

Review

Molecularly Imprinted Plasmonic Sensors for the Determination of Environmental Water Contaminants: A Review

Patrícia Rebelo *, Isabel Seguro , Henri P. A. Nouws , Cristina Delerue-Matos  and João G. Pacheco *

REQUIMTE/LAQV, Instituto Superior de Engenharia do Porto, Instituto Politécnico do Porto, Rua Dr. António Bernardino de Almeida 431, 4249-015 Porto, Portugal; mgsp@isep.ipp.pt (I.S.); han@isep.ipp.pt (H.P.A.N.); cmm@isep.ipp.pt (C.D.-M.)

* Correspondence: patricia.rebelo@graq.isep.ipp.pt (P.R.); jpgpa@isep.ipp.pt (J.G.P.)

Abstract: The scarcity of clean water leads to the exploration of the possibility of using treated wastewater. However, monitoring campaigns have proven the presence of emerging contaminants, such as pharmaceuticals, pesticides and personal care products, not only in trace amounts. Various analytical methodologies have been developed over the last years for the quantification of these compounds in environmental waters. Facing the need to achieve a higher sensitivity, fast response and practical use via miniaturization, the potential of plasmonic sensors has been explored. Through the introduction of molecularly imprinted polymers (MIPs) as recognition elements, MIP-based plasmonic sensors seem to be a good alternative for monitoring a wide range of analytes in water samples. This work attempts to provide a general overview of this form of sensor, which has been reported as being able to sense different contaminants in waters using surface plasmon resonance (SPR) and surface-enhanced Raman-scattering (SERS) techniques. Particular emphasis is given to the fabrication/recognition procedure, including the preparation of MIPs and the use of metals and nanomaterials to increase the performance characteristics of the sensors.

Keywords: molecularly imprinted polymers; plasmonic sensors; surface plasmon resonance; surface-enhanced Raman scattering; environmental monitoring; water



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1. Introduction

The world's freshwater sources are currently facing a serious challenge. While pollution is reducing the water supply, climate change, population growth, urbanization and industrialization are all driving up water demand [1,2]. As a result, alternative water sources are being explored to ensure sustainable water management [3–5].

The reclaiming of treated wastewater has emerged as an additional and alternative water supply source than is able to buffer the impacts of water scarcity [6–8]. However, the successful implementation of wastewater reuse is strongly dependent on appropriate treatments in accordance with the type of use and water quality requirements, where the main concern is still the determination what compounds must be completely removed and to what extent in order to safeguard public health and protect the environment [3,9,10].

Pharmaceuticals, personal care products, pesticides, insecticides, heavy metals and other anthropogenic chemicals constitute a significant class of contaminants of emerging concern (CECs) detected in wastewater effluents and influents, surface water, groundwater, seawater and tap water around the world at concentrations higher than expected [11]. CECs can enter the environment through multiple sources, but currently, it has been recognized that the presence of many CECs in water bodies is closely connected with discharges from wastewater treatment plants (WWTPs), in which these compounds are poorly eliminated [12–14]. To respond to this situation, advanced chemical, physical and biological treatments have been explored to improve the efficiency of the treatments before discharge of water [15,16]. At the same time, there is still a need to better investigate individual CECs by developing rapid, accurate and cost-effective measurement techniques

able to first characterize and quantify these compounds in different environments [17]. Although their potential ecotoxicity and adverse effects on human health have been widely documented throughout the last decade, most remain unregulated [18–21].

Conventional analytical methods for the detection and quantification of the above contaminants in water samples include chromatographic techniques, such as gas chromatography mass spectrometry (GC-MS) and high-performance liquid chromatography mass spectrometry (HPLC-MS) [22–24]. These methods exhibit good detection sensitivity and specificity but are limited by the costs and long analysis time associated with the analytical procedure, which make them unsuitable for real-time monitoring [25]. As an alternative, biological and chemical sensors have been widely considered for the development of new detection strategies. In particular, intense research is being conducted on bio-inspired molecularly imprinted polymers (MIPs) sensors. Based on a combination with a variety of transducers, MIPs have found applications in various fields, including biology, chemistry and the environment, due to their ease and cost-friendly preparation, high stability and selectivity, as well as versatility in terms of working conditions [26,27]. Despite electrochemical transducers being the most commonly used for sensor development, plasmonic platforms have witnessed special attention in the field of optical sensing. Their ability to characterize molecular interactions with impressive sensitivity and provide label-free detection has the potential to revolutionize disciplines such as environmental monitoring [28].

Surface plasmon resonance (SPR) and surface-enhanced Raman scattering (SERS) are two key-surface plasmon techniques that allow the identification of trace amounts of a wide variety of different analytes [29]. SPR sensors, a metal film-based sensor, have been the basis of current research on plasmonic sensors, and several recent publications have shown that the design of SPR sensors combined with MIPs as recognition element is very favorable for highly sensitive and selective analysis. The sensing mechanism relies on the optical measurement of the plasmon shift caused by the binding of target analytes to MIPs immobilized onto noble metal-coated substrates, namely gold (Au) or silver (Ag) [30–32]. SPR are highly responsive to deviations in the refractive index (RI) of the medium in direct contact with the metal film, and their efficiency could be further enhanced using different plasmonic nanostructures, whose behavior also provides the basis for SERS effects. SERS is another phenomenon that arises due to the SPR mechanism, making use of the enhanced electromagnetic fields near metallic nanostructures to study the molecular information of adsorbed analytes [33]. Despite the engineering of ultra-high-quality substrates having been focused on SERS sensor development, enhancing selective responses in the presence of a complex matrix have emphasized a MIPs–SERS combination approach [34].

Theoretically, MIP-based SPR and SERS sensors can be prepared for any molecule of interest. Their utility and versatility are widely recognized. Moreover, their ultrasensitive chemical sensing has shown great potential in addressing challenges in water contaminants monitoring. Piezoelectric sensors, such as quartz crystal microbalance (QCM) sensors, which are one of the most used mass-sensitive sensors in the MIP community, also offer high sensitivity to mass changes occurring on their surfaces and present versatile sample compatibility [35]. Additionally, QCM sensor coatings are very versatile, and the technique requires less complex instrumentation in comparison to optical sensing. However, QCM sensors typically require a relatively higher sample volumes for effective measurements than SPR and SERS sensors [36].

The scope of this review is to provide an overview of current approaches of MIP-based SPR and SERS sensors reported for the analysis of a vast array of contaminants in environmental water samples, including sensing principles and signal enhancement mechanisms. Recent examples in this field are presented with a focus on the polymerization technique, functional monomers and sensing platforms and the comparison of their performances. Lastly, the challenges and perspectives regarding the use of this kind of sensors for contaminant analysis are discussed.

2. Molecular Imprinting Technology

MIPs are tailor-made synthetic materials that mimic natural receptors using imprinting technology to provide selective binding sites to recognize a specific target molecule. MIPs were reported for the first time 50 years ago by Wulff and Sarhan [37]. Initially, these polymers were used for the resolution of racemates, focusing on separation and extraction techniques, but, over the years, they found numerous applications based on the principles of molecular recognition. Today, they are employed in various different research fields, such as drug delivery systems, chromatographic separation, reagent purification, industrial safety and chemical sensing [38–40].

The molecular imprinting technique involves the copolymerization of a target molecule, acting as a template, with functional monomers in the presence of cross-linking agents to form a three-dimensional polymer network (Figure 1). The polymerization reaction is triggered by an initiator [41]. After this process, the removal of the imprinted molecules reveals specific binding sites that are complementary in shape and size to the analyte, generating a highly specific molecular recognition element [42]. To determine the imprinting efficiency of the prepared MIP, a non-imprinted polymer (NIP) is also prepared in the same conditions but without the template molecule.

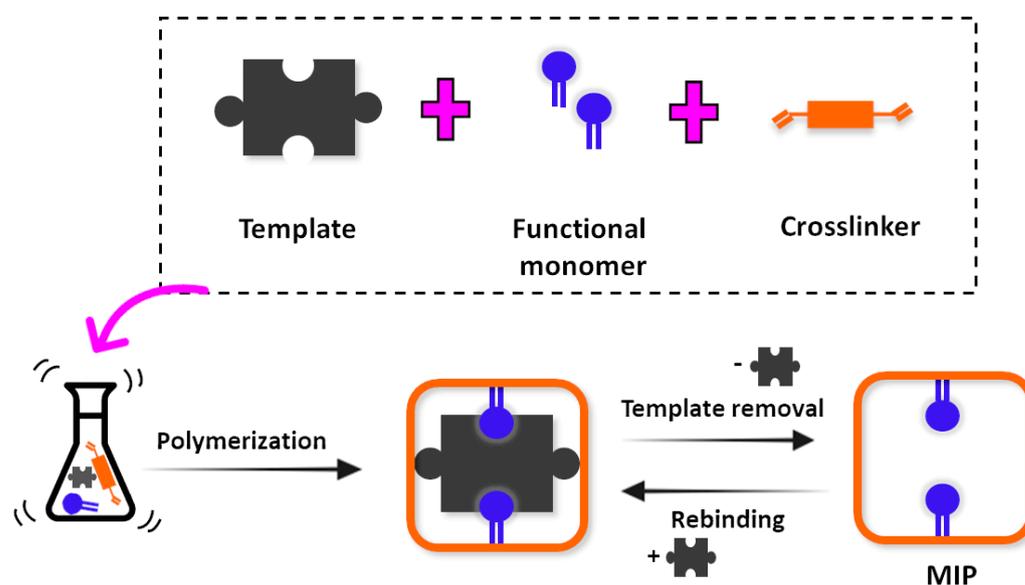


Figure 1. MIP preparation process.

There are two major molecular imprinting strategies that differ in the type of interactions between the template and the functional monomer, namely, the covalent approach reported by Wulff and co-workers in the early 1970s and the non-covalent approach pioneered by Mosbach et al. in the 1990s [43,44]. Covalent imprinting is suitable for reversible condensation reactions, which are limited, so this approach is the less flexible [45]. Furthermore, the strong interactions in this type of imprinting method drive the slow binding and removal of templates. In the non-covalent imprinting approach, the interaction of the template molecule with functional monomers is mainly based on ionic interactions, van der Waals forces, π - π interactions and hydrogen bonding (the most popular). This process is simpler and the removal and rebinding of the molecules in the polymeric matrix is faster. Therefore, non-covalent imprinting has become the most widespread method for preparing MIPs.

MIPs as Recognition Elements for Sensors

MIP-based recognition elements have been integrated into many sensing devices to translate molecular binding into a measurable signal. This combination has allowed the

detection of a wide range of analytes in various mediums using different procedures and imprinting methods [27].

The most conventional synthesis approaches for generating MIPs range from bulk polymerization to other new imprinting strategies, such as emulsion, suspension, seed and precipitation polymerization, where the initiation process can be triggered by thermal, photochemical or radiation energy. While bulk polymerization results in polymer monoliths that require mechanical grinding, emulsion, suspension and seeds, precipitation polymerization provides spherical MIPs, ranging from low-micron to sub-micron sizes which are ready for different analytical applications [46,47]. More recently, the fabrication of MIPs using sol-gel techniques was introduced. Molecular imprinted sol-gel systems involve the use of silica-based materials to integrate the template into rigid inorganic or inorganic–organic networks [48]. This approach has been reported as a good method for improving MIP sensor performance due to its inherent porosity, optical transparency, large surface area and high thermal stability with controllable pore size [49,50].

In fact, synthesizing surface-imprinted polymers directly on the surface or outer layer of a specific carrier has demonstrated an improvement in the sensitivity and selectivity of MIPs, as well as in the reproducible performance of the receptors. In surface imprinting, binding sites are located at or close to the polymer surface and are readily exposed to targets, facilitating the removal and subsequent rebinding of template molecules [51,52]. A surface-grafted MIP film can be obtained by depositing the pre-polymer first and imprinting it through soft lithography techniques, such as microcontact imprinting or growing polymer thin films directly onto a conductive substrate [52,53]. Here, electrochemical deposition has gained a special emphasis, stemming from its simple, fast and highly reproducible procedure [54]. Using electroactive functional monomers, an adherent polymeric film is formed in the presence of the desired template by applying a suitable potential or range of potentials that causes its oxidation or reduction. Electropolymerization does not require the use of a cross-linking agent or an initiator. Moreover, the polymer film thickness can be controlled by varying the charge transferred during the synthesis (potential range, scan rate and number of cycles) [55].

In the literature, we can find various reports describing the successful development of integrating MIPs as a selective recognition layers with a wide variety of transducers [56]. Among electrochemical and mass-based sensors, optical MIPs sensors have received significant research interest mostly due to their simplicity in preparation and signal acquisition, as well as low achievable detection limits [51,57]. Indeed, optical sensors have emerged as a prospective strategy to satisfy the sensitivity requirements for monitoring environmental pollution, where the analysis of samples can be performed by using the unique emission and excitation wavelengths of a specific analyte of interest [57,58].

Optical changes resulting from the interaction between the analyte and the sensor surface are transformed into electrical signals by employing different transduction techniques [57]. Fluorescence, spectroscopy, SPR and SERS are the most commonly used optical sensing systems. Nevertheless, with the rapid development of technology, optical sensors based on SPR and SERS have been increasingly studied and applied in the field of environmental monitoring [28]. The first approach analyzes plasmon resonance variations in the presence of an analyte, while SERS aims to expand the intensity of the signals associated with the target analyte [59]. Both mechanisms are described below, as well as their performances in the detection and quantification of contaminants in aqueous media.

3. SPR Sensors

SPR is an optical physical phenomenon arising from the interaction of a polarized light with free electrons at the interface of a dielectric medium and a metal film. This technique generates an electromagnetic field with an exponentially decaying intensity into both the medium—a surface plasmon wave—and, under certain conditions, resonance effects, thereby reducing the reflected light intensity [60,61].

The first scientific record of surface plasmons dates back to 1902, when Wood observed anomalies in the light diffracted on a metallic diffraction grating [62]. Later, Fano concluded that these anomalies were associated with surface waves supported by the grating structure. In 1968, the optical excitation of surface waves was demonstrated by Otto [63] and Kretschmann [64] using different configurations. On basis of the attenuated total reflection (ATR), Otto suggested coupling the metal surface with a prism, allowing it to collect all the light. In this configuration, there was a thin air gap between the prism base and the metallic film, in which the surface plasmon waves were created [31]. On the other hand, Kretschmann proposed another configuration of the ATR method, where the metal layer was directly deposited on the prism instead of air, enabling a more efficient and simpler plasmon generation. These pioneering works established a convenient method for the excitation of surface plasmons and the potential of SPR for the study of metal interfaces, gas detection and biosensing was recognized in the early 1980s. The first commercial SPR biosensor was introduced to the market in 1990 by Biacore AB (originally Pharmacy Biosensor AB) to recognize protein–protein interactions [65,66]. Since then, SPR-based biosensors have shown significant advances, becoming powerful tools for characterizing and quantifying molecular interactions with one of the most important features: label-free detection ability [67].

The sensing principle of SPR sensors relies on the use of the evanescent field of surface plasmon to measure changes in the refractive index (RI) of the dielectric environment occurring in the vicinity of the sensor surface [68]. Consequently, any change that may occur near the plasmonic surface, such as the adsorption of molecules, causes changes in the local RI, which in turn causes changes in the characteristics of the surface plasmon wave [69]. Thus, SPR sensors are able to provide a very sensitive and real-time response to the binding or unbinding of target molecules on the sensor chip surface [70].

Generally, SPR sensor systems comprise three essential components: an optical unit, a transducing medium which interrelates relevant optical and (bio)chemical domains, and a detector [71]. The optical unit generates a light beam of a required wavelength to excite and interrogate surface plasmon waves. Three different optical systems are used: systems with prisms, gratings and wavelength guiders (for example, optical silica fiber). Prism couplers, also called instruments in the Kretschmann configuration, represent the most frequently used scheme for SPR sensing. The light wave passes through a glass prism with a high refractive index, and it is entirely reflected at a certain angle at the base of the prism coated with a thin metal layer. A surface plasmon excited propagates along the metal film, and field probes are introduced into the medium in contact with the metal film. Detection is accomplished by measuring the changes in the reflected light properties via a detector, which is based on the modulation approach used and records the intensity, wavelength or angular spectrum of the attenuated light [69]. A dark band can characterize the event and the incident angle at the resonant condition is called SPR angle or resonant angle. For real-time signal interpretation, this measurement is translated into a graphical depiction, where a dip in the curve presents the occurrence of surface plasmon resonance [67]. A typical scheme is depicted in Figure 2.

Resonance or response units (RIU) are used to describe the signal change that can be monitored to obtain a SPR sensorgram.

In surface plasmonic sensors, there are two distinct surface plasmon modes: the localized surface plasmon resonance (LSPR) and the propagating surface plasmon polaritons. The LSPR is characterized by the collective oscillations of electrons limited to metallic nanostructures that are excited independently of the incident angle, inducing an ultra-high localized electric field around the nanostructure. Unlike LSPR, the propagating surface plasmon polaritons are typically characterized through the oscillations of surface electrons on thin planar metal sheets [31,72]. Both modes have been described to have similar sensitivity towards the binding molecular events. However, surface processing is very important to improve the sensitivity, specificity and fixation rate of these sensors, and over the years, studies have explored novel surface-modified materials [73].

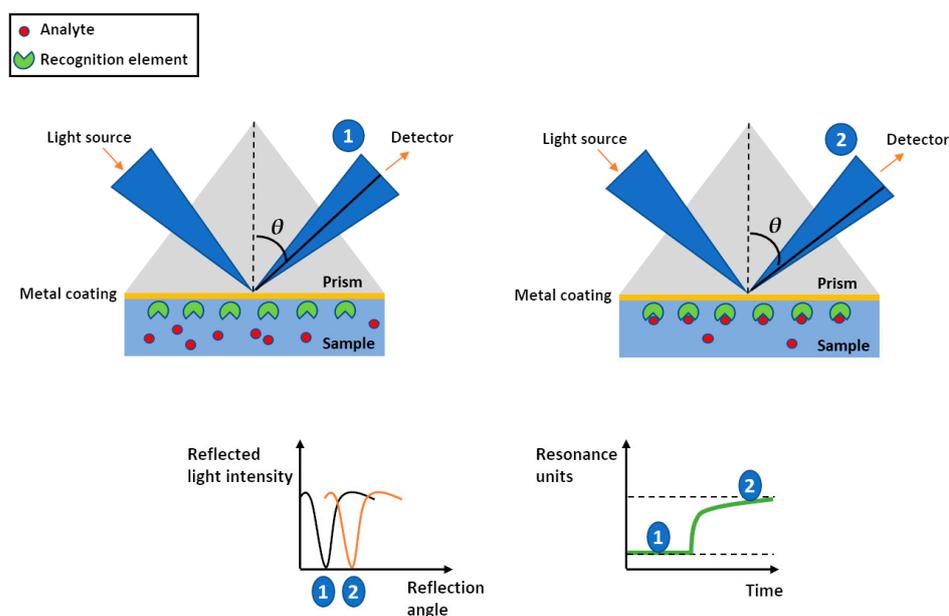


Figure 2. SPR-based sensing mechanism. The SPR angle shifts from (1) to (2) after molecular interaction on the sensor surface.

3.1. SPR Based (Bio)sensing-MIPS

In SPR (bio)sensing, (bio)recognition elements are immobilized on a SPR chip platform (typically a glass prism with a thin Au layer) and used to recognize and interact with the desired analyte in a liquid sample. Target molecules are generally transported through a microfluidic system by a buffer fluid and, when the recognition binding event takes place, an increase in the RI is detected and directly correlated with the amount of analyte/ligand complex formed at the sensor surface (Figure 3) [69]. In this sense, an appropriate surface functionalization plays a pivotal role in the sensor performance that can be specially affected by non-specific binding interactions [59]. Anything with the potential to modify the RI at the sensor surface will interfere with the detection procedure and generate a false positive signal. Considering that, several strategies have been developed to improve the selectivity of SPR sensing. An attractive and feasible strategy is molecular imprinting. The integration of nanoparticles, such as synthetic affinity receptors, into sensors has made a significant contribution to the recognition field.

One of the first applications of MIPS in SPR sensors was published by Lai et al. [74] for the on-site detection of theophylline, caffeine and xanthine in aqueous media. Since then, the possible fields of application of MIP-based bioreceptors in SPR sensors have expanded to medical diagnosis, environmental monitoring and food safety thanks to their high selectivity, simple construction, easy operation, rapid response, low reagent consumption, label-free and in situ monitoring, as well as no purification of the sample being required and their non-destructive analysis [75]. Such characteristics are especially attractive for satisfying the growing demand for the detection and identification of environmental contaminants, and consequently, MIPS have risen as a promising alternative to conventional environmental analyzing techniques.

As recognition units of SPR sensors, MIPS can be used either in film or nanostructured formats, in which it is very important to control the thickness of the polymer layer on sensor surface to guarantee reproducibility. Moreover, it should be taken into account that thinner films provide faster diffusion of the target molecules, contributing to an easier and more effective extraction and rebinding process, while offering better stability during longer SPR analysis [76].

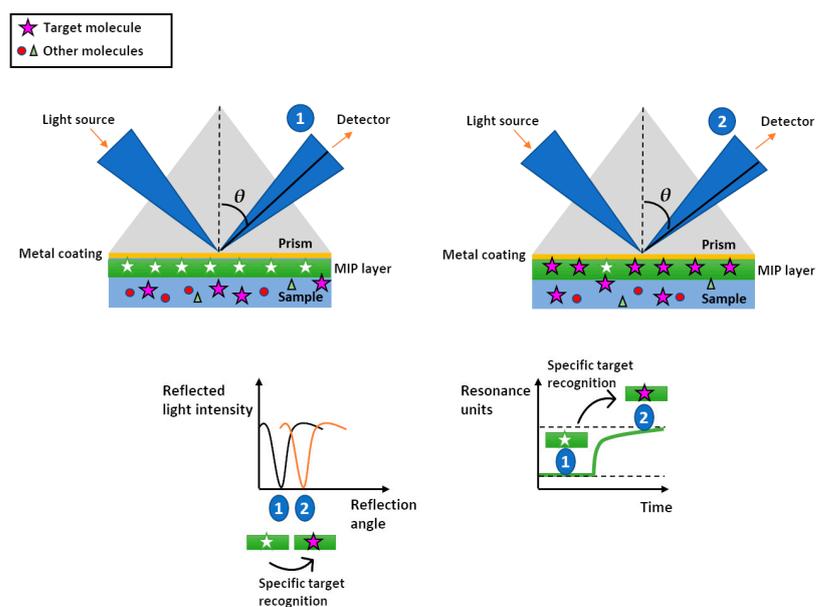


Figure 3. General process of MIP-based SPR sensing. The SPR angle shifts from (1) to (2) after the rebinding of the target molecule on the sensor surface.

Application of MIP-SPR Sensors in Water Contaminant Detection

Pharmaceuticals, pesticides, insecticides, metals and other contaminants, such as personal care products and industrial chemicals, are ubiquitous micropollutants in water bodies. Some of these compounds are considered to be endocrine disruptors and others are proven carcinogens and mutagens [77].

Since pharmaceuticals are continually emitted into the environment, they are one of the most persistent groups of contaminants that can harm living organisms even at minimal concentrations [1,78]. Over the last few years, a large number of publications have discussed their fate, transport and exposure regarding the environment. Along the same lines, several studies have presented different methods for pharmaceuticals detection and remediation [20,79]. Although there are few papers on the development of MIP-based SPR sensors applied to the detection of pharmaceuticals in water samples, the promise of low limits of detection with high selectivity encouraged the development of novel affinity-based detection systems for pharmaceutically active compounds. Table 1 summarizes the main characteristics of different MIP-based SPR sensors for the detection of various contaminants in water samples, and their characteristics are discussed below.

Table 1. MIP-SPR sensors for the detection of contaminants in water samples.

Analyte	Use	Polymerization Method/ Transducer	Functional Monomer	Water Matrices	Linearity Range (nM)	LOD (nM)	Reference
Amoxicillin	Antibiotic	Sol-gel, Au SPR sensor	Methacrylamide	Tap water	0.1–2.6	7.3×10^{-2}	[76]
Ciprofloxacin	Antibiotic	Miniemulsion, Au SPR sensor	MAA	Synthetic wastewater	$0.60\text{--}3.02 \times 10^2$	21.4	[80]
Theophylline	Bronchodilator	Visible light, Au SPR sensor	MAA	Wastewater	$0.10\text{--}1.0 \times 10^3$	0.10	[81]
17 β -estradiol	Estrogen steroid hormone	UV light, Au SPR sensor	MAA	Seawater	$2.50 \times 10^{-4}\text{--}2.50$	2.50×10^{-4}	[82]
		UV light, Au SPR sensor	MAA and HEMA	Tap water	$2.50 \times 10^{-7}\text{--}2.50$	1.41×10^{-8}	[83]
Profenofos	Insecticide	Thermal polymerization, Au SPR sensor	MAA	Tap water	$2.7 \times 10^{-1}\text{--}2.68$	9.64×10^{-1}	[84]
		Thermal polymerization, optical fiber	MAA	Tap water and drinking water	$3.02 \times 10^{-8}\text{--}3.02 \times 10^{-1}$	7.54×10^{-6}	[85]
Cadmium	Metal	UV light and miniemulsion, Au SPR sensor	N-methacryloyl-L- cysteine	Wastewater	$8.9 \times 10^{-1}\text{--}4.45 \times 10^2$	8.9×10^{-2}	[86]
Bisphenol A	Manufacturing of plastics and resins	UV light, Au SPR sensor	N-Methacryloyl-L- phenylalanine and 1-vinyl imidazole	Tap water and synthetic wastewater	$8.76 \times 10^{-1}\text{--}43.8$	2.63×10^{-1} and 3.50×10^{-1}	[87]
Triclosan	Antibacterial and antifungal agent	UV light, Au SPR sensor	Methacryloylamido glutamic acid	Wastewater	$1.73 \times 10^{-1}\text{--}3.45$	5.9×10^{-2}	[88]
3,3'-Dichlorobenzidine	Manufacturing of dyes	UV light, Au SPR sensor	MAA	Tap water	$9.0 \times 10^{-3}\text{--}0.5$	1.86×10^{-3}	[89]
1,3,5-trinitroperhydro- 1,3,5-triazine	Energetic material	Electropolymerization, Au SPR sensor	<i>p</i> -Aminothiophenol	Groundwater	$1.0 \times 10^{-3}\text{--}50$	7.20	[90]

In 2018, Ayankojo et al. [76] synthesized a hybrid organic–inorganic MIP film combined with a SPR sensor for the determination of amoxicillin, one of the most frequently consumed antibiotics in European countries. In this work, the MIP film on SPR Au sensor surface was prepared via the sol-gel polymerization technique using methacrylamide as a functional monomer and vinyltrimethoxysilane to form a stable and rigid polymeric film. The spin-coating technique was used to control the thickness of sol-gel MIP layers. Rebinding experiments were performed after the injection of amoxicillin samples and analyzed following the Langmuir–Freundlich model, which revealed an imprinting factor of 16 compared with NIP. The sensor detected the amoxicillin with a LOD value of 7.3×10^{-2} nM, and no cross-reactivity against other similar antibacterial compounds was observed. Additionally, it was successfully applied in tap water fortified with three different concentrations with recovery values of 93–96%. With the growing awareness of antimicrobial resistance, a great deal of attention was focused on detecting antibiotics in environmental water bodies, indicating the need for facile and selective analytical tools to detect these substances at trace levels [91]. In the same year, Sari et al. [80] reported the detection of ciprofloxacin via molecularly imprinted nanoparticles synthesized through two-phase miniemulsion polymerization. Methacrylic acid (MAA) was chosen as a functional monomer and mixed with the antibiotic in the oil-phase. For the fabrication of the SPR sensor, a dispersion of MIP nanoparticles was spread on the gold SPR chip under UV light for 30 min. After immobilization and characterization steps, the correlation between the shifts on the refractive index of SPR sensor and ciprofloxacin concentration were recorded, showing a good linearity ($0.60\text{--}3.02 \times 10^2$ nM) and sensitivity. With this system, the LOD was found to be 21.4 nM in synthetic wastewater. No apparent response was observed when the real-time response of the SPR sensor was also investigated for both tetracycline and enrofloxacin.

On the basis of light-controlled radical polymerization, MAA was also chosen as a functional monomer for the sensitive detection of theophylline [81] and 17- β -estradiol [82,83]. Theophylline is used to prevent and treat respiratory-related diseases, such as asthma. In addition, it can be found in green tea, chocolate and cocoa and coffee beans and is frequently detected in river waters with concentrations at the ng L^{-1} level [92]. Jing et al. [81] proposed a simple and rapid methodology for the preparation of a water-compatible theophylline MIP using an optical SPR sensing system. To achieve this, an aliquot of the aqueous polymerization mixture composed of the theophylline, MAA, N,N'-methylenebisacrylamide and the photoredox initiator system (methylene blue and sodium p-toluenesulfinate) was sandwiched between a gold SPR chip and a cover glass to be irradiated using a laser diode of 365 nm wavelength. Under the irradiation of visible light, the polymerization reaction was performed for 2 h at room temperature and the cover glass plate was ultimately peeled off. Subsequently, the binding of the theophylline molecules to the imprinted film was determined from the measured changes in the SPR reflectivity during the spike of phosphate-buffered solution with theophylline at concentrations ranging from 0.10 to 1.0×10^3 nM. The SPR MIP sensor exhibited a very good linearity, an LOD of 0.10 nM and minimal interferences of structurally similar compounds (caffeine and theobromine). The LOD obtained was more than one order of magnitude lower when compared with UV-Vis spectral analysis, a surface-enhanced Raman scattering and an electrochemical biosensor. Its applicability was tested in wastewater, which weakened the affinity binding between the template and the recognition sites, an effect attributed to higher ionic strength and the influence of matrix effect.

The synthesis of MIPs by photopolymerization is continuously growing. The use of visible light has attracted significant attention. The lower energy and heat of visible light sources are less likely to produce unwanted effects on the ingredients of polymerization mixture, while allowing more specific light-induced processes [93]. Despite these advantages over conventional UV polymerization, the last technique is still widely used with good imprinting efficiency, as observed in the work produced by Tan and Wei [82]. The authors produced a novel double-layer MIP film on Au surface of an SPR chip for

the determination of the small molecule 17- β -estradiol in spiked seawater samples. This endocrine disruptor compound has been extensively monitored in environmental compartments because of its ability to interfere with the hormonal systems of many species in the ecosystem. In this study, the Au surface was previously modified with 1-dodecanethiol to form a self-assembled monolayer and the double-layer of the MIP film was prepared using MAA as functional monomer. Although the results showed an excellent sensitivity (LOD = 2.50×10^{-4} nM) and selectivity, it was highlighted that the double-layer had a much higher adsorption capacity in comparison with a single layer, and a better sensitivity (LOD = 1.41×10^{-8} nM) for the detection of 17- β -estradiol in aqueous media was reported by Jiao et al. [83]. Following similar procedures, the authors chose two functional monomers, MAA and hydroxyethyl methacrylate (HEMA), to construct the MIP film via UV polymerization. This combination improved the hydrophilicity and the survival of the MIP films in aqueous media and, consequently, the performance of the sensor. The detection process revealed a good linearity between the reflectivity changes and 17- β -estradiol concentrations in a wide range of 2.5×10^{-7} –2.50 nM. The performance of the MIP film-based SPR sensor was successfully tested using tap water samples.

Another important endocrine disruptor is the plastic monomer and plasticizer bisphenol A. Shaikh et al. [87] designed a water-compatible MIP membrane to identify bisphenol A in tap and synthetic wastewater. To prepare the polymer on the SPR chip surface via UV light, two functional monomers, N-Methacryloyl-L-phenylalanine and 1-vinyl imidazole were used. The linearity of the sensor response was confirmed in spiked tap water and synthetic wastewater. Detection limits for these samples were 0.263 and 0.350 nM with the recovery values of 100.6 and 102.7%, respectively. Similarly, an imprinted poly(2-hydroxyethylmethacrylate–methacryloylamidoglutamic acid) [p(HEMAGA)] nanofilm was developed to trace triclosan in wastewater. An Au–MIP-modified SPR sensor chip exhibited a linearity range between 1.73×10^{-1} and 3.45 nM, and an LOD of 5.9×10^{-2} nM, compared with other complicated triclosan analytical techniques, such as GS-MS, demonstrated a comparable or better performance. In wastewater samples, the recovery rates were found to be 98–102%. Moreover, the triclosan-imprinted SPR chip was around 15 times more selective for triclosan than methyltriclosan and triclocarban.

MIP sensors can also play an important role in screening pesticide residues to ensure food safety, safeguard the ecosystem and prevent diseases [94]. Despite their significant role in modern agriculture, organophosphorus pesticides are among the most harmful toxins added to the environment [95]. Profenofos, an insecticide with low toxicity and environmental persistence, has caused much discussion, mainly due to its overuse and abuse. For the detection of profenofos in water samples based on SPR and molecular imprinting techniques, we identified two sensors designed through thermal polymerization, in which MAA was the functional monomer used [84,85]. When compared with UV polymerization, thermal polymerization exhibits some advantages, since it does not require special equipment to inhibit oxygen and control temperature. So, through surface-initiated thermal polymerization, where the initiator was immobilized on the surface prior to the polymerization, an ultra-thin MIP film was prepared on Au chips functionalized with 11-mercaptopundecanoic acid [84]. The response of the sensing system was translated into SPR angle shift versus the logarithm of profenofos concentration within 2.7×10^{-1} –2.68 nM. The MIP film showed high sensitivity (LOD = 9.64×10^{-1} nM) and the responses of the analogs were significantly lower than those of the profenofos. Its application in tap water exhibited satisfactory recoveries (89.81–100.99%). In order to enhance the feasibility for on-site analysis, Shrivastav et al. [85] developed an optical fiber MIP-SPR sensor for profenofos detection. The sensing probe was fabricated through the coating of the unclad portion of the fiber with a thin film of Ag followed by the dip-coating of the target-specific MIP (Figure 4). To polymerize, the fiber was dipped into the polymerization solution for 16 h in the oven. After all procedures resulted in the generation of binding sites, a red shift in resonance wavelength was observed as a result of target recognition, and an excellent detection limit of 7.54×10^{-6} nM was reported. To confirm its relevance in aqueous

applications, the MIP-modified SPR sensor was used to measure profenofos in drinking and tap water samples.

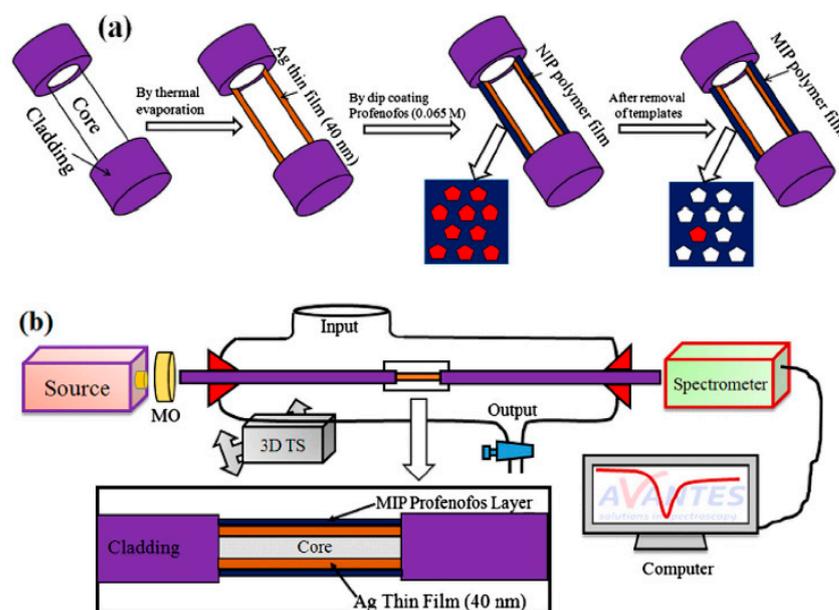


Figure 4. Schematic illustration of (a) MIP-sensing probe fabrication and (b) experimental setup of SPR for the detection of profenofos. Reproduced from [85] with permission from Elsevier.

The intermediates used to manufacture some of the pesticides' ingredients have, unsurprisingly, been detected in water resources. 3,3'-dichlorobenzidine, also an important intermediate in the production of dyes, is on the list of priority substances of most countries [96]. In 2014, Zhou et al. [89] presented a novel strategy based on the conjugated responsive imprinted gels for the fabrication of a MIP-SPR sensor for 3,3'-dichlorobenzidine. SPR-sensing gel film was prepared via surface initiated radical polymerization using acrylamide and a small amount of *N,N'*-methylenebisacrylamide (crosslinker), which was described as a key point to enable the reversible changes of the resultant networks on the Au surface. Thus, the sensing of 3,3'-dichlorobenzidine was established through the responsive shrinkage of the MIP triggered by the target binding. Its response was quantified through the variations of the SPR-reflectivity minimum wavenumber shift, achieving a linearity in the range of 9.0×10^{-3} to 0.5 nM and high affinity to the template molecules. The authors reported an LOD of 1.86×10^{-3} nM for tap water.

To meet and highlight the need of portable SPR instruments for the one-site sensing of hazardous chemicals, Brulé et al. [90] reported a fast and portable SPR sensor modified with a selective MIP for 1,3,5-trinitroperhydro-1,3,5-triazine contamination in the groundwater near to a military site. The manipulation of this energetic material (also known as an explosive) has resulted in significant levels of groundwater and soil contamination. The imprinting process was conducted through the electropolymerization of *p*-aminothiophenol solution prepared with functionalized Au nanoparticles. Results obtained in the SPR shift were cross-validated using the standard HPLC method (EPA method 8330b), demonstrating that accurate environmental sensing with SPR systems and MIP combinations is achievable in the field.

Environmental pollution arising from heavy metals is a well-known issue. Cadmium, a non-essential metal, is widely distributed in the environment, showing higher toxicity and mobility than other metals [97]. The guidelines of the World Health Organization (WHO) for drinking-water quality established a health limit of $3 \mu\text{g L}^{-1}$, but its continuous monitoring is essential to minimize exposure and harm to humans. The SPR sensing of cadmium ions experimentally using an ion-imprinted technology was carried out by Bakhshpour and Denizli [86]. They demonstrated the benefits of three different approaches

for the real-time sensing of cadmium, namely, poly(hydroxyethylmethacrylate) (pHEMA) thin film, pHEMA-based nanoparticles (poly-NPs) and gold nanoparticles (AuNPs). The polymerization was initiated through UV light with N-methacryloyl-L-cysteine as functional monomer, and the results revealed that all techniques use a selective detection ability. However, the attachment of poly-NPs and AuNPs on the sensor surface significantly improved the sensitivity of the sensor ($\text{LOD} = 8.9 \times 10^{-2} \text{ nM}$). Wastewater samples were used to display the practical applicability of the sensor with recoveries of between 78.7 and 88.7%.

4. SERS Sensors

SERS, derived from the inelastic light scattering (Raman effect), can be seen as a surface mechanism amplified through plasmonic nanostructures (mainly of Ag and Au) that modifies the wavelength of the incident light [98]. A SERS spectrum can provide detailed information about vibrational frequency and the intensity of the molecules adsorbed on a SERS-active substrate as a result of the synergistic cooperation of two mechanisms: electromagnetic field enhancement and chemical enhancement. Electromagnetic enhancement is generally considered to be the main contribution to the SERS signal, which originates from the formation of LSPR or “hot spots” on the nanostructures of metals upon the interaction of light, while the chemical mechanism is due to the charge transfer between the metal and chemisorbed molecules [98,99]. In order to improve the Raman signal, both mechanisms require the target molecule to be close to the surface of the SERS substrates, whose intensity can reach up to 14 orders of magnitude in some nanomaterial systems, enabling the ultra-trace detection of a wide variety of different analytes, even down to the single-molecule level [100]. In addition to its tremendous sensitivity, this spectroscopic technique also has noteworthy properties, including (i) the unique spectral signature of analytes, (ii) multiplexing and high-throughput detection, (iii) resistance to photodegradation and photobleaching and (iv) no interference from water [72]. With these intrinsic features, along with the continuous advances in nanofabrication techniques, SERS is progressively expanding into the viable detection of environmental contaminants, as well as gaining popularity among the sensor community [101–103].

Since SERS is a surface enhancement technology, it has been widely established that the engineering of high-quality substrates is a prerequisite for SERS analysis [104]. Taking this into account, SERS investigations have been mostly focused on the modification of SERS substrates materials [105,106]. However, the key to constructing efficient SERS sensors is the development of a substrate that must have not only high SERS activity but also the specific recognition property. Substrates with a strong affinity to their targets are of extreme importance for addressing the critical change of sample matrix interference, where the most promising method is a combination of MIPs [34,107,108].

4.1. MIP-Based SERS

By introducing recognition ability and insulating the substrate surface, MIPs have been applied to improve the features and properties of SERS-active surfaces [109]. Similarly to other MIP-based sensors, MIP-SERS sensors are mainly composed of SERS substrates and MIP layers decorated on the substrates [110,111]. When the target molecules bind selectively to the imprinted cavities, SERS signals are generated under the activation of the incident light (Figure 5). The vibrational signature of the adsorbed molecules allows the identification of the binding and the release of target molecules to and from MIPs, respectively. In this process, nanomaterials that support the plasmon resonance are responsible for the enhancement factor, and their shape, size and aggregation state should be carefully controlled in order to achieve a strong electromagnetic field [112]. Moreover, it has been reported that hot spots produced at the tips of the nanostructures can induce the significant enhancement of SERS signals.

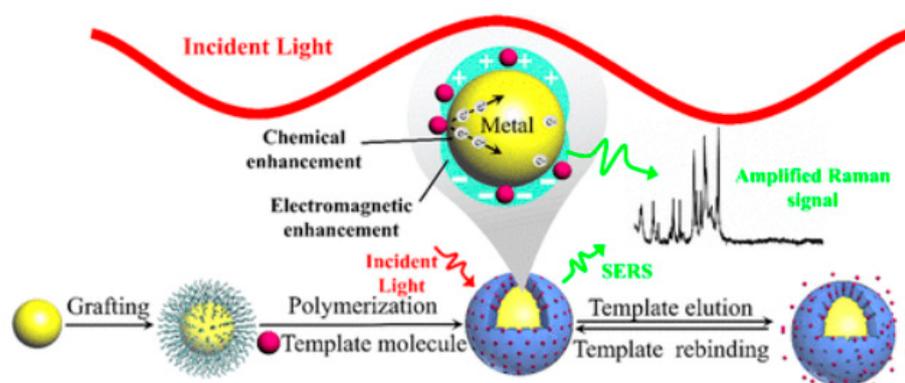


Figure 5. Sensing principles of MIP-SERS construction. Reproduced from [110]. Copyright 2020 American Chemical Society.

There are two conceptualized detection modes for MIP-SERS sensors: direct or label-free detection and indirect detection [110]. Label-free detection is used for analytes with inherent Raman signals, where the SERS detection requires only the adsorption of the molecules on the nanostructured plasmonic material [113]. In contrast, the label method is for substances with a weak Raman signal, relying on the use of SERS probes with strong and well-characterized spectral properties to transduce the sensing mechanism.

Application of MIP-SERS Sensors in Water Contaminant Detection

As can be seen in Table 2, various strategies have been adopted to develop MIP-SERS sensors with applications in water samples. As mentioned previously, MIPs ensure selectivity, while SERS provide sensitivity and identification. Owing to the surface plasmon resonance characteristics, Au and Ag NPs were the first choice as substrates and building blocks for the further preparation of assembled SERS. Special focus was given to Ag NPs as a direct consequence of their controllable morphology, high Raman signal enhancement and easy preparation [114]. Nevertheless, the use of single noble metal particles has some weaknesses, such as poor stability over time, easy aggregation and difficulties with in terms of recycling, that can hinder their practical application [115]. To overcome these limitations and improve electron transfer, NPs have been conjugated with other functional materials known to form effective hot spots, including magnetic particles, carbon- and silica-based materials, as well as semi-conductors and non-metal materials.

Table 2. MIP-SERS sensors for the detection of contaminants in water samples.

Analyte	Use	Polymerization Method/SERS Substrate	Functional Monomer	Water Matrices	Linearity Range (nM)	LOD (nM)	Reference
Enrofloxacin hydrochloride	Antibiotic	Self-polymerization/Fe ₃ O ₄ @Ag NPs	Dopamine	Dam water	1.0–200	1.2×10^{-2}	[114]
Spiramycin	Antibiotic	Sol-gel/MWCNTs@Ag NPs	APTES	River water	1.0×10^{-2} – 1.0×10^3	1.0×10^{-2}	[116]
Bisphenol A	Manufacturing of plastics and resins	Sol-gel/Au NPs	3-(triethoxysilyl)propyl isocyanate	River water	2.19×10^3 – 9.99×10^4	5.26×10^2	[117]
		Sol-gel/SiO ₂ @Ag NPs	TEOS	Tap water and lake water	1.7×10^{-2} – 1.75×10^2	1.5×10^{-2}	[118]
		Precipitation polymerization/Ag NPs	4-vinylpyridine	Tap water	1.0 – 1.0×10^6	1.0	[119]
2,6-Dichlorophenol		Precipitation polymerization/SiO ₂ -Au NPs	Acrylamide	Lake water	1.0 – 1.0×10^4	1.0	[120]
		Precipitation polymerization/Ag-CdTe quantum dots	MAA	Lake water	1.0 – 1.0×10^4	1.0	[121]
		Precipitation polymerization/SiO ₂ -rGO-Au NPs	MAA and acrylamide	Dam water	1.0–100	2.0×10^{-2}	[122]
		Precipitation polymerization/Cu ₂ O@Ag NPs	MAA	Lake water and wastewater	10.0 – 1.0×10^6	5.8	[123]
		Precipitation polymerization/Ag/IP6@MIL-101(Fe)	Acrylamide	Lake water	1.0 – 1.0×10^7	1.0	[124]
Pyrene	Polycyclic aromatic hydrocarbon	Precipitation polymerization/Au NPs	MAA and divinylbenzene	Creek water and seawater	0.10 – 1.0×10^4	1.0	[125]
p-Nitroaniline	Manufacturing of dyes	Precipitation polymerization/defect GO-Ag	Methacrylamide	River water	1.0×10^{-5} – 1.0×10^5	2.5×10^{-6}	[126]
Caffeine	Stimulant	Precipitation polymerization/Ag NPs	MAA	River water	0 – 5.6×10^2	5.6×10^{-1}	[127]
Malachite green	Synthetic organic dye	Precipitation polymerization/Fe ₃ O ₄ @Ag NPs	MAA	Tap water	5.0×10^{-3} –100.0	1.5×10^{-3}	[128]

Table 2. Cont.

Analyte	Use	Polymerization Method/SERS Substrate	Functional Monomer	Water Matrices	Linearity Range (nM)	LOD (nM)	Reference
Carbendazim	Insecticide	Precipitation polymerization/Ag@SiO ₂	Methyl acrylamide	Tap water	1.0–1.0 × 10 ⁶	1.0	[129]
Paclobutrazol	Insecticide	Precipitation polymerization/Fe ₃ O ₄ @SiO ₂ -Au@Ag	Acrylamide	River water	2.55 × 10 ² –3.49 × 10 ⁴	2.55 × 10 ²	[130]
Fenvalerate	Insecticide	Precipitation polymerization/SiO ₂ @TiO ₂ @Ag	Acrylamide	River water	1.0–100	0.2	[131]
Cyfluthrin	Insecticide	Precipitation polymerization/Fe ₃ O ₄ @GO@Ag	Acrylamide	River water	10.0–1.0 × 10 ⁶	10.0	[132]
		Precipitation polymerization/ZnO@GO@Ag	Acrylamide	River water	20–500	4.0 × 10 ⁻²	[133]
Cyhalothrin	Insecticide	Precipitation polymerization/Ag NPs	Acrylamide	River water	100.0–1.0 × 10 ⁴	13	[134]
λ-cyhalothrin	Insecticide	Precipitation polymerization/SiO ₂ @rGO@Ag	MAA and acrylamide	Dam water	1.0–1.0 × 10 ⁴	3.8 × 10 ⁻¹	[135]

$\text{Fe}_3\text{O}_4@Ag$ and $\text{CNTs}@Ag$ nanocomposites were used as active SERS substrates in combination with MIPs to detect and quantify antibiotics residues in water samples, reaching excellent and similar LODs [114,116]. Using enrofloxacin hydrochloride and dopamine acting as both a functional monomer and a crosslinker in the self-polymerization procedure, Li et al. [114] reported a magnetic core-shell SERS-imprinted sensor. Firstly, Fe_3O_4 NPS were synthesized by the hydrothermal method and modified with polydopamine. Then, Ag NPs were dispersed on the surface of the prepared Fe_3O_4 NPs, forming a nanocomposite substrate that increased the hot spot area during SERS analysis. $\text{Fe}_3\text{O}_4@Ag$ surface was, subsequently, wrapped with layers of imprinted polymers to synthesize the imprinted structure for the selective detection of enrofloxacin. Before Raman detection, $\text{Fe}_3\text{O}_4@Ag@MIP$ substrates were separated via the external magnetic field and dropped on the glass slide. Raman intensity and the concentration of enrofloxacin hydrochloride exhibited a good linear relationship (1–200 nM) and the LOD was calculated as 1.2×10^{-2} nM. This system presented not only sensitivity but also selective capacity, which was reflected through the adsorption investigation of $\text{Fe}_3\text{O}_4@Ag@MIP$ on other interferential antibiotics. Recovery values ranging from 94 to 111% in dam water confirmed the potential of this SERS sensor to explore emerging properties in environmental water systems monitoring. More recently, Li et al. [116] presented a novel SERS-imprinted membrane to detect spiramycin in river water. The authors selected eggshell membrane, which contains a large number of amino and carboxyl groups, as a support to anchor the multi-walled carbon nanotubes (MWCNTs), which are able to promote the surface plasma effect of Ag NPs and, consequently, the Raman intensity. The imprinting process on $\text{CNTs}@Ag$ NPs were created using the sol-gel method with traditional 3-aminopropyl triethoxysilane (APTES) as functional monomer. In this work, it was proven that polymerization can protect Ag NPs from being oxidized when the SERS intensity of the prepared sensor did not show significant changes after 90 days. The results revealed a linear correlation between the SERS intensity and the spiramycin concentration across a wide linear range (1.0×10^{-2} – 1.0×10^3 nM) with an LOD of 1.0×10^{-2} nM.

Despite the strong Raman active scattering activity of active pharmaceutical ingredients due to their aromatic or conjugated domains [136], we verify that MIP-SERS sensors are not yet the first choice for the analysis of pharmaceuticals in water samples. In contrast, there are several recent works covering their application for monitoring other contaminants in water, demonstrating the upsurge of the interest in this field. Additionally, using sol-gel polymerization, two different researchers prepared the bisphenol A-imprinted sensors based on SERS. In 2013, Xue et al. [117] introduced a Au core coated with a thin MIP layer using 3-(triethoxysilyl)propyl isocyanate monomer and TEOS as crosslinker. In conjugation with a small portable Raman spectrometer, the sensor was capable of detecting bisphenol A in spiked river water, achieving an LOD of 5.26×10^2 nM. Later, Yin et al. [118] adopted a different strategy by adding silica (SiO_2) nanospheres as the core and Ag NPs as the shell (Figure 6). Furthermore, MIP was synthesized on the surface of the modified Ag NPs using TEOS and APTES as a functional monomer and crosslinker, respectively. This approach exhibited a more pronounced Raman intensity and imprinting efficiency and, consequently, a better sensitivity (LOD = 1.5×10^{-2} nM) was achieved. To verify the potential utility of the proposed method, lake water and tap water were spiked with 1.79×10^{-3} nM of bisphenol A, resulting in quantitative recoveries of 89.98% and 101.31%. In another study, a simple procedure of integrating MIP into Ag NPs via precipitation polymerization enabled the detection of bisphenol A up to 1.0 nM [119]. Spiked tap water was chosen to evaluate the applicability of the developed sensor. The results again showed that $Ag@MIP$ provided more Raman hot spots than bare Ag microspheres, highlighting the potential of the $Ag@MIP$ hybrids to detect bisphenol A in complicated matrices.

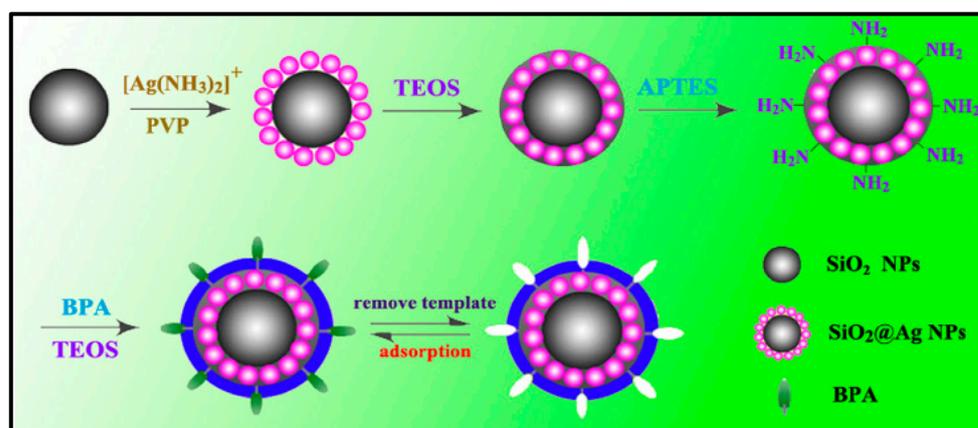


Figure 6. Schematic representation of the synthesis of SiO₂@Ag NPs composites for the selective detection of bisphenol A. Reproduced from [118] with permission from Elsevier.

Among heterogeneous polymerization systems, precipitation polymerization has been the most widely used approach for the fabrication of MIP layers adsorbed on SERS substrates, as noted by Table 2. Although large quantities of polymerization solvent are required, its easy operation, no need for any surfactant or stabilizer and the direct access to homogeneous polymeric nanoparticles make the method very attractive [137]. Acrylamide and/or MAA have been the top choice between the different classes of functional monomers suitable for radical polymerization. Along these lines, MIPs were constructed on the surface of different SERS composite materials to detect 2,6-dichlorophenol [120–124], pyrene [125], p-nitroaniline [126], caffeine [127], malachite green [128] and several other pesticides [129–135] in water bodies. Aiming to increase the sensitivity of SERS through participation in the charge transfer mechanisms, the determination of 2,6-dichlorophenol was carried out using Au NPs anchored onto SiO₂ nanospheres [120], Ag NPs modified with the cadmium telluride (CdTe) quantum dots [121], cuprous oxide (Cu₂O) semiconductors [123] and, more recently, Ag NPs embedded in an MIL-101 (Fe) metal–organic framework (MOF) [124] as the SERS substrates. All of these works reported good and selective detection properties after molecular imprinting and an LOD of around 1.0 nM. However, their sensitivity was significantly improved by linking reduced graphene oxide (rGO) with traditional Au NPs, using SiO₂ to reduce agglomeration [122]. Moreover, a combination of two functional monomers (MAA and acrylamide) was used during the precipitation polymerization procedure to increase the potential for the template recognition of the formed cavities. Thus, the best LOD found for 2,6-dichlorophenol was 2.0×10^{-2} nM. The prepared SiO₂@rGO@AuNPs@MIP sensor displayed an excellent analytical performance, which was tested in dam water. The efficiency of same procedure for the selective detection of the organic pesticide λ -cyhalothrin in water samples had already been revealed [135], emphasizing that this approach could be extended to the detection of other contaminants.

In fact, GO as a layer coating on metal nanostructures have attracted much attention in the SERS field, since it has the ability to control the metal NPs size while providing hydroxyl, epoxy and carboxyl groups for the next reaction. Compared to other SERS materials, GO has excellent molecular adsorption capacity, which, in combination with MIPs, has emerged as a promising platform for detection analysis. Based on GO, Wang et al. [132] and Li et al. [133] also developed SERS-imprinted sensors that prepared Fe₃O₄@GO@Ag and zinc oxide (ZnO)@GO@Ag nanocomposites for the sensing of cyfluthrin. Employing precipitation polymerization and acrylamide as functional polymers in both works, the ZnO@GO@Ag@MIP sensor displayed a better sensitivity (LOD = 4.0×10^{-2} nM), which can be attributed to the high refractive index of ZnO nanorods. The sensors were successfully applied in river waters. By introducing structural defects in GO and increasing the surface area and porosity, Chen et al. [126] focused on the detection of p-nitroaniline. The defects

were created via the acid etching of the GO surface to support and fix Ag NPs. This substrate provided excellent interclass selectivity and was able to detect analytes in river water as low as an LOD of 2.5×10^{-6} nM.

5. Conclusions and Perspectives

The global demand for water has triggered a change in how water is utilized, managed and shared. Both water pollution control and water reuse are important strategies for managing water resources in a sustainable way, and it is well-known that the large number of contaminants in environmental waters and wastewaters is one of the main barriers in practice. In particular, their occurrence at trace levels has challenged existing analytical tools and water treatment technologies.

In this review, we highlighted the potential of MIPs in the integration into plasmonic sensors to detect contaminants in water samples. Due to their simple, rapid and ultrahigh sensitive detection, SPR and SERS sensors are regarded as promising plasmonic detection candidates, in which the employment of MIPs endows SPR and SERS with excellent capture selectivity and stability improvement. Au and Ag are typically the metallic materials preferred for MIP-SPR and -SERS analysis. Additionally, the researchers have explored the application of other plasmonic nanostructures, such as magnetic nanoparticles for amplifying the signals.

Regarding the imprinting techniques, UV and precipitation polymerization are widely used to build MIP-based SPR and SERS sensors, respectively. Although the considered studies demonstrated their capabilities of recognizing a broad range of contaminants in water samples, the detection of active pharmaceutical compounds still remains poorly explored.

Undoubtedly, plasmonic MIP-sensing platforms have great potential for the generation of high selective, sensitive, fast and real-time responses through the easier preparation and lower costs in comparison with traditional instrument techniques. As a result, the number of publications on MIP-based SPR and SERS sensors has increased in the last few years. Nevertheless, the need for extremely low LODs in measuring and controlling contaminants in the water remains an unsolved challenge, increasing the distance between laboratory research and real environmental applications. Further improvements regarding miniaturization/portability and the development of more compact and more stable sensors and the exploration of novel imprinting technologies are expected to be presented in upcoming research in this field. Future works should also include more efforts to design sensors using the principles of green chemistry. Accordingly, the development of molecular modelling and computational studies to clearly understand the interaction between MIPs and target contaminants, as well as to pre-screen the preparation conditions, should be undertaken.

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