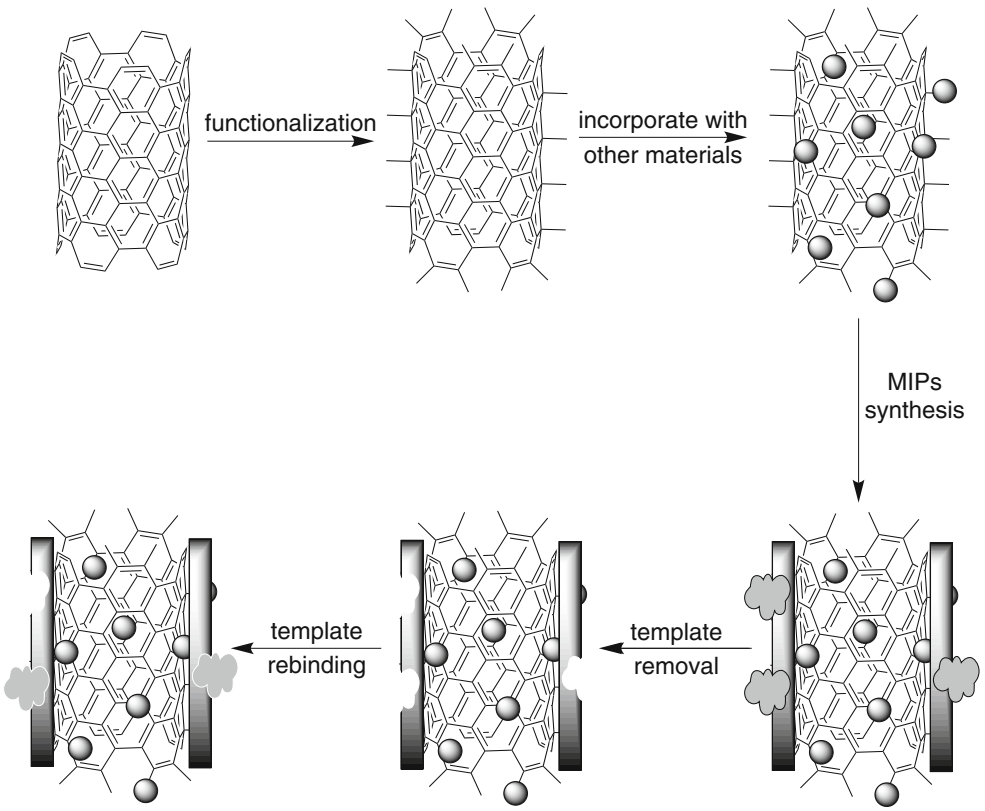

Fig. 2 Schematic protocols for the preparation of CNTs@MIPs

Properties of CNTs

Many studies have been carried out to use CNTs as analytical tools. Some of the most salient properties of CNTs are summarized below for facilitating further research. There are also some inclusive reviews recommended for reading in case of further interest [48, 49].

(1) Nonpolar bonds and high aspect ratios (length to diameter ratio) lead to the insolubility of CNTs in water and their spontaneous aggregation. Meanwhile, in a few kinds of organic solvents, such as DMF (dimethyl formamide), DMAc (dimethyl acetamide) and dimethyl pyrrolidone, they show passable dispersibility [50]. Their insolubility and inclination to aggregation diminish the actual surface/area ratio [51]. High surface/area ratio is one of the useful properties of CNTs, hence, intensified research on their disaggregation has been conducted.
(2) As many other organic materials, CNTs can be functionalized covalently [52, 53]. In most case, CNTs are chemically inert. But defects on the walls and small bond angle of the orifices makes carbon atoms in the defects and orifices more prone to be oxidized [54]. Under extreme chemical conditions, hydroxyl or carboxyl groups can be grafted onto the pipe walls and pipe orifices.
(3) High electron mobility and electrical conductivity are also remarkable properties of CNTs. The arc-produced MWNTs are not be damaged under the current densities of $J>10^7$ A·cm^{-2} [55]. These properties have been exploited to develop electrochemical sensors. These characteristics are contributed by the π orbital electrons delocalized across their hexagonal atomic arrays. Indeed, the arrangement of the hexagonal arrays determine the electronic capability of CNTs. As a result, CNTs can be metallic or semiconducting.
(4) Owing to their high surface area to volume ratio and excellent physisorption performance, CNTs had been applied to solid-phase extraction (SPE), sensing, and hydrogen storage devices for years [56], and the absorption behaviors of CNTs towards many chemicals have been studied [57–60].

Synthesis of molecularly imprinted polymers on the surface of CNTs

To date, non-covalent approach is prevailing in the analytical molecular imprinting field, so the following discussion is specifically concerned with non-covalent approach. In general, synthesis steps of CNTs@MIPs include: First, commingle the templates (i.e. analytes) and functional monomers in solution, after incubation, the templates and functional monomers interact via non-covalent bonds. Then, initiated by an initiator and helped by crosslinkers, the monomers are polymerized around the templates. After polymerization, the materials are washed repeatedly by large amount of eluent (solvents that can dissolve the templates) to remove the templates, thus there are special cavities exposed. They can specifically rebind the template molecules [61]. To create high performance MIP, it is quite significant to select the templates, monomers and other reagents and apply efficient polymerization methods.

Selecting the templates

MIPs were often prepared for designated analytes. Binding sites in the cavities are determined by the structure and functional groups of the analyte. The norm of selecting templates contains the necessity, availability, cost etc. Most important, the chemical properties of templates should be considered. First, there should be certain chemical groups on the template for interacting with functional monomers. In non-covalent approach, because of the weak interplay, templates with multiple binding sites should be favored for strengthening self-assembling. Templates of commercialized MIPs contain aromatic rings or groups capable of hydrogen bond (clenbuterol [62], beta-agonists [63] and tobacco-specific nitrosamine [64]). Second, the templates should be stable under the reaction conditions, otherwise the imprinted molecules would be random by-product of the templates. Finally, there should not be any groups in the templates which might inhibit or participate in the polymerization.

For most cases, the molecules imprinted and rebound are the same, but when the templates were hard to obtain, inappropriate for the syntheses [65, 66] or hard to be completely removed from MIPs, structural substitutes (i.e. dummy templates) can be used in the syntheses. When using MIPs as SPE materials, for avoiding templates leakage, the dummy templates could be used. This approach shows its significance in the trace or ultra trace detection field because any template leakage should be different from the analyte and could be easily detected. The substitutes should conform to the target analytes in respect of shape, size and characteristic groups. According to the structure of dummy templates, this technology can be divided into fragment imprinting [67] and interval immobilization [68], progress in this field has been reviewed by Chen [9].

Selecting the other reagents

Methacrylic acid (MAA), 2-or 4-vinylpyridine (2-VP or 4-VP) and several silylating agents are widely used as functional monomer, tailor-made functional monomers were also reported [69, 70]. Apparently, monomers capable of strong

interactions with templates were favored. Computational design and nuclear magnetic resonance was exploited for selecting functional monomers [71, 72]. The strength of interactions can be simulated and easily tested between various kinds of functional monomers and templates. In the work of M.B. Gholivand et al. [73], they tested 18 kinds of functional monomers and various kinds of solvents using molecular modeling. NMR of functional monomers and template mixture can also assist evaluating the interactions [36]. These methods increase the time and effort required for synthesis and charcterization. Recently, C. Baggiani et al. reported a theory that the MIP binding properties is corresponding with NIP (nonimprinted polymer) binding properties [74]. Using this theory, a huge amount of work might be economized.

The choice of crosslinkers is also very significant since the binding capacity is affected by different crosslinkers [75]. In the work of C. Michailof et al. [76], pentaerythritol triacrylate (PETRA), ethylene glycol dimethacrylate (EDMA) and divinylbenzene (DVB) were compared for synthesizing MIPs for caffeic acid. The binding effect can be impacted by the content and proportion of crosslinkers [77].

Choosing of porogen is very critical since the assembly between the functional monomers and templates was correlated with the chemical and physical properties of porogen. In one hand, the porogen should be able to dissolve the templates and the monomers. In the other, the porogen should not interfere the interplay between the functional monomers and templates. In free radical polymerization approach, a non to medium polar solvent is used as porogen, most importantly, this solvent should be aprotic (e.g. toluene, chloroform, DMF and DMSO). So, under protic conditions, metal chelating method is preferred because metal coordination interaction is still effective in protic solvents. Recently, there were studies reported of using methanol, ethanol even water as porogen [78, 79], however, no such articles has been found in the CNTs@MIPs field. In sol–gel approach, porogen is not so restricted, alcohol, ACN and water were used as porogen [80–82].

Some works are reported in Table 1 for comparison of different functional monomers, crosslinkers, initiators and porogen solvents. And some of the pioneering advances made to date are illustrated in Fig. 3.

Steps and methods of synthesizing CNTs@MIPs

Generally, surface imprinting means creating thin MIP films on suitable substrates, which exploit the concept of core-shell system. Using this system, the thickness of MIP shell can be accurately controlled by regulating the time span of syntheses and amounts of monomers. High absorbance is obtained by thick MIP shell and when frequent mass transfer was needed, thin MIP shell can be employed.

Functionalization of CNTs

First, the MWNTs should be functionalized to improve their reaction activity and dispersity. The methods can be divided into covalent and non-covalent functionalization. Covalent approach involves serial stages: (1) The crude MWNTs were treated with strong acids or strong oxidants to remove impurities as amorphous carbon and metal catalyst, and to obtain shorter MWNTs with carboxylic groups. (2) MWNTs-COCl was subsequently obtained by treating with thionyl chloride. (3) Allyl alcohol or allylamine was used for producing MWNTs-CH=CH_2 [84, 90]. These groups enhance the solubility and dispersity of MWNTs, and also increase the jointing strength between MWNTs and MIP films.

The first to graft MIP films on the surface of functionalized CNTs was reported by Lee et al. [99]. CNTs were decorated with acrylated Tween 20 by hydrophobic interactions. Then they were incubated with photoinitiator for polymerization. This method has a main flaw that the polymerization takes place in solution because the photoinitiator might be dissociated in solution. So they modified their method by introducing 3-chloropropyl groups then photoactive iniferter to the surface of Tween 20 decorated CNTs [100]. With iniferter bounded to CNTs, this problem was basically solved. A 9-vinylanthracene functionalized CNTs@MIPs were reported, this method was facile and environment-friendly [101]. These foregoing approaches are functionalizing CNTs through non-covalent adsorption.

Materials incorporated with CNTs@MIPs

In our knowledge, various kinds of nanoparticles were incorporated on MWNTs (e.g. gold, SiO_2 and Fe_3O_4 nanoparticles [13, 80, 102]). Gold nanoparticles are easy to prepare and possess a large surface area, most important, they were added for improving the electroconductivity of MIPs. So gold nanoparticles incorporating was common in the area of MIP based sensors [95, 96, 103, 104]. SiO_2 often form into shells which provided a biocompatible and hydrophilic surface, and prevented oxidation of Fe_3O_4. Furthermore, silanol groups simplifies chemical modification on the surface of Fe_3O_4@SiO_2 [80, 105, 106]. Once formed, the Fe_3O_4 nanoparticles become magnetic, which enables the entire CNTs@MIPs easily separated under an external magnetic field [14, 86, 93, 102, 107]. Table 2 shows some works using different kinds of materials incorporated on MWNTs.

Polymerization methods

Free radical polymerization and sol–gel process are two main developed methods to obtain CNTs@MIPs, some of the typical work were also summarized by Table 2. In the free radical

Table 1 Examples of different methods and conditions for MIP preparation

Target analyte[a]	Functional monomer[b]	Crosslinker[c]	Solvent[d]	Initiator/Catalyst[e]	Ref.
triclosan	APTES or PTMOS	TEOS	ethanol	HAc	[80]
ofloxacin	Pyrrole	None	H_2O	NaOH	[88]
prometryn	MAA	TRIM	toluene	AIBN	[89]
erythromycin	acryloyl-β-CD, MAA	EGDMA	ACN	AIBN	[81]
uric acid	MAA	TRIM	ACN,toluene	AIBN	[90]
TCP	MA, 4-VP	EGDMA	DMSO	AIBN	[91]
oxacillin	PTMOS, MTMOS	TEOS	ethanol	HCl	[92]
Streptomycin	APTMS	TEOS	PEG, EE, H_2O	HCl	[93]
p-nitrophenol	PTMOS, MTMOS	TEOS	ethanol, H_2O	HCl	[82]
tyramine	PTEOS	TEOS	ethanol, H_2O	HCl	[61]
theophylline	o-Phenylenediamine	None	HAc-NaAc buffer	None	[94]
triazophos	o-hydroxyphenol	None	H_2O	$NaClO_4$	[95]
chlortetracycline	CSDT	EGDMA	DMSO	APS	[96]
Troponin T	Acrylamide	NNMBA	buffer solution	APS	[97]
dopamine	NPA	EGDMA	DMSO	BDC	[98]
insulin	AEP	EGDMA	DMSO	AIBN	[69]

[a] *TCP* 2,4,6-Trichlorophenol

[b] *APTES* aminopropyltriethoxysilane; *PTMOS* phenyltrimethoxysilane; *MAA* methacrylic acid; *β-CD* beta-cyclodextrin; *MTMOS* Methyltrimethoxysilane; *CSDT* chitosan derivative; *NPA* 4-nitrophenyl acrylate; *AEP* (p-acryloylaminophenyl)-{(4-aminophenyl)-diethyl ammonium}-ethylphosphate

[c] *TEOS* tetraethylorthosilicate; *EGDMA* ethylene glycol dimethacrylate; *NNMBA* N,N-methylenebisacrylamide

[d] *PEG* polyethylene glycol; *EE* ethoxyethanol

[e] *APS* ammonium persulfate; *BDC* N,N-diethyldithiocarbamate

polymerization method, polymerization of vinyl or acrylic monomers are initiated and accelerated by free radicals which are attained by thermal or photic decomposition of initiators. While azo-initiators, especially azo-bisisobutyronitrile (AIBN), were commonly used, photo-initiators allow preparing MIPs at mild temperature, which enables temperature-sensitive templates to be imprinted [108]. Novel technologies (as controlled/living free radical polymerization (CLRP), microwave-assisted heating and ionic liquid as porogen [109–111]), considered advantageous, were applied in traditional MIPs synthesis, but they were not reported in the CNTs@MIPs field yet.

Free radical polymerization remains the most commonly applied method for the preparation of CNTs@MIPs. The radicals decomposed from initiators allow reaction with various monomers and diversified templates, which expand the application area in molecular imprinting. But the high catalytic activity of these radicals can result in unnecessary

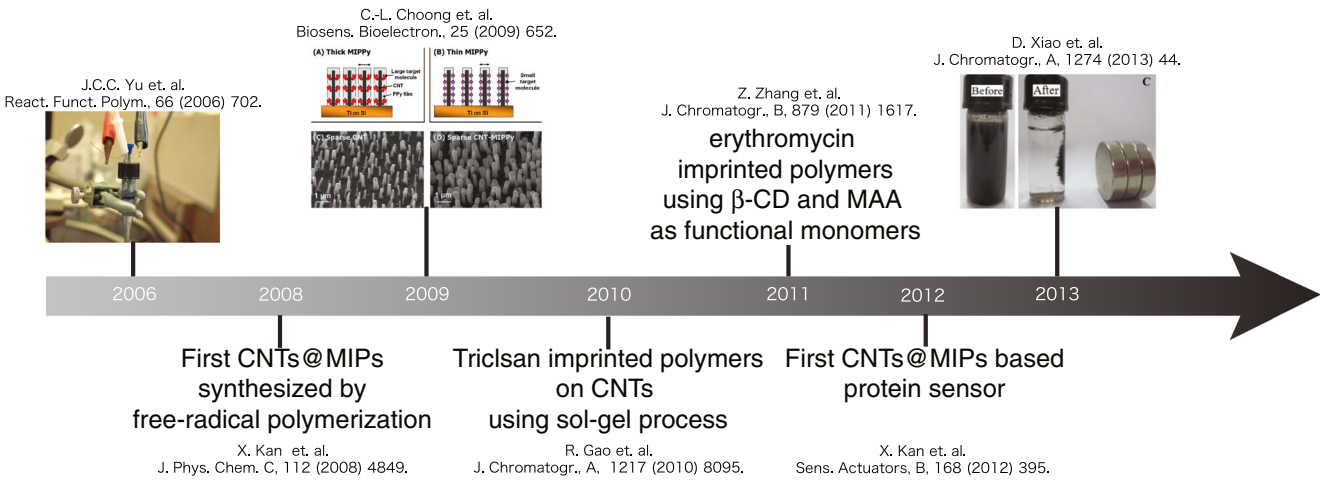

Fig. 3 Timeline showing recent published works regarding CNTs@MIPs. Reproduced from Refs. [80, 81, 83–87]

Table 2 Examples of different materials incorporated on MWNTs for MIP preparation

Target analyte	NPs or materials[a]	Strategies	Ref.
triclosan	SiO2	sol–gel process	[80]
BSA	MNPs/CS	Electropolymerization	[86]
mercury(II)	Gold NPs	Electropolymerization	[103]
Estrone	SiO2	Semi-covalent imprinting	[106]
oxacillin	Cobalt NPs/CS	sol–gel process/electrodeposition	[92]
Streptomycin	Fe_3O_4@Au-CS nanocomposites	sol–gel process/electrodeposition	[93]
p-nitrophenol	ZnO NPs/CS	sol–gel process/electrodeposition	[82]
tyramine	Gold NPs/ CS	sol–gel process/electrodeposition	[61]
chlortetracycline	Au-PAMAM nanocomposites	Free radical polymerization	[96]
BSA	Fe_3O_4 NPs	Free radical polymerization	[14]

[a] *MNPs/CS* chitosan coated magnetic nanoparticles; *NPs* nanoparticles

subsidiary reaction, and the rigid condition of porogen confines the imprinting of many water-soluble molecules.

In sol–gel process, silicon alkoxide monomers are hydrolyzed and then polycondensated to produce an imprinted silica polymer network, these reactions are catalyzed by acids or bases [112]. In this fashion, the pH of pre-polymerization mixtures can be adjusted based on the requirements of templates, protic solvents such as water and alcohol should be used, and nitrogen is no longer required. Enjoying the versatile process and mild condition, a wider range of molecules can be imprinted in sol–gel process.

Electropolymerization was commonly used in the area of MIP-based sensors. This method was comprehensively reviewed by several teams, their works are recommended for reading [72, 113, 114], some of the typical research papers are as listed [115, 116].

Polymerization methods can be also sorted into "grafting-to" and "grafting-from", according to the growing pattern of the polymers [117, 118]. As the name implies, "grafting-to" method is physically coupling macromolecular polymers on the materials or chemically coupling polymers on reactive groups of the materials, "grafting-from" method concerns covalently attaching initiators on the substrates and then grafting polymers in situ. Exploiting grafting-from method, polymerization in the solution can be remarkably reduced, thus the synthetic efficiency and regularity of the polymers is greatly enhanced. In the field of molecular imprinting, little research has been done exploiting the "grafting-from" methods [119]. But we foresee that these theories will be an inspiration for the synthesis of MIPs.

Applications

As observed from Fig. 4, the number of research articles about CNTs@MIPs augmented over the years due to their excellent properties and great versatility, illustrating their potential in multiple fields.

Solid phase extraction (SPE)

Most of the trace analytes existing in environmental or biological samples are critical for human health. Industrial materials unlawfully added into food products [120] or food contaminants [83] were considered as toxic or carcinogenic; the residues of some widely used antibiotics [88] in the environment and food chain may cause the spread of drug resistant microbes; some of these chemicals are accumulated through the food chain. These exigencies encourage researchers to develop fast and sensitive analytical methods applicable in aqueous samples.

Given its rapidity (when compared to traditional methods), conventional SPE has become a major procedure for sample treatment. It can precontrate target compounds but cannot eliminate most of the interferences. In view of its high selectivity, MIP-based SPE can determine even low-concentration analytes without intricate pretreatments and diminish most interferences.

On-line solid phase extraction

Though ease of commercialization and rapidity while analysis is enjoyed, the fabrication of MIP-based on-line SPE devices is more complicated than off-line ones. So the progress in recent years is not significant as expected. The devices were mainly produced in the format of columns [120] and steel frits [83].

An SPE microcolumn for Sudan IV online detection was achieved by Zhang and his team, using APTES-MWNTs as functionalized MWNTs, PTMOS and MTMOS as functional monomers, TEOS as crosslinker, acetone as porogen solvent [120]. The enrichment ratio of the CNTs@MIPs is up to 741-fold and the MIPs shows good recognition ability for Sudan

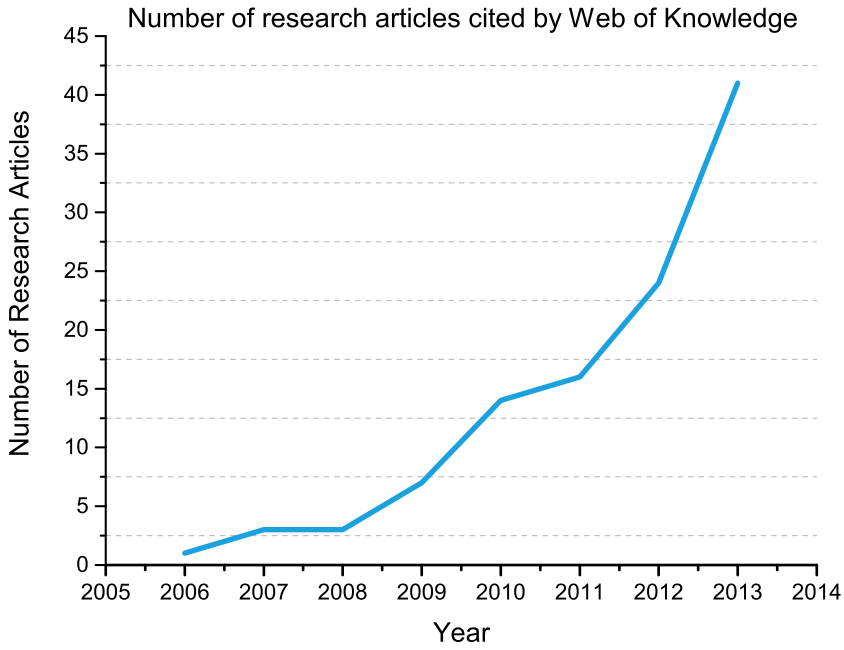

Fig. 4 Number of research articles about CNTs@MIPs which cited by Web of Knowledge

IV. However, beyond the pH range of 6.0–6.8, the performance of imprinted column showed a notable decrease. Using "grafting-from" method, the author claimed that APTES assists the polymerization taking place on the MWNTs, but no experimental evidence was given. They also implied experimental results would be better with binary functional monomers, which was proved by many other papers [81, 121, 122].

Yu et al. obtained a molecular imprinted polypyrrole (MIPPy)/MWNTs steel frit by electropolymerization for on-line SPME (solid phase micro extraction) coupled with HPLC analysis of ochratoxin A [83]. The schematic diagram of this device was shown in Fig. 5. The results demonstrated a significant enhancement of selective binding for OTA compared with a C_{18}-SPE cartridge. Using red wine volume of 30*100 μL for preconcentration, the detection and quantification limits are down to ppt scale. Nevertheless, the reproducibility is not good as traditional methods because this method needs multiple sample injection.

Off-line solid phase extraction

There are many forms of off-line MIP SPE, e.g. fiber [88], cartridge [81] and syringe [123]. Different synthetic methods are listed in the following text by reviewing several representative works, such as electropolymerization [88], binary functional monomers [81], ion imprinting [124], sol–gel process [80] and free radical polymerization [87, 125].

An MIPPy/MWNTs/Pt fiber for SPME of fluoroquinolones (FQs) was made by Liu et al. [88]. The device was shown in Fig. 6 The MWNTs were deposited electrophoretically onto a Pt wire, then pyrrole was electropolymerized. This fiber can simultaneously extract six types of FQs.

An CNTs@MIPs cartridge was synthesized by Zhang and his team using acryloyl-β-CD, MAA as functional monomers for the examination of erythromycin abuse in chicken breeding [81]. The MIPs using binary functional monomers took shorter time to reach adsorption saturation than traditional MIPs. Because the hydrophobic cavities of acryloyl-β-CD forms complexes with the water-insoluble erythromycin, the binary monomers MIPs exhibited more specific selectivity and better adsorption capacity. However, the performance of the SPE cartridge had not been compared with traditional SPE.

A Ga(III) (a heavy metal widely used in IT technology) ion-imprinted MWNTs column and a gold ion-imprinted column was synthesized recently [124, 126]. These methods were accurate and precise enough and performed good selectivity and cleanliness of the matrices but its linear range was not wide enough for various kinds of usage. The flaws should be blamed for the narrow linear range of atomic absorption spectrometry, not for the absorption capacities of MIPs.

A CNTs@MIPs column for selective removal and determination of triclosan was obtained by Gao et al. through sol–gel process [80]. In environmental water samples, after applied with their method, the peak of triclosan augmented distinctly and the peaks of other compounds were almost eliminated, while under direct injection, the peak of triclosan can not be seen (the results were presented in Fig. 7).

There is also primary form that directly blending SPE material with sample solutions. Though this blending approach is not advanced as other forms, it is quite simple if the imprinted materials can be separated from the sample

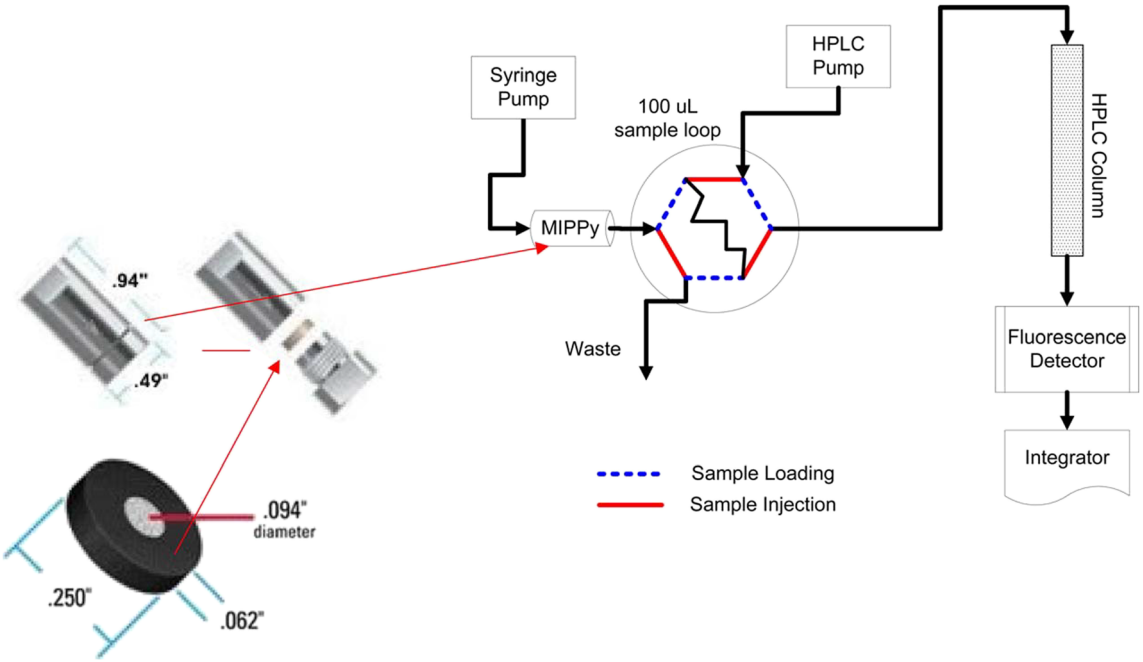

Fig. 5 MIPPy/CNT-μSPP-PE-HPLC-FLD instrumentation [79]

solutions by a straightforward way. Our team [87, 125] and some other researchers [127] have been working on CNTs@MIPs with magnetic property, which can be easily separated from the sample solution by an external magnet. We synthesized MIPs on the surface of magnetic CNTs for directly determining gatifloxacin in serum samples [87], and the simultaneous extraction of four FQs from egg samples [125].

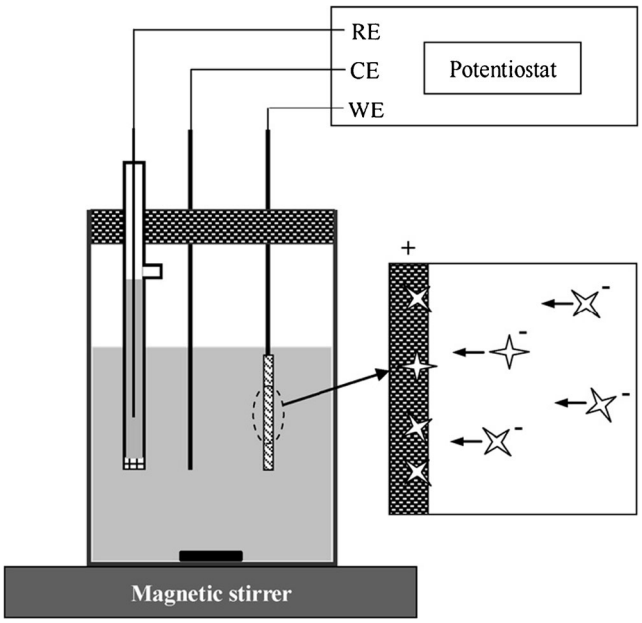

Fig. 6 Schematic diagram of EE-SPME extraction device based on molecularly imprinted conductive polymer/MWCNTs coating on Pt wire [119]

Chemical sensors

Sensitive and highly selective sensors were required for determining low content, hazardous substances or indicative, online-monitoring-needed compounds in complex matrices. Contributed by the premium electric properties of CNTs, high selectivity and robustness of MIPs, chemical sensors were held to be the most promising CNTs@MIPs applications (in the Web of Science database, the number of papers concerning CNTs@MIPs sensors was bigger than any other applications of CNTs@MIPs). The superiority of CNTs@MIPs over MIP sensors and CNTs sensors were also demonstrated by many publications [104, 128, 129].

CNTs@MIPs sensors were fabricated, in the main, by a simple drop-dry method. In particular, CNTs@MIPs were first synthesized, and templates were removed. Then the MIP suspension was dropped and dried on the surface of polished electrodes. Though it was believed that the stability and electronic activity of drop-dry sensors might not be good as electropolymerized or "grafting-from" ones [127], the reusability was yet quite outstanding because of the robustness of the imprinted cavities, and the sensors were functional after the electrodes were eluted by washing solutions [89].

In this part, we also chose some typical works in this area to elaborate on different methods of MIP-based sensor fabrication.

To the best of our knowledge, the first article reported CNTs@MIPs based biosensors were achieved by Zhang et al. [130]. Although preparing and working mechanisms of this sensor are not exactly conformed to general ones, but this initiative work has inspired considerable successors. The

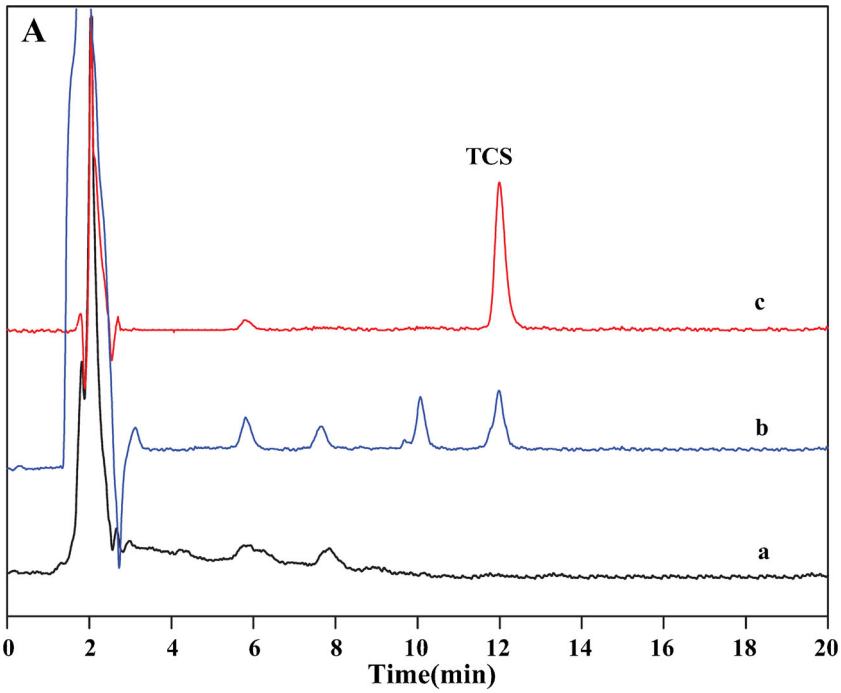

Fig. 7 Extracts from the original chromatograms of river water samples. **a** Samples spiked with TCS at the concentration of 0.5 μg L^{-1}, elution of (**b**) CNTs@NIPs and (**c**) CNTs@TCS-MIPs washed with a mixture of ethanol/6 M HCl (1:1, v/v) after CNTs@TCS-MIPs and CNTs@NIPs adsorbing 100 mL of river water spiked samples [76]

authors covalently attached the cofactor (NAD+) of glucose dehydrogenase to biopolymer CS, and the CNTs were added, ultimately, a CNTs-macrocomplexes film electrode detecting glucose was achieved. Because of the intricacy of the mechanism, sensitivity, stability and linear range of the sensor were moderate compared with up-to-date sensors.

Choong et al. electropolymerized an imprinted polypyrrole (PPy) film on carbon nanotubes which directly grow on a silicon substrate (the SEM images are shown in Fig. 8) [85]. The advantages of this method are remarkable: the thickness of the PPy film can be adjusted according to the molecular weight of the templates. And the binding capacity can be modulated by simply changing the CNTs height, density (number of nanotubes per area) and the thickness of the PPy. Cai et al. developed a similar but more elaborate constructed molecular imprinting sensors made for human ferritin and human papillomavirus derived E7 protein with sub pg L^{-1} sensitivity [131]. Though too complicated to be practical, this work offered us an innovative design in the field of MIP sensors [132].

A sensor based on free radical polymerized CNTs@MIPs for parathion-methyl (a highly toxic pesticide) determining was prepared by Zhang et al. [133]. This sensor was successfully applied in the detection of parathion-methyl in pear and cucumber samples with recoveries ranging between 94.9 and 106.2 %, and RSD less than 5 % (n=5). However, so many processes were employed in the real sample pre-treatment, that the practicability of this sensor should be doubted. Based on free radical polymerization, an electrode coated with CNTs@MIPs and gold NPs for the detection of chloramphenicol were fabricated [104]. It is worth mentioning that in the concentration range of 2–40 mg L^{-1}, the recoveries and RSDs of chloramphenicol sensor were quite close to HPLC method (92.5–105 % vs 95.5–110 %, 3.2–12.5 % vs 0.9–14.8 %).

Several CNTs@MIPs real sample detecting electrodes were fabricated by Prasad et al. using state-of-the-art technologies, such as tailor-made functional monomer for insulin detection [69], tailor-made functional monomer and crosslinker for bovine serum albumin (BSA) detection [108]. For the insulin sensor, the excellent performance (for blood serum samples, the linear range is between 0.068 and 5.682 nmol L^{-1} with RSD of 0.9 %, n=3) should be attributed to the fact that the tailor-made functional monomer restricts non-specific proteins adsorption. Tailor-made functional monomer and crosslinker were used for the water compatibility of the MIPs. They also fabricated a dopamine electrode using "grafting-from" method [98]. When synthesizing dopamine electrode, the MWNTs were coated by iniferter (initiator transfer agent terminator) first, because of the immobilized iniferter, polymerization occurs on the surface of CNTs.

Synthesized through electrochemical copolymerization, based on $Ru(bpy)_3^{2+}$-Au nanoparticles, a molecularly imprinted electrochemiluminescence (ECL) sensor was proposed by Wu et al. to selectively determine isoniazid (a wonder drug for tuberculosis but has serious adverse effects when overdosing) [129]. For tablet samples, the analytical data were consistent with China Pharmacopoeia method (RSD=3.2 % while the RSD of Pharmacopoeia method is 3.6 %) and the sensor was also successfully applied to determine isoniazid in human urine and pharmaceutical samples

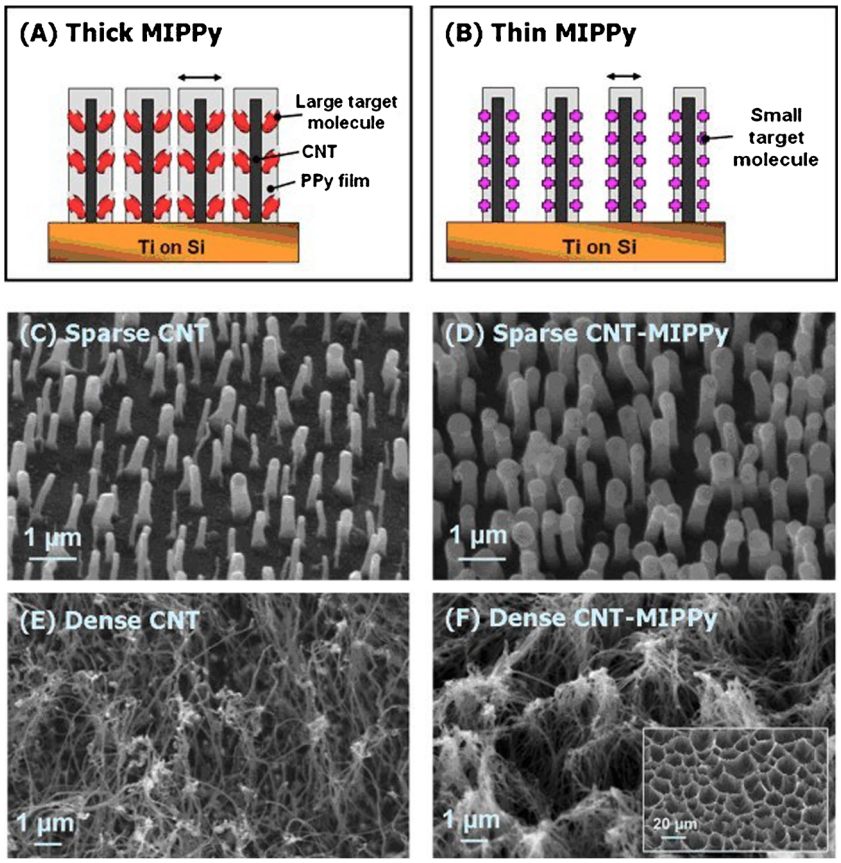

Fig. 8 **a** and (**b**) Schematic illustration of the concept of high density, surface molecular imprinting technique using CNTs array. SEM images of a sparse CNTs array (**c**) before and (**d**) after caffeine imprinting electropolymerization. SEM images of a dense CNTs array (**e**) before and (**f**) after caffeine imprinting electropolymerization [81]

with the recovery of 96–102.5 %. It is worth mentioning that untreated urine samples can be analyzed.

Santos et al. made an imprinted sensor for caffeine using sol–gel process. Compared with previous works [134–136], the recoveries were excellent (98.0–103.8 %) for untreated real drink samples [137]. An indium tin oxide electrode modified by CNTs@MIPs via sol–gel technology was prepared by Zhang et al. for the detection of L-histidine [128]. It was successfully employed to detect L-histidine in human blood serum (the recovery is 96.7–101.4 %). The authors did not specify what treatment they used in the serum sample. If raw serum were used, this method is quite promising in clinical test.

Conclusions and perspectives

The current status, synthetic approaches and highlighted applications of CNTs@MIPs have been described in this review. In conclusion, CNTs@MIPs retain the affinity and selectivity of antibodies, enzymes or biological receptors, while adding several benefits including high mechanical strength, large specific surface area and chemical stability. Much work has been performed to resolve the existing problems hindering the development of CNTs@MIPs and the commercial potential has been proved by considerable MIP products during past years.

Although remarkable achievements have been attained in CNTs@MIPs, there are still substantial development challenges and opportunities. We attempt to tackle some important exploration initiatives as follows: (1) to improve the dispersibility of the CNTs in organic phase or aqueous phase, reaching high efficiency of molecular imprinting process; (2) to design and exploit new, convenient polymerization methods (e.g. CLRP, microwave-assisted heating) for molecular imprinting on the surface of CNTs for higher binding capacity and selectivity; (3) to explain the recognition mechanism and the role of CNTs at the molecular level with the aid of advanced equipment, especially the imprinting mechanism of sol–gel method; (4) to broaden imprinting targets from small molecules to proteins in order to make CNTs@MIPs a truly practical tool for molecular recognition and a promising commercial product for real applications.

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