

## Review

# Biosensing Applications of Molecularly Imprinted-Polymer-Based Nanomaterials

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**Abstract:** In the realm of sensing technologies, the appeal of sensors lies in their exceptional detection ability, high selectivity, sensitivity, cost-effectiveness, and minimal sample usage. Notably, molecularly imprinted polymer (MIP)-based sensors have emerged as focal points of interest spanning from clinical to environmental applications. These sensors offer a promising avenue for rapid, selective, reusable, and real-time screening of diverse molecules. The preparation technologies employed in crafting various polymer formats, ranging from microparticles to nanomaterials, wield a profound influence. These techniques significantly impact the assembly of simplified sensing systems, showcasing remarkable compatibility with other technologies. Moreover, they are poised to play a pivotal role in the realization of next-generation platforms, streamlining the fabrication of sensing systems tailored for diverse objectives. This review serves as a comprehensive exploration, offering concise insights into sensors, the molecular imprinting method, and the burgeoning domain of MIP-based sensors along with their applications. Delving into recent progress, this review provides a detailed summary of advances in imprinted-particle- and gel-based sensors, illuminating the creation of novel sensing systems. Additionally, a thorough examination of the distinctive properties of various types of MIP-based sensors across different applications enriches the understanding of their versatility. In the concluding sections, this review highlights the most recent experiments from cutting-edge studies on MIP-based sensors targeting various molecules. By encapsulating the current state of research, this review acts as a valuable resource, offering a snapshot of the dynamic landscape of MIP-based sensor development and its potential impact on diverse scientific and technological domains.

**Keywords:** molecular imprinting; molecularly imprinted polymers; nanomaterial; nanoparticle; nanofilm; nanogel; sensor applications



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## 1. Introduction

The sensor, a versatile device meticulously designed to detect and measure an array of physical properties and environmental conditions, stands as a cornerstone in technological landscapes. Its role transcends monitoring, extending into critical functions such as control and response mechanisms across diverse fields like electronics, engineering, industrial processes, medical applications, and environmental monitoring. Operating as a sentinel, sensors discern parameters such as temperature, pressure, light, motion, and sound, providing indispensable input for informed decision making and the seamless automation of myriad systems and devices [1,2]. The trajectory of sensor evolution has witnessed a revolutionary phase with recent technological strides, enabling the detection of target molecules at the molecular level. This progress, underpinned by key factors such as selectivity, sensitivity, reusability, and storage stability, has catapulted sensor development into unprecedented realms [3]. Central to evaluating sensor prowess is the detection limit, an indispensable metric representing the lowest discernible amount of a target molecule with a predefined level of confidence [4]. This metric is meticulously derived from parameters including the

blank mean, blank deviation, calibration curve slope, and determined confidence factor, underscoring the precision demanded in contemporary sensor technologies [5].

The amalgamation of diverse disciplines—chemistry, physics, nanotechnology, electronics, and bioengineering—defines the interdisciplinary nature of sensors, rendering them pivotal in monitoring and management endeavors. With the rapid development of automation engineering and the internet of things, the demand for associated sensors is increasing [6]. The distinctive properties of sensors, characterized by specificity, ease-of-use, sensitivity, and real-time monitoring capabilities, underscore their ubiquity across a spectrum of applications [7]. At its core, a sensor serves as a detection tool, seamlessly integrating a sensing molecule with a transducer (optic, electrochemical, and/or piezoelectric). The intricate dance between target molecules and recognition elements within this apparatus yields a measurable signal [8]. This transformative amalgamation offers advantages such as rapid, real-time detection, user-friendly operation, heightened sensitivity, selectivity, storage stability, cost-effectiveness, and portability—ushering in a paradigm shift from conventional, laborious sample pre-processing procedures [9]. Sensors, transcending their conventional roles, have redefined established techniques and methodologies. Their far-reaching impact spans critical domains such as food safety, environmental screening, drug development, and clinical applications, embodying three fundamental components: a sensing element, a transducer, and a detector [10–15]. The sensor operates on a fundamental principle—target molecules interacting with a sensing element, which, in turn, recognizes these molecules through intricate physical and/or chemical interactions. Subsequent to this intricate dance, a transducer meticulously converts alterations into a measurable signal, evaluated with precision by a detector [16]. This dynamic synergy encapsulates the essence of sensor technology, propelling it into the vanguard of scientific and technological progress. The landscape of sensor studies has undergone a rapid and expansive evolution in recent years, showcasing a diverse array of applications [17–19]. Contemporary research endeavors are distinctly focused on elevating the selectivity and sensitivity of detection platforms. This concerted effort involves a multifaceted approach, encompassing improvements in sensor production quality, the fine-tuning of surface chemistry methods, enhancements in ligand–target affinity, and the strategic incorporation of diverse materials for signal amplification [20].

A notable trend in this progressive trajectory is the escalating utilization of sensors based on molecularly imprinted polymers (MIPs). The molecular imprinting method, a sophisticated technique, facilitates the creation of polymeric materials endowed with specific binding sites tailored for a predefined template. This intricate process involves polymerization procedures, integrating templates, functional monomers, cross-linkers, and initiators within a suitable solvent solution. The subsequent initiation of polymerization, whether induced through photo- and/or thermal-initiation, coupled with electropolymerization, further refines the composition. A critical juncture in this methodology is the removal of the template, an indispensable step that unveils specific cavities, paving the way for subsequent recognition sites in various applications [21–27]. This innovative approach represents a paradigm shift, holding immense promise for advancing the capabilities of sensors and broadening their applications in diverse fields.

Nanomaterials, characterized by structures, properties, or performance traits that manifest at the nanoscale—typically with dimensions below 100 nanometers in at least one dimension—stand as a remarkable frontier in material science. The distinctiveness of nanomaterials stems from their diminutive size, resulting in a heightened surface area-to-volume ratio and the accentuation of quantum effects at the nanoscale [28]. This category encompasses various forms, including nanoparticles, nanotubes, and nanogels. The allure of nanomaterials lies in their unique properties, which can markedly differ from their bulk counterparts. With applications spanning electronics, medicine, energy, materials science, and beyond, nanomaterials have become pivotal in advancing diverse fields. However, the novelty of their characteristics prompts concerns regarding potential impacts on health and the environment. Consequently, ongoing research endeavors seek to comprehensively

support understanding and mitigating any associated risks [29]. Within this dynamic landscape, molecularly imprinted nanomaterials emerge as a distinctive subset, offering a multitude of advantages such as selectivity, sensitivity, stability, and reusability. These attributes render them exceptionally valuable in diverse applications. The collective impact of these advantages propels the burgeoning interest and application of molecularly imprinted nanomaterials across various domains, including sensing technologies, drug delivery systems, catalysis, and environmental monitoring [30]. As a result, molecularly imprinted nanomaterials stand poised at the forefront of innovative solutions, promising transformative breakthroughs in technology and contributing to the evolution of scientific and industrial practices.

In this comprehensive review, we commence by providing concise insights into various types of sensors and the molecular imprinting method. The subsequent focus is on the recent advancements in molecularly imprinted polymer (MIP)-based sensors, elucidating their diverse platforms and conducting a thorough examination of the prospects these sensors offer across different applications. The review is designed to foster a critical discussion that aims to unravel promising trends in the field. By navigating through the intricate landscape of sensor technologies and molecular imprinting methods, we endeavor to offer a holistic understanding of the current state of the art factors, emphasizing the transformative potential of MIP-based sensors in addressing a spectrum of real-world challenges.

## 2. Sensors

A sensor, be it a biosensor, nanosensor, or nanobiosensor, represents a sophisticated detecting platform endowed with the remarkable capability to recognize the presence of a specific target molecule. The fundamental architecture of a sensor integrates key components—transducers, receptors, and detectors—in a synergistic ensemble [31]. This orchestrated mechanism begins with the receptor engaging with the target molecule, instigating a molecular interaction. Subsequently, the transducer undertakes the crucial task of translating this interaction into a measurable signal, thereby facilitating the conversion of molecular events into quantifiable data. For example, in the realm of piezoelectric sensors, the detection process involves quantifying a mass change resultant from the formation of the analyte–receptor complex. Conversely, optic and electrochemical sensors gauge alterations in light intensity and conductivity, and current or potential changes, respectively [32]. These sensors function as adept observers of molecular interactions, each employing unique methodologies to capture nuanced aspects of the target recognition process. The culmination of this intricate process is the measurement of the observable change magnitude, a task executed through a recording system. In essence, sensors serve as indispensable tools in capturing and interpreting molecular events, paving the way for nuanced insights and advancements across diverse scientific and technological domains [33].

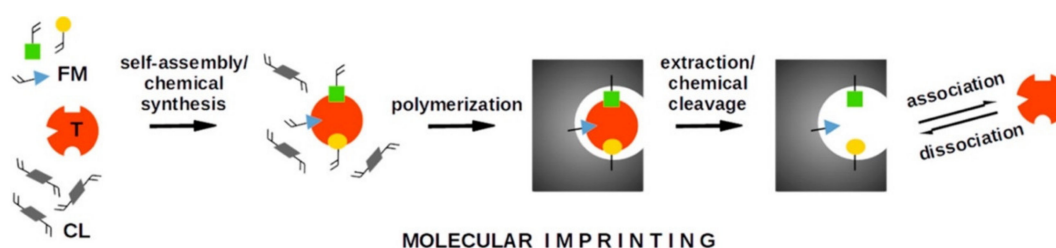
Electrochemical sensors stand as versatile tools with a wide array of applications, providing a robust platform through the utilization of screen-printed electrodes and semi-conductors. These sensors operate by detecting alterations in dielectric properties, dimensions, shape, and charge distribution during interactions on the surface of the electrode. Categorically, they fall into major sub-groups, namely amperometric, potentiometric, and impedimetric, demonstrating their adaptability for the detection of diverse target molecules [34–36]. Piezoelectric sensors, on the other hand, are adept at evaluating changes in acceleration, pressure, strain, temperature, and force by converting them into a charge. Quartz crystal micro-balance sensors, a prominent subset of piezoelectric sensors, assess the viscoelasticity and mass changes on sensor surfaces by recording alterations in frequency and quartz crystal resonator damping. Due to their sensitivity to environmental conditions, the operation of piezoelectric sensors necessitates isolation hardware to mitigate obstacles such as vibration. These sensors find utility in an expansive range of applications, including the detection of low-molecular-weight target molecules [37–39]. Optic sensors focus on detecting alterations in the optic properties of the transducer plane when the target molecule interacts with the recognition element. They are divided into sub-groups, with

direct ones relying on the complex formation of the transducer plane. In contrast, indirect optic sensors use different labels, such as fluorophores and chromophores, to enhance the binding activity and response. While indirect optic sensors can generate robust signals, they contend with non-specific interactions and involve high-cost labeling procedures. Various types of optic sensors, including time-resolved fluorescence, optrode-based fiber, surface plasmon resonance, evanescent wave fiber, interferometric, and resonant mirror sensors, have been extensively explored in the literature. These sensors boast broad detection windows, enabling the identification of diverse molecules [40–42].

### 3. Molecular Imprinting Method

Molecular identification constitutes a pivotal event with profound implications across diverse applications. For instance, antibodies and enzymes, quintessential biomolecules, harbor specific recognition sites facilitating interactions with their corresponding antigens and substrates [43–45]. These interactions, serving as inspiration, have catalyzed the development of various recognition materials, among which molecularly imprinted polymers (MIPs) hold a significant position. Referred to as “plastic antibodies,” MIPs emulate the functionalities of natural molecules, culminating in the creation of synthetic polymers with tailored recognition capabilities. While the embryonic stages of imprinting processes trace back to the 1930s when Polyakov pioneered experiments to modify silica for chromatographic applications, the contemporary applications of MIPs gained substantial momentum through the groundbreaking studies of Wulff and Mosbach in the 1970s and 1980s [46–48]. These pioneers laid the foundation for a new era in molecular identification, fostering the development of MIPs as versatile and artificial recognition materials with wide-ranging applications.

MIPs, often referred to as biomimicry polymers, stand out for their remarkable ability to exhibit high selectivity and affinity toward a diverse array of template molecules, spanning from ions to peptides, organic molecules, proteins, viruses, and even entire cells [49–54]. The distinctive feature of MIPs lies in their preparation methods, where these polymers are synthesized in the presence of template molecules to establish specific binding cavities. Illustrated in Figure 1, a crucial stage in the preparation of MIPs involves pre-complex formation, a process reliant on non-covalent interactions between functional monomers (FMs) and template molecules (T) [55]. The functional monomers intricately bind with the template molecules, creating a pre-complex that subsequently undergoes polymerization in the presence of a cross-linker (CL). This pre-complex, interwoven with the cross-linker, undergoes polymerization, culminating in the formation of a three-dimensional polymeric structure. Post polymerization and elution, the resultant polymeric matrix manifests specific cavities intricately shaped, sized, and distributed in a manner that precisely complements the attributes of the template molecule [56]. This meticulous process ensures that the MIPs are tailor-made to selectively recognize and bind with the template molecules, showcasing their biomimetic prowess and positioning them as invaluable tools across a spectrum of applications.



**Figure 1.** Preparation scheme of molecularly imprinted polymers [43]. Functional monomers (FMs) assemble around a template molecule (T) to form a pre-polymerization complex, which undergoes polymerization in the presence of a cross-linker (CL). Upon template extraction, specific binding sites become available for the template molecule rebinding.

MIPs emerge as remarkable entities characterized by their physical and chemical stability, durability, robustness, ease of preparation, and cost-effectiveness, attributes inherent to their polymeric nature. Leveraging these advantageous features, MIPs find extensive utility across various domains requiring molecular recognition, encompassing applications such as affinity separation [57,58], drug delivery [59,60], bioimaging [61,62], cosmetics [63,64], catalysis [65,66], and sensing [67–73]. The proliferation of MIP-related research is evident in the substantial number of publications available in the literature. Utilizing “imprint” as a keyword for statistical categorization on the Science Direct website, a staggering total of 150,934 publications is identified. Notably, this number exhibits a consistent upward trend, underscoring the sustained interest and evolving landscape of MIP-related research. A significant subset of this research pertains to the realm of sensors, particularly MIP-based sensors. In the past two decades, the latest studies in this domain have found applications in critical areas such as food safety, medical applications, and environmental monitoring [74]. Traditional and commercial analytical methods, often entailing complex equipment, specialized personnel, and meticulous protocols, pose limitations in terms of accessibility and readiness for use in resource-limited settings [75]. Consequently, the imperative to advance low-cost, specific, and user-friendly sensors is underscored [76,77]. The wealth of publications on MIP-based sensors, identified using “imprint” and “sensor” as keywords, amounted to a notable 23,961 total. This is further emphasizing the dynamic growth and relevance of MIP-based sensor research, showcasing a trajectory that aligns with the increasing demand for innovative and practical solutions in diverse fields [78].

Furthermore, the inclusion of information about existing biosensing platforms that incorporate MIPs in the market can be highly beneficial for several reasons such as real-world relevance, technology validation, market trends and adoption, diversity of applications, user considerations, and inspiration for innovation [79]. Providing information about commercially available biosensing platforms incorporating MIPs adds a layer of real-world relevance. It helps researchers understand that MIP-based sensors are not just theoretical concepts but have practical applications in the market [80]. The existence of commercial biosensing platforms incorporating MIPs serves as a validation of the technology’s effectiveness and practical utility. It reinforces the idea that MIPs are not just promising in research settings but have crossed the threshold into actual products [81]. Information about existing biosensing platforms offers insights into market trends and the level of adoption of MIP-based technology. This can be valuable for researchers, industries, and investors looking to understand the current landscape and potential areas for growth [82]. Commercial biosensing platforms often span a range of applications. Including information about these platforms allows readers to appreciate the diverse fields where MIPs are making an impact, such as healthcare, environmental monitoring, food safety, and more [83]. In summary, incorporating information about existing biosensing platforms that utilize MIPs in the market adds depth and practicality. It enhances the understanding of the technology’s current standing, its applications, and the challenges and successes in real-world scenarios.

#### 4. MIP-Based Sensors and Applications

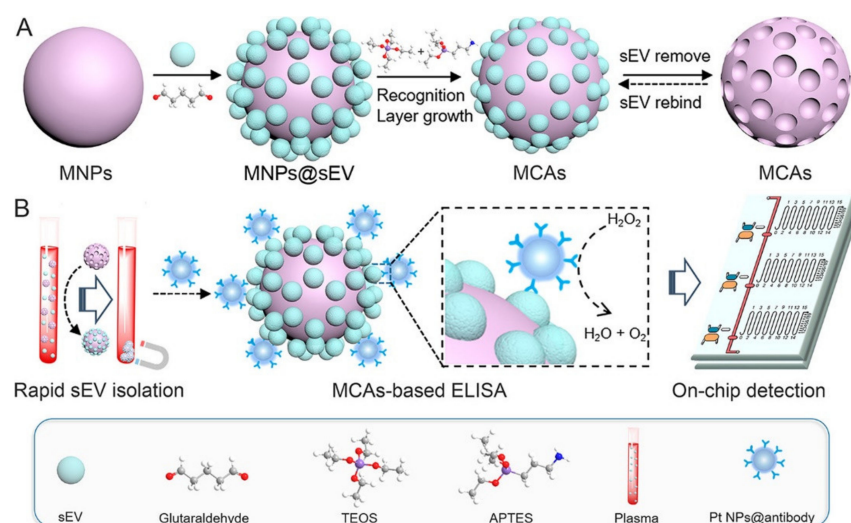
The quest for sensors with enhanced performance has found its most promising avenue in molecularly imprinted-polymer-based technologies. Leveraging the myriad advantages of imprinted polymers, these technologies have permeated various fields for sensor applications. Their preparation procedures are generally straightforward, rendering them cost-effective polymers that can be easily modified and functionalized with diverse target molecules [84]. One remarkable aspect of molecularly imprinted-polymer-based sensors is their versatility in participating in sensing operations or serving as support materials for monitoring units. This adaptability extends to the ability to tailor the chemical and physical structure of these polymers, thereby enhancing sensitivity, selectivity, reactivity, flexibility, and biocompatibility [85]. The dynamic nature of these polymers makes them valuable tools for refining sensor capabilities and addressing specific appli-



cation requirements. Nanotechnology, characterized by the manipulation of materials at dimensions less than 100 nm, transcends disciplines such as chemistry, biotechnology, and engineering. This manipulation of materials to nanosizes results in profound changes in their properties, be they chemical, electrical, magnetic, or optical [86]. Capitalizing on these features, nanotechnology enables the creation of more efficient, rapid, stable, space-efficient, and biocompatible materials while utilizing fewer resources [87,88]. This convergence of molecularly imprinted-polymer-based sensors and nanotechnology heralds a new era of advanced sensing technologies, promising innovations that transcend the limitations of conventional sensor platforms.

#### 4.1. Imprinted-Particle-Based Sensors

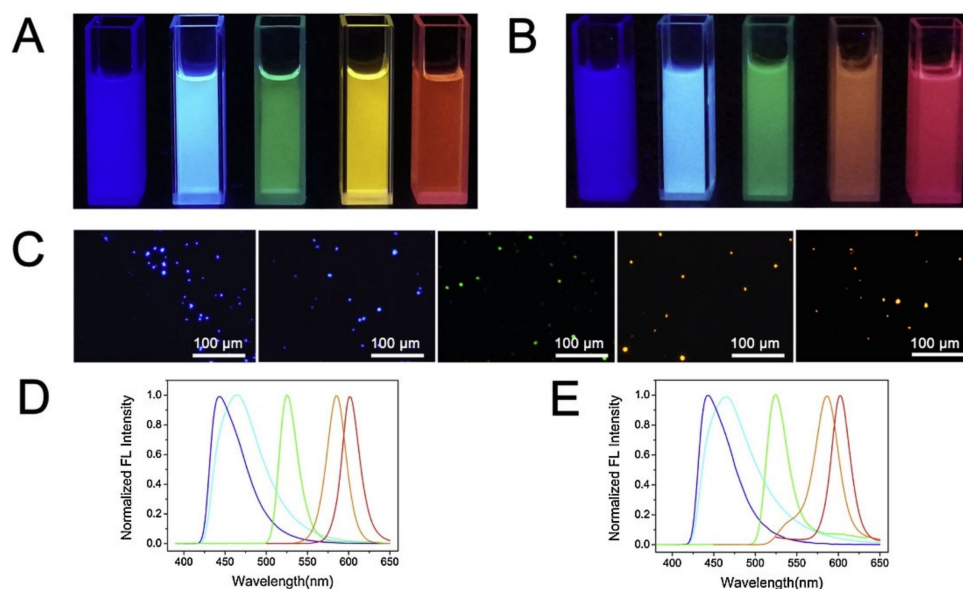
There are several methods for the synthesis of imprinted particles in the literature [89–91]. However, most of these methods have some disadvantages, such as amorphous particles, broad size distribution, surfactant remnants, and deep binding sites. So, new sensor systems are developed every day to eliminate these disadvantages [92–94]. For instance, Karaseva et al. synthesized imprinted particles for trypsin detection using mini-emulsion polymerization. They optimized the effect of the cross-linker and incubation time on the properties of the microparticles and obtained 200 nm as the size of the particles with a high binding affinity and selectivity. They used these particles as a recognition element for the piezoelectric sensor to sense trypsin and also obtained a linear response in the 0.125–2  $\mu\text{g/mL}$  concentration range with a detection limit value of 0.07  $\mu\text{g/mL}$ . They also observed the behavior of the piezoelectric sensor in pharmaceutical samples [95]. Yang et al. improved magnetic colloid antibodies (MCAs) using MIPs for the analysis of small extracellular vesicles (sEVs). As depicted in Figure 2, they developed a synthetic strategy to prepare MCAs using a surface imprinting approach, which was based on the formation of a supramolecular complex of organosilane monomers together with template sEVs after polymerization. Magnetic nanoparticles (MNPs) were chosen as a carrier material and organosilanes serving as building blocks were used to form a recognition layer, affording MCAs the ability of recognizing, binding, and sensing sEVs based on the shape and size. The MCAs showed a high affinity to sEVs both in cell culture media and in dilute plasma, resulting in sEV enrichment on the surface of MCAs contributing to a further sEV phenotype protein analysis. They also presented that these MCAs had a higher detection yield with more than three-times enrichment of sEVs checked with the conventional centrifugation method. Furthermore, these MCAs also highlighted reusability with the stability of the organosilica detection layer [96].



**Figure 2.** Preparation of magnetic colloid antibodies (A) and point-of-care application of magnetic colloid antibodies for extracellular vesicle isolation and detection using microfluidic chips (B) [96].

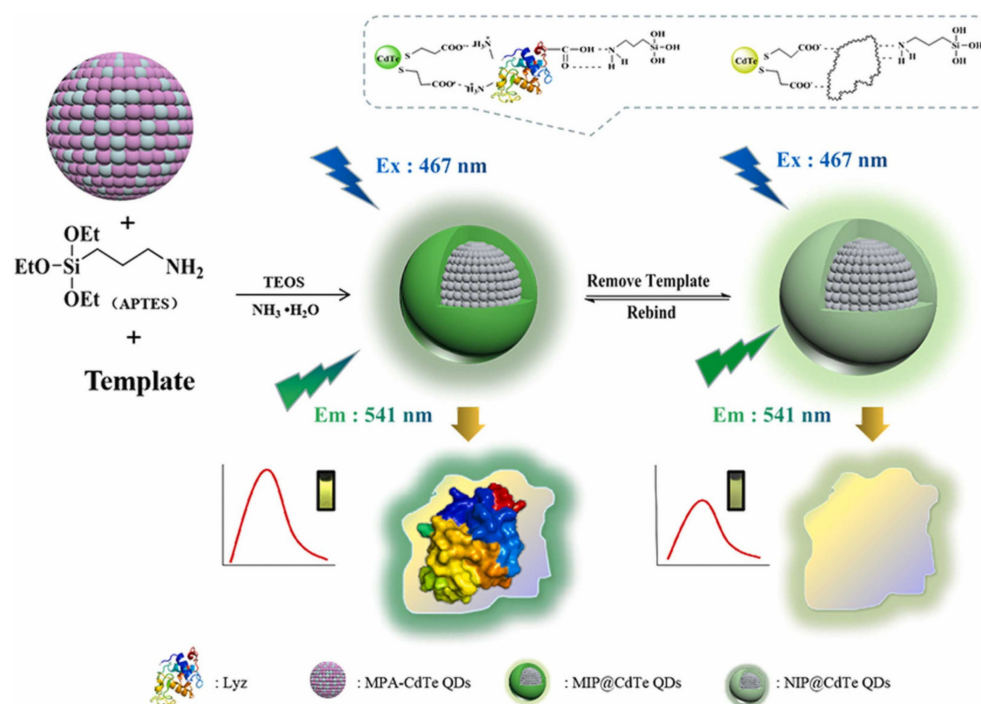
Li et al. prepared an electrochemical sensor using a carbon paste electrode and imprinted particles to detect methyl parathion. They investigated the morphology, surface area, size distribution, and adsorption performance of imprinted microparticles and then adopted them to prepare the sensor. The electrochemical properties were also characterized using electrochemical methods. Checked with only an imprinted particle-packed sensor, a carbon-paste-electrode-modified sensor demonstrates a higher reply toward methyl parathion in the range of  $8 \times 10^{-9}$ – $1 \times 10^{-12}$  mol/L with a low detection limit ( $3.4 \times 10^{-13}$  mol/L). Finally, the sensor was employed to determine methyl parathion in soil and vegetable samples with only simple pretreatment [97]. Gui et al. designed dual-emission imprinted mesoporous particles for the detection of malachite green. They modified the fluorescence sensor with green fluorescent quantum dots doped into the core of silica particles and then the red fluorescent quantum dots were embedded around the pores of the silica particles. They observed a color change from orange to green when the photoluminescence of red quantum dots was selectively quenched in the presence of malachite green. The sensor has a linear response in the broad concentration range (27.4 nM–137  $\mu$ M) with a limit of detection value (17.0 nM). Moreover, they evaluated satisfactory results through the determination of malachite green in river and lake water samples [98].

Zhao et al. also demonstrated encoded quantum dot-imprinted fluorescence sensors with a new encoding strategy. The sensor established a multi-color signal as shown in Figure 3. They studied the fluorescence performance and intensity to validate the strategy and the compatibility of different polar quantum dots, respectively. Pure quantum dots and encoded imprinted particles exhibited remarkable bright fluorescence images under a 365 nm UV lamp, suggesting the successful encoding process and “universal” encoding ability for quantum dots of differing polarity. During the encoding process, the porous structure of the embedding matrix plays an important role for the formation of the high-performance fluorescence bead, which could promote quantum dots to penetrate deeply into the embedding matrix and improve the brightness of resulting encoded particles. They synthesized water-compatible imprinted particles and then utilized them as a fixing matrix for one-by-one incorporation with different quantum dots. They used this sensor for dopamine detection in the 1–300  $\mu$ g/L range and the detection limit was calculated as 0.5  $\mu$ g/L [99].



**Figure 3.** Fluorescent images under a 365 nm UV lamp of pure quantum dots (A) and encoded imprinted particles (B), fluorescent micrographs of encoded imprinted particles (C), fluorescent spectra of pure quantum dots (D) and encoded particles (E) [99].

Nanoparticles are one of the most significant classes of nanostructures. They have a great surface-to-volume ratio and improve chemical reactivity, uniform geometry, stability, binding capacity, and smooth dispersion, and also supply high accessibility of binding sites for template molecules [100]. Additionally, other features of nanoparticles including high electrical conductivity and magnetic permeability supply many benefits including usage in imaging, analyses, and molecular diagnostics [101]. For example, Wang et al. proposed a study about a silica-cross-linked-imprinted-nanoparticle-integrated fluorescence sensor for determining the lysozyme. The synthesis procedure and detection principle of 3-mercaptopropionic acid (MPA)-modified CdTe quantum dot (QD)-embedded imprinted nanoparticles are illustrated in Figure 4. The MPA served as a modifier to embellish the appearance of QDs, and the sulfhydryl group of MPA could chelate with nanoparticles of QDs. They used TEOS as the reaction precursor and  $\text{NH}_3 \cdot \text{H}_2\text{O}$  as an initiator to prepare silica nanoparticles through the hydrolysis. They observed that the fluorescence intensity of the sensor would increase with the coating CdTe QDs after combining the lysozyme. They obtained a linear range at 10–120  $\mu\text{g}/\text{mL}$  of lysozyme concentration with 3.2  $\mu\text{g}/\text{mL}$  as the detection limit. They also endeavored to determine the lysozyme in human serum and chicken egg white with high recovery values (95.6–99.2%) [102].

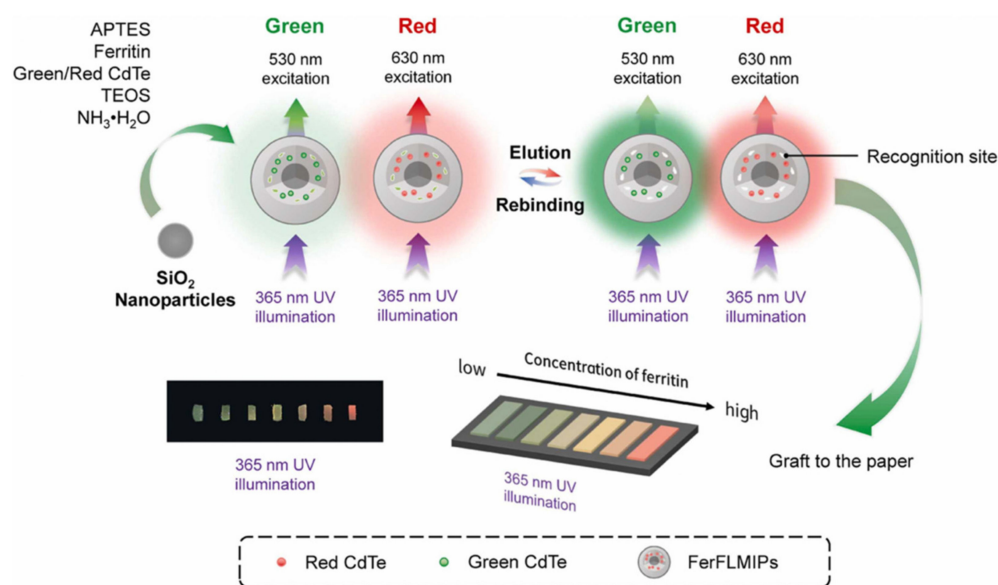


**Figure 4.** Synthesis of MPA-CdTe-QD-embedded-imprinted-nanoparticle-integrated fluorescence sensor for lysozyme detection [102].

Li et al. prepared a test strip for the detection of ferritin using an imprinted-nanoparticle-modified fluorescence sensor.  $\text{SiO}_2$  was selected as a core to synthesize the imprinted nanoparticles using the sol–gel method (Figure 5). The green and red imprinted nanoparticles were prepared individually; thus, the electron transfer or energy transfer between green CdTe and red CdTe could be avoided. The imprinted nanoparticles were light-transmissive, which was conducive to the naked eye detection of fluorescence emission. After nanoparticles were loaded on the test paper, the fluorescence color changed gradually from green to red as the ferritin concentration increased. This ensures that the detection can be carried out with the naked eye. In addition, the imprinted-nanoparticle-modified fluorescence sensor displayed a rapid kinetic affinity and experimental data fit a pseudo-second-order kinetic model. They also performed selectivity experiments and observed that the sensor had a much higher specificity for ferritin than other control proteins. They concluded this sensor



offers a controllable and fast detection method via combining imprinted nanoparticles and test strips [103].



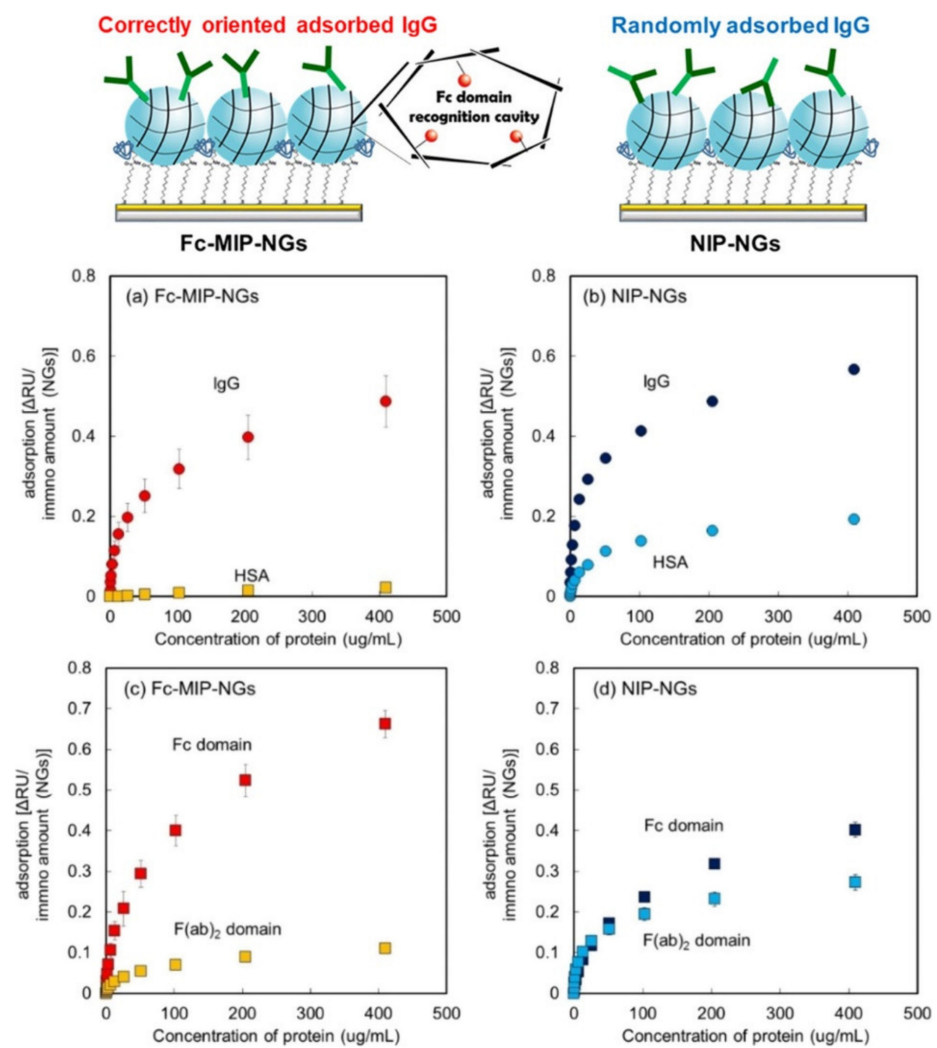
**Figure 5.** Preparation of imprinted-nanoparticle-modified fluorescence sensor for ferritin detection [103].

Zhao et al. also prepared a fluorescence sensor with thermo-sensitive imprinted carbon dots for bovine hemoglobin detection. Thanks to the combination of fluorescence sensitivity of these carbon dots and the high selectivity of the imprinting shell, the sensor had high detection performance relative to the bovine hemoglobin in a range of 0.31–1.55  $\mu\text{M}$  with 1.55  $\mu\text{M}$  as the limit of detection. They also utilized this sensor to detect bovine hemoglobin in real urine with high recovery values (98.6–100.5%) [104]. Rahtuvanoğlu et al. described an imprinted-nanoparticle-immobilized optic sensor to detect histamine in cheese and tuna food samples. Following several characterization experiments, the sensor was used for a kinetic analysis in a broad range (0.001–10  $\mu\text{g/mL}$ ) with a limit value (0.58  $\text{ng/mL}$ ). They observed that this sensor shows high sensitivity, and also the interaction between histamine and imprinted-nanoparticle optic sensors was homogeneous according to the Langmuir isotherm model [105]. Jyoti et al. developed imprinted-nanoparticle-based differential pulse voltammetry and electrochemical impedance spectroscopy sensors for cilostazol and its pharmacologically active primary metabolite detection in human plasma. They provided the optimum structure and predicted the stability of the pre-complex using molecular simulations. After that, they obtained limit of detection values at the signal-to-noise ratio (3) using the ferrocene redox probe as 93.5 and 86.5 nM cilostazol in the concentration range extended from 134 nM to 2.58  $\mu\text{M}$  for both sensors, respectively. Furthermore, the sensors were used for selectivity experiments with cholesterol, glucose, and dehydroaripiprazole and showed that detection was highly selective to common biological interferences (cholesterol and glucose), and less selective to structurally similar dehydroaripiprazole [106]. Cruz et al. prepared an electroactive imprinted-nanoparticle-based sensor tagged with a redox probe for insulin detection. For this aim, imprinted nanoparticles were first computationally designed using “in-silico” insulin epitope mapping and synthesized using solid-phase polymerization. Following the characterization experiments, the electrochemical sensor was developed through chemical immobilization of the imprinted nanoparticles on screen-printed platinum electrodes for kinetic studies. The sensor displayed high sensitivity and selectivity to insulin with a limit of detection of 26 and 81 fM in the buffer and human plasma, respectively, in the 50–2000 pM concentration range. Moreover, the sensor showed high storage stability (168 days) for several rounds of the insulin analysis [107].

#### 4.2. Imprinted-Nanogel-Based Sensors

The development of nanogels stimulates different applications, especially for biomedical purposes. Molecularly imprinted-polymer-based nanogels are beneficial for these applications because of their great safety form to functionalize the morphology and responsive features [108–110]. As an example, Takeuchi et al. synthesized molecularly imprinted nanogels for protein detection using an optic sensor. They obtained fluorescence resonance energy transfer imaging of rhodamine-labeled albumin and fluorescein-conjugated imprinted nanogels that depicted albumin was conquered by nanogels following the injection. They compared the retention behaviors in liver tissue and concluded imprinted nanogels circulated in the blood for longer than non-imprinted nanogels. They also observed that imprinted nanogels passively accumulated in tumor tissue [111]. Cheubong et al. prepared imprinted nanogels for porcine serum albumin detection using a piezoelectric sensor in beef extract samples. After the characterization and kinetic studies, the sensor demonstrated great selectivity and affinity toward porcine serum albumin checked against reference serum albumins from several animals. They obtained high porcine serum albumin specificity of imprinted nanogels that led to the determination of pork contamination with a detection limit of 1% at 0–2000 µg/mL of porcine serum albumin concentration. They mentioned that the molecularly imprinted nanogels are encouraging candidates for food control [112]. Hayakawa et al. demonstrated the regulation of nanomaterial–cell interaction utilizing an optic sensor that was modified with imprinted nanogels for the determination of immunoglobulin G (IgG). They preferred to use the fragment crystallizable domain of IgG due to the distinctive domain recognition feature concluded in the suppression of the immune-response-receptor-possessing macrophages and natural killer cells. They observed that hindrance of the crystallizable domain triggers an immune response. In addition, the acquisition of stealth ability was prosperously shown *in vivo*. As seen in Figure 6, they utilized binding isotherms using an optic sensor of IgG, human serum albumin, and domains in imprinted and non-imprinted nanogels [113]. They examined Fc and F(ab')<sub>2</sub> domains to investigate the Fc domain recognition property, the binding properties of Fc-imprinted nanogels and non-imprinted nanogels. In Fc-imprinted nanogels, the amount of the bound Fc domain was significantly higher than that of the F(ab')<sub>2</sub> domain, and Fc-imprinted nanogels showed excellent selectivity toward the Fc fragment. On the other hand, the difference in adsorbed amounts between the Fc and F(ab')<sub>2</sub> domains was smaller in non-imprinted nanogels, indicating that the non-imprinted nanogels had a low selectivity to the Fc domain. Pellizzoni et al. designed fluorescent imprinted nanogels for the detection of an anticancer drug (sunitinib). The effectiveness of these nanogels in directly detecting sunitinib in human plasma was demonstrated through the fluorescence quenching mechanism inherent in nanogels. The detection process involved straightforward dilution of the plasma sample, enabling the recovery of varying amounts of sunitinib. The concentration of sunitinib was quantified using a well-established calibration curve. The limit of detection (LOD) achieved was an impressive 400 nM, showcasing the sensitivity of the developed nanogels. Furthermore, the within-run variability was found to be less than 9%, day-to-day variability was less than 5%, and the accuracy in recovering sunitinib from spiked samples was commendable. These findings collectively underscore the efficacy and reliability of the synthesized fluorescent molecularly imprinted nanogels as a robust platform for sunitinib detection, particularly in complex biological matrices like human plasma [114].

The comparative analysis between MIPs for biosensing applications is depicted in Table 1. There are several parameters including material and sensor types, target molecule, detection range, limit of detection (LOD) values, selectivity, and real sample applications. The results showed that they can be combined with other methods, technologies, and platforms. Among these biosensing platforms, some of them aim at developing the quality and enabling reliability to detect diseases in their early stages for human health.



**Figure 6.** Binding isotherms obtained from optic sensor of immunoglobulin G and human serum albumin (a,b), and domains (c,d) in imprinted (a,c) and non-imprinted nanogels (b,d) [113].

**Table 1.** Comparative analysis between MIPs for biosensing applications.

Ref.	Material	Sensor	Target	Range	LOD	Selectivity	Real Sample
[95]	Nanoparticle	Piezoelectric	Trypsin	0.125–2 µg/mL	0.07 µg/mL	Bovine serum albumin, pepsin, thermolysin, penicillin G, and salbutamol	Pharmaceutical formulations
[96]	Magnetic nanoparticle	Microfluidic chip	Extracellular vesicles	$5 \times 10^2$ – $10^9$ sEVs/mL	400 sEVs/mL	EpCAM and CD24	Mouse and human plasma
[97]	Microsphere	Electrochemical	Methyl parathion	$1 \times 10^{-12}$ – $8 \times 10^{-9}$ mol/L	$3.4 \times 10^{-13}$ mol/L	Methamidophos and parathion	Soil and vegetables
[98]	Microsphere	Fluorescence	Malachite green	27.4 nM–137 µM	17 nM	Atrazine, glufosinate, ametryn, trifluralin, and pendimethalin	River water and lake water
[99]	Microsphere	Fluorescence	Dopamine	5–300 µg/L and 1–100 µg/L	2 µg/L and 0.5 µg/L	Ions, amino acids, sugars, structural analogues, and other co-existing substances	Human urine, pork kidney, and rabbit serum
[102]	Quantum dot	Fluorescence	Lysozyme	10–120 µg/mL	3.2 µg/mL	Cytochrome c, bovine serum albumin, bovine hemoglobin, and ovalbumin	Human serum and chicken egg white

Table 1. Cont.

Ref.	Material	Sensor	Target	Range	LOD	Selectivity	Real Sample
[103]	Quantum dot	Fluorescence	Ferritin	1–6 $\mu$ M	0.1868 $\mu$ M	Bovine serum albumin, lysozyme, and bovine hemoglobin	Human urine
[104]	Carbon dot	Fluorescence	Bovine hemoglobin	0.31–1.55 $\mu$ M	1.55 $\mu$ M	Bovine serum albumin, ovalbumin, and lipase	Urine
[105]	Nanoparticle	Optic	Histamine	0.001–10 $\mu$ g/mL	0.58 ng/mL	Histidine, tryptophan, and dopamine	Fish and cheese
[106]	Nanoparticle	Electrochemical	Cilostazol	134 nM–2.58 $\mu$ M	86.5 nM	Cholesterol, glucose, and dehydroaripiprazole	Human plasma
[107]	Nanoparticle	Electrochemical	Insulin	50–2000 pM	26 fM	Human proinsulin C-peptide and insulin-like growth factor 1	Human plasma
[111]	Nanogel	Fluorescence	Human serum albumin	35–55 mg/mL	Not available	Fibrinogen and immunoglobulin G	Liver cells
[112]	Nanogel	Piezoelectric	Porcine serum albumin	10–2000 $\mu$ g/mL	12 $\mu$ g/mL	Bovine, human, goat, sheep, and rabbit serum albumin	Pork and beef
[113]	Nanogel	Optic	Immunoglobulin G	0.4–410 $\mu$ g/mL	Not available	Human serum albumin	Mice blood
[114]	Nanogel	Fluorescence	Sunitinib	0–4.5 $\mu$ M	400 nM	SN38 and paclitaxel	Human plasma

## 5. Conclusions

In conclusion, this review has provided a succinct overview of various sensor types and the molecular imprinting method, followed by an in-depth exploration of the recent progress in MIP-based sensors and their diverse applications. As we reflect on the current landscape, it is evident that these sensors exhibit tremendous potential in revolutionizing detection platforms across multiple domains, including environmental monitoring, healthcare, and beyond. Looking toward the future, several exciting perspectives emerge. Firstly, further advancements in sensor technology are anticipated to enhance not only the sensitivity and selectivity of MIP-based sensors but also their integration with emerging technologies such as artificial intelligence and the internet of things. This synergy could usher in a new era of smart and adaptive sensing systems, capable of a real-time data analysis and autonomous decision making. Moreover, the exploration of novel nanomaterials and innovative fabrication techniques holds promise for refining the performance of molecularly imprinted polymers. The quest for sustainable and eco-friendly sensor materials aligns with the growing emphasis on green technologies and environmental consciousness. In the ever-evolving landscape of sensor systems, recent advances have ushered in a transformative era, significantly enhancing the capabilities for characterizing and quantifying target molecules. These advancements not only promise undeniable advantages across diverse applications but also mark a paradigm shift in sensing technologies. The intrinsic benefits of sensors contribute to their indispensability in various fields, offering (i) simple, selective, and sensitive detection, (ii) long-period and automated measurements, (iii) new functional materials for real-time binding, (iv) rapid monitoring and multi-analyte investigation, (v) miniaturization and integration with electronics and microfluidics, (vi) wireless communication networks, and (vii) long-term and online determination capability.

While the potential of MIP-based sensors to revolutionize detection is evident, challenges persist in achieving higher accuracy. Continued research and innovation are essential to overcoming these challenges and unlocking the full efficiency of MIP-based sensors. As we look ahead, the dynamic landscape of sensor technology holds the promise of not only addressing current challenges but also paving the way for unprecedented advancements, making sensors indispensable tools in the pursuit of knowledge and progress.

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