

Chapter 1

Overview of Molecular Recognition and the Concept of MIPs



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1.1 Introduction

Molecular recognition is a fundamental phenomenon governing the interaction between molecules in the realm of chemistry and biology. It plays a central role in a diverse range of processes, spanning from the precise interaction of enzymes to their substrates in biological systems to the selective capture of target molecules in chemical sensors and separation technologies (Tashiro and Shionoya 2020). At its core, molecular recognition involves the ability of molecules to selectively recognize and interact with one another based on their unique structural and chemical characteristics (Gellman 1997). One intriguing aspect of molecular recognition is the development and utilization of molecularly imprinted polymers (MIPs). MIPs represent a remarkable approach in the field of materials science and nanotechnology, where synthetic polymers are designed to mimic the selective binding capabilities of natural receptors, such as antibodies and enzymes (Zhou et al. 2022). This concept has paved the way for the creation of tailor-made materials with the ability to bind and recognize to specific target molecules with high selectivity and affinity (Haupt et al. 2011). Molecular imprinting represents a unique process in which the target molecule or its modified version, serves as a template. This template guides the arrangement and copolymerization of interacting monomers, resulting in the creation of a solid shell resembling a cast. Initially, these monomers form complexes with the template, facilitated by non-covalent or covalent interactions (Murdaya et al. 2022). After the polymerization process and the subsequent template removal, the polymer develops

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binding sites. These binding sites possess a congruence in size, shape and functional group positioning with the original template and they are securely anchored within the cross-linked structure (Saylan and Denizli 2019). Essentially, the polymer retains a molecular memory that enables it to selectively rebind the template molecule. Consequently, molecularly imprinted polymers exhibit a crucial characteristic shared with biological receptors: the skill to specifically bind and recognize particular target molecules (Saylan et al. 2020a). Nonetheless, from a structural viewpoint, MIPs exhibit substantial differences compared to biological receptors. In proteins, individual monomers (amino acids) are meticulously arranged in a sequence, ultimately folding into well-defined secondary and tertiary structures (Zhang et al. 2022). In contrast, MIPs incorporate monomers randomly, lack control over chain length and exhibit a highly intricate, chaotic network due to extensive cross-linking. While the imprinting process creates specific binding sites, their population often remains diverse, influenced by equilibria governing template-monomer complex formation and dynamic polymer chain growth before complete polymerization (Refaat et al. 2019). The resulting varied pore size distribution in the end material, along with the confinement of binding sites within the bulk, can result in slow mass transfer. It's worth noting that MIPs may contain thousands or even millions of binding sites, a notable difference from biological receptors, which generally have few or just one (Rahman et al. 2022). Although not universally problematic, these characteristics can limit the substitution of MIPs for antibodies in certain applications (Refaat et al. 2019). Consequently, current research in the field of MIPs is directed toward identifying solutions or alternative approaches to address these potential limitations. One of the appealing aspects of molecular imprinting is its versatility, allowing it to be applied to a wide array of target molecules (Ali and Omer 2022). The technique has been successfully employed to imprint small organic molecules, such as sugars, steroids, nucleotides, peptides, amino acids, pesticides and pharmaceuticals (Bozal-Palabiyik et al. 2020). This technique is now considered a well-established and nearly routine practice. Additionally, MIPs can be synthesized in various physical forms such as quasi-soluble nanogels, nanocomposites, nanostructured films, thin films, nanowires, nanospheres and including porous microspheres (Rahman et al. 2022).

In this chapter, we will delve into the fascinating world of molecular recognition and explore the underlying principles of MIPs. We will discuss the key concepts, applications and the intricate molecular imprinting process that allows scientists and engineers to engineer materials capable of molecular recognition. Furthermore, we will explore the diverse range of applications where MIPs have found utility, from pharmaceuticals and environmental monitoring to medical and biotechnology. As we delve deeper into this topic, we will gain a better understanding of how molecular recognition and MIPs are shaping the landscape of modern science and technology.

1.2 Molecular Recognition

Molecular recognition is a fascinating and vital phenomenon that underpins numerous processes in chemistry, biology and materials science. Molecules can interact selectively with one another based on their unique structural and chemical properties (Cao et al. 2019). This selective interaction is akin to a molecular handshake, where molecules recognize each other and form specific, complementary bonds, enabling a wide array of essential functions and applications (Chen et al. 2020; Persch et al. 2015).

- The basic principles of molecular recognition are as follows:

Lock-and-key principle: The fundamental concept of molecular recognition can be likened to a lock-and-key mechanism. In this analogy, molecules act as keys, and their binding sites or receptors serve as locks. For a successful interaction to occur, the key (molecule) must precisely fit into the lock (receptor), ensuring a secure and specific connection (Chatterji 2016).

Complementary interactions: Molecular recognition is driven by various intermolecular forces, such as hydrophobic effects, electrostatic interactions, van der Waals forces and hydrogen bonding. These forces play a pivotal role in determining the strength and specificity of molecular interactions (Paleos et al. 2001).

Specificity and affinity: Molecular recognition is highly specific, meaning that a molecule will typically bind selectively to its cognate receptor or target. This specificity arises from the precise geometric and chemical complementarity between the interacting molecules. Additionally, molecular interactions can exhibit varying levels of affinity, reflecting the strength of the bond formed between the molecules (Skerra 2007).

- The biological significance of molecular recognition is as follows:

Enzyme–substrate binding: Enzymes recognize and bind to specific substrates, facilitating chemical reactions essential for metabolism and cellular functions.

Antigen–antibody interactions: The immune system relies on molecular recognition to neutralize and identify foreign invaders, such as viruses and bacteria (Ciferri 2021).

Hormone–receptor interactions: Hormones bind to receptors on target cells, triggering a cascade of cellular responses that regulate bodily functions (Behncken and Waters 1999).

Cell–cell communication: Cells recognize and respond to signaling molecules, enabling coordination within tissues and organs (Krengel and Bousquet 2014).

- Some of the technological applications of molecular recognition are as follows:

Chemical sensors: Molecularly selective materials are used in chemical sensors to detect specific analytes, ranging from pollutants in the environment to biomarkers in medical diagnostics (Pirondini and Dalcanale 2007).

Drug design: Understanding molecular recognition is crucial in designing pharmaceutical compounds that selectively interact with their target proteins, minimizing side effects and maximizing therapeutic efficacy (Babine and Bender 1997).

Separation technologies: Molecular recognition-based materials, such as Molecularly Imprinted Polymers (MIPs), are employed in chromatography and filtration for the separation and purification of molecules (Moyer et al. 2013).

Molecular electronics: Researchers are exploring molecular recognition for the development of molecular switches and devices, potentially revolutionizing the field of electronics (Heath and Ratner 2003).

1.3 Molecular Imprinting Method

The molecular imprinting method is a fascinating and powerful technique in the field of materials science and chemistry. It is designed to create highly specific recognition sites, often referred to as molecular memory, within a polymer matrix. These recognition sites are tailored to bind selectively with a particular target molecule, making molecular imprinting an essential tool for various applications, including sensors, drug delivery and chromatography (Chen et al. 2016). The process of molecular imprinting begins with the selection of a template, known as the target molecule. This template molecule serves as the blueprint for creating complementary binding sites within a polymer matrix (Tarannum et al. 2020). The template is mixed with a functional monomer, which can form reversible covalent bonds with the template. Cross-linking agents are also introduced to link the monomers together, creating a three-dimensional polymer network (Piletsky 2006; Whitcombe et al. 2014). Once the polymerization process is complete, the template molecule is removed, leaving behind cavities or imprints with specific sizes, shapes and chemical functionalities that precisely match the template molecule (Saylan and Denizli 2020). These imprints are essentially the molecular memory of the target molecule (Arabi et al. 2021; Kandimalla and Ju 2004). Usually, there are two primary approaches for creating MIPs, relying on interactions between the functional monomer and the template. Covalent imprinting, which operates in a stoichiometric manner, ensures that functional monomer residues are exclusively present within the imprinted cavities (Huang et al. 2021). This approach is traditional and frequently relies on reversible condensation reactions involving Schiff's base, ketals/acetals, and boronate esters. Nonetheless, covalent imprinting is seen as somewhat rigid, primarily due to the constraints imposed by reversible condensation reactions. Additionally, achieving thermodynamic equilibrium can be challenging because strong covalent interactions lead to slow binding and dissociation (Dong et al. 2021).

In contrast, noncovalent imprinting relies on p-p interactions, van der Waals forces, hydrogen bonding, and ionic interactions. Among these, hydrogen bonding, especially between methacrylic acid (MAA) groups and primary amines in nonpolar

solvents, stands out as the most prevalent form of noncovalent interaction (Włoch and Datta 2019). Lately, noncovalent imprinting has garnered attention as a common synthesis approach, owing to its straightforward operation and the rapidity of binding and removal processes. Nonetheless, noncovalent imprinting is sensitive to even slight disruptions in the interactions that stabilize the complex, such as the presence of water, rendering it less robust (Ndunda 2020). To amalgamate the longevity associated with covalent imprinting and the swift target uptake observed in noncovalent imprinting, a novel technique referred to as semicovalent imprinting has surfaced (Chen et al. 2016). This approach offers an intermediate solution in which the template is covalently linked to the functional monomer, while the process of template rebinding relies on noncovalent interactions (Akgönüllü et al. 2023).

1.4 Molecularly Imprinted Polymers

MIPs stand as a captivating and groundbreaking category of materials, finding application in a diverse array of fields. These engineered polymers possess a distinctive ability: the capacity to selectively identify and attach to precise target molecules at the molecular level. Often referred to as plastic antibodies, MIPs mimic the role of their biological counterparts in molecular recognition (Piletsky et al. 2001). The primary advantage of MIPs lies in their capacity to selectively identify and attach to the template molecule or molecules that closely resemble its structure (Lusina and Ceglowski 2022). This selectivity emerges from the precise molecular interactions between the imprints within the polymer and the target molecule. These interactions can encompass electrostatic attractions, van der Waals forces and hydrogen bonding (Shimizu and Stephenson 2010; Wang et al. 2023c). This selectivity makes MIPs invaluable in various applications where precise molecular recognition is required (Mahony et al. 2005). MIPs are created through a process known as molecular imprinting. This process involves polymerizing a mixture of cross-linkers and monomers in the presence of a template molecule (Lusina and Ceglowski 2022). The template molecule is the specific molecule to which the resulting MIP will be designed to bind. After the polymerization process reaches its conclusion, the template molecule is removed, resulting in binding sites within the polymer network that match the size, shape and functionalities of the target compound (Aghoutane et al. 2020). These imprinted polymers are characterized by their stability, resilience and ability to withstand a broad spectrum of pH levels, solvents and temperature variations (Cormack and Elorza 2004). Therefore, MIPs emulates the selective retention of target molecules (similar to antibody-antigen interactions) without the associated stability constraints observed in natural receptors (Mujahid et al. 2023).

Moreover, the production of MIPs is notably uncomplicated and budget-friendly, presenting a practical substitute for utilizing natural receptors. There are three primary methodologies for MIP synthesis: covalent, noncovalent and semi-covalent methods. (Włoch and Datta 2019). In the covalent approach, reversible covalent

bonds are established between the template molecule and monomers before polymerization. Following this, the template is removed from the polymer by breaking the corresponding covalent bonds, which are then reformed upon the rebinding of the target compound (Li et al. 2019). This technique yields a polymer with a comparatively consistent distribution of binding sites, thereby diminishing the presence of nonspecific sites owing to the robust stability of template-monomer interactions (Pandey et al. 2023). Nonetheless, the covalent approach comes with limitations because it can be challenging to design a template-monomer complex in which covalent bond formation and cleavage can readily take place under mild conditions (Rajpal et al. 2023). The semi-covalent approach provides an intermediate alternative. In this scenario, the template is covalently linked to a functional monomer, but the process of template rebinding relies exclusively on noncovalent interactions (Ensafi and Nasr-Esfahani 2021). The noncovalent approach, pioneered by Arshady and Mosbach, revolves around the establishment of relatively weak noncovalent interactions, including hydrogen bonds and ionic interactions, between the template molecule and chosen monomers before the polymerization process begins (Arshady and Mosbach 1981). This approach is the most adopted method for producing MIPs, primarily due to its simplicity and the extensive selection of available monomers (Ding et al. 2020; Saylan et al. 2023; Turiel and Martín-Esteban 2010).

1.4.1 Concept of MIPs

MIPs represent a pioneering concept in the realm of materials science and molecular recognition. They are a class of synthetic polymers engineered with a specific purpose: to selectively bind and recognize target molecules with a high degree of precision (Wulff 2013). The foundational principle of MIPs revolves around the concept of molecular imprinting, a process that mirrors the natural lock-and-key mechanism of molecular recognition but within a synthetic framework (Zaidi 2020). At the heart of MIPs lies the concept of molecular imprinting. This intricate process begins with the selection of a target molecule, often referred to as the template. This template molecule possesses unique structural and chemical characteristics that are of interest for selective recognition (Muratsugu et al. 2020). The template is then embedded within a mixture of monomers and cross-linkers (Suzaei et al. 2023; Tse Sum Bui et al. 2023). During polymerization, these monomers and cross-linkers form a polymer network around the template molecule. This polymerization process imprints the template's molecular structure onto the polymer matrix, creating binding sites that are specifically complementary in terms of chemical functionality, shape and size to the template (Mayes and Mosbach 1997). A standard MIP synthesis protocol consists of several key components, including a solvent, a polymerization initiator, a cross-linker, a functional monomer and template (Refaat et al. 2019). To enhance the properties of MIPs, numerous endeavors have been undertaken, as the polymerization reaction is affected by a variety of factors. These factors include the monomer and cross-linker type and quantity, the selection of solvent and initiator, and

the temperature and duration of the polymerization process (Madikizela et al. 2022). A summary of the various templates, monomers, various production techniques and applications of MIPs is given in Table 1.1.

Functional monomers: Functional monomers play a crucial role in the formation of templates with pre-polymerization complexes. These monomers possess specific functional groups that engage in interactions and binding with the template molecules (Zhang et al. 2010). The choice of an appropriate functional monomer is of paramount importance to establish a robust connection with the template, ultimately leading to the creation of well-defined antibody-antigen complexes or donor-receptor during the polymerization process (Chen et al. 2016). The selection of the most suitable functional monomer is a critical factor in tailoring specific cavities designed to mimic template molecules. It's worth noting that the quantity of functional monomers employed in the creation of MIPs is finite, which can impose limitations on their selectivity and potential applications (Hasanah et al. 2021).

To establish a strong and precise interaction with the template, it is imperative to design and incorporate a novel functional monomer characterized by a high degree of specificity and selectivity towards the target analyte (Elaine et al. 2022). Functional monomers typically feature two common domains: one for molecular recognition and another for polymerization. The interactions and mechanisms between the template molecule and the functional monomer take place during the pre-polymerization

Table 1.1 Various templates, monomers, fabrication techniques and applications of MIPs

Template	Monomers	Fabrication techniques	Applications
Proteins	Methacrylate derivatives, acrylic acid	Surface imprinting, covalent imprinting	Bio-sensing, drug targeting, biomimetic catalysis
Peptides	Methacrylates, styrene derivatives	Mini-emulsion polymerization, sol-gel polymerization	Biomolecular recognition, diagnostics
Nucleotides	Methacrylates, vinyl monomers	Electrochemical polymerization	DNA sensing, diagnostic devices
Amino acids	Methacrylates, acrylamide derivatives	Molecularly imprinted membranes	Enantioselective separation, chiral recognition
Drugs	Acrylates, methacrylates	Suspension polymerization	Controlled drug release, therapeutic delivery
Environmental pollutants	Methacrylates, acrylamide derivatives	Emulsion polymerization, bulk polymerization	Water purification, sensor development
Small molecules	Acrylamide, methacrylate derivatives	Bulk polymerization, precipitation polymerization	Drug delivery, sensing, separation

phase, and the outcome is heavily influenced by the quantity and quality of the recognition component within a MIP (Cowen et al. 2020). Functional monomers encompass various types, including carboxylic acids, sulfonic acids, heteroaromatics, anilines and pyrroles, among others (Pratama et al. 2020). Examples of carboxylic acid-based monomers comprise benzoic acid, acrylic acid and methacrylic acid (MAA) (Nishchaya et al. 2023). On the other hand, sulfonic acid monomers encompass compounds like acrylamide methylpropane sulfonic acid, while heteroaromatic base monomers encompass vinylimidazole and vinylpyridine (BelBruno 2018).

Templates: The choice of a template plays a crucial role in organizing functional groups within functional monomers. The functional group within a template, which may include ester, amide, hydroxyl, carboxyl or amino groups, significantly influences the performance of MIPs (Kadhem et al. 2021). Templates with highly polar groups can facilitate the creation of high-performance MIPs because they lead to the formation of more stable molecular complexes. Polymers that can establish hydrogen bonds with functional monomers have the potential to display a high degree of affinity and selectivity, thanks to the directional, saturating and strong nature of hydrogen bonds (Morsi et al. 2023). The goal of molecular imprinting is to synthesize MIPs that closely resemble biological receptors, with the potential to replace them in various applications (Wang et al. 2023a). An ideal template must meet three key criteria: first, its functional groups should not hinder the polymerization process; second, it should demonstrate exceptional chemical stability throughout polymerization; and third, its functional groups should be capable of forming complexes with functional monomers (Ensafi et al. 2021). Templates for specific targets find broad application in various fields, including clinical, industrial, chemical, pharmaceutical, biological and environmental domains (Haupt 2010). The creation of molecular imprints for organic molecules like tyrosine, tetracycline and atrazine, as well as ion-imprinted polymers tailored for toxic heavy metals such as aluminum ions, mercury ions and chromium ions, has been effectively accomplished. While similar approaches can be used to imprint biological macromolecules like proteins or viruses, the imprinting technique for these complex templates remains a challenge (Soufi et al. 2021). Macromolecules like proteins are exceptionally complex and have nonspecific recognition sites on their surfaces, often due to the presence of charged residues (Janiak and Kofinas 2007).

Initiators: An initiator acts as a substance that initiates the beginning of polymer chains and accelerates the polymerization process. The quantity of initiators used is considerably less than the number of functional monomers. The techniques utilized in MIP preparation include electropolymerization, photopolymerization, and free radical polymerization (FRP) (Chen et al. 2016). FRP can be initiated either through the application of heat (thermal) or exposure to light (photochemical). It is versatile and can be applied to a broad spectrum of functional groups and template structures. (Malik et al. 2019). Various types of initiators find use in the MIP preparation process, with common ones including potassium persulfate (KPS), dimethyl acetal of benzyl (BDK), benzoyl peroxide (BPO), azobisdimethylvaleronitrile (ADVN) and azobisisobutyronitrile (AIBN) (Pratama et al. 2020; Xu et al. 2020a). Photopolymerization, a form of FRP, commences through exposure to light. This approach

offers several advantages, lower reaction temperatures, minimal waste generation, increased productivity and reduced energy consumption (Lee et al. 2001). However, the depth of light penetration is constrained and depends on the wavelength and spectral distribution. The photochemical initiation process involves subjecting relevant photoinitiators to UV irradiation (Paruli et al. 2021). Typically, organic photoinitiators are employed in photopolymerization. Organic polymerization photoinitiators are categorized into various classes based on their function (Fuchs et al. 2012). Often, a mixed type of photoinitiator is used to achieve the best overall curing speed and minimal color formation. Commonly used organic photoinitiators include cationic photoinitiators, thioxanthenes, miscellaneous compounds, benzophenone, benzyl/benzoin compounds and acetophenone (Pratama et al. 2020). Electropolymerization is a commencement procedure that manages the quantity of cycles or amperage directed towards an electrode to produce a polymer film with a predetermined thickness (Zembrzuska et al. 2019). An electrosynthesized polymer can serve as the framework to anchor MIP particles and enable their interaction with the electronic surface. In this method, MIP particles are dispersed in a monomer solution, and then polymerization takes place. Electropolymerization proves to be a valuable approach for creating MIPs, especially when crafting electrochemical sensors (Peng and Su 2015; Roushani and Zalpour 2021).

Solvent: Porogens play a vital role in the polymerization process by serving as dispersing agents and agents for creating pores within the polymer matrix. These substances are responsible for dissolving all the components used in the synthesis of MIPs (Song et al. 2022). The polarity of a porogen can profoundly influence the relationships between functional monomers and the template, especially in non-covalent interaction systems. In non-covalent imprinting techniques, it is common to use a non-polar or less polar organic porogen, like chloroform, acetonitrile or toluene, to attain the highest level of imprinting efficiency (Esfandyari-Manesh et al. 2011). Ultimately, the selection of solvent or porogen is what dictates the adsorption and morphological attributes of the resulting polymer (Schmidt et al. 2005).

Crosslinkers: A crosslinker plays a crucial role in arranging the functional monomers around template molecules as the polymerization takes place. Integrating these elements into the production of MIPs leads to the formation of a polymer that is extensively interconnected and rigid once the template has been extracted (Yan and Row 2006). The specificity and binding capacity of an MIP are directly impacted by the specific crosslinking agents chosen and the amount used. Generally, an inadequate crosslinker can result in mechanical instability in the MIP (Du et al. 2014). Conversely, the increased use of crosslinker reduces the quantity of recognition sites within the MIP. In the preparation of MIPs, a combination of non-covalent and covalent interactions is employed (Bonatti et al. 2021). There is a distinct interaction that takes place between the functional monomer and the template when the analyte is present. In the context of covalent imprinting, the resulting imprinted cavity retains a portion of the functional monomer and upholds a stoichiometric ratio (Spivak 2005). Covalent imprinting relies on reversible covalent bonds and typically employs crosslinkers such as triallyl isocyanurate (TAIC) (Rahman et al. 2012), bis-(1-(tert-butylperoxy)-1-methylethyl)-benzene (BIPB) (Pratama et al. 2020) or

dicumylperoxide (DCP) (Idil et al. 2021). In contrast, non-covalent imprinting relies on π - π interactions, Van der Waals forces, hydrogen bonds and ionic interactions (He et al. 2020). Of these, hydrogen bonds are the most frequently utilized. Non-covalent imprinting methods have gained wider recognition in MIP production and utilize crosslinkers like ethylene glycol dimethacrylate (EGDMA) (Iturralde et al. 2014), methylenediacylamide (MBAA) (Lanza and Sellergren 2004), divinylbenzene (DVB) (Ma and Row 2018), diisopropenylbenzene (McCluskey et al. 2007), bisacryloylamidopyridine (Divya et al. 2023), N,O-bismethacryloyl ethanolamine (NOBE) (Sibrian-Vazquez and Spivak 2004), glycidyl methacrylate (GMA) (Wang et al. 2020) and trimethylene trimethylolpropane (TRIM) (Muhammad et al. 2012).

1.4.2 Commercialization of MIPs

MIPs have emerged as a versatile and promising technology with a wide range of applications, driving their commercialization in various industries (Gkika et al. 2024). So, these synthetic polymers are designed to mimic the molecular recognition properties of natural receptors, such as antibodies and enzymes. The ability to selectively bind to specific target molecules makes MIPs valuable in numerous real-world contexts (Bräuer et al. 2021). Key benefits stem from the inherent stability, chemical inertness, reusability, and scalability of these imprinted materials (Chen et al. 2016). In recent years, there has been a growing interest in the commercialization of MIPs, driven by their unique properties and versatile applications (Wang et al. 2023a; Ayivi et al. 2023; Suzaei et al. 2023). One of the notable applications of MIPs is in sensing and diagnostics. These polymers can be tailored to recognize and capture specific analytes, such as toxins, pathogens, or biomarkers. In the medical field, MIP-based sensors are employed for the detection of diseases, offering rapid and accurate diagnostic results. The commercialization of MIP-based diagnostic tools is gaining traction, particularly in point-of-care testing and personalized medicine (Li et al. 2024). MIPs find extensive use in environmental monitoring for the detection and removal of pollutants (Rahman et al. 2022). They can be designed to selectively adsorb contaminants like heavy metals, pesticides, or hydrocarbons. The commercial applications of MIPs in water and air purification systems contribute to sustainable environmental practices, ensuring the safety of ecosystems and human health (Ostovan et al. 2022). In the pharmaceutical industry, MIPs are utilized for drug delivery systems and separation processes (Zaidi 2016). The tailored molecular recognition properties of MIPs enable controlled release of drugs, enhancing therapeutic efficacy while minimizing side effects. The commercialization of MIP-based drug delivery platforms is a promising avenue for pharmaceutical companies seeking innovative solutions for patient care (Bodoki et al. 2021). Moreover, MIPs are increasingly finding applications in the food and beverage industry, particularly in the detection and removal of contaminants or undesirable compounds (Basak et al. 2022). They are employed in the production of high-quality and safe food products by selectively capturing toxins, allergens, or unwanted flavors. The commercial use of MIPs in food safety ensures

compliance with regulatory standards and meets consumer demands for quality assurance (Lehotay and Chen 2018). In forensic science, MIPs play a crucial role in the identification and detection of specific substances, such as drugs or explosives. These polymers can be tailored to recognize the molecular signatures of illicit substances, aiding law enforcement agencies in forensic investigations. The commercialization of MIPs in forensic applications enhances the precision and efficiency of substance analysis (Karadurmus et al. 2022). MIPs are also integrated into various industrial processes for purification, catalysis, and separation. Their use in chromatography and solid-phase extraction contributes to the efficiency of manufacturing processes across industries such as petrochemicals, cosmetics, and materials science. The commercial adoption of MIPs in industrial applications promotes cost-effectiveness and sustainability (Saylan et al. 2024). As research continues to advance, MIPs are likely to play an increasingly pivotal role in addressing complex problems and meeting the evolving needs of various industries (Ostovan et al. 2022). As the commercialization of MIPs continues to progress, collaborations between research institutions and industry players are crucial for developing scalable and cost-effective production methods (Ayankojo et al. 2022). The versatility of MIPs across different sectors highlights their potential to revolutionize various aspects of technology, healthcare, and manufacturing (Leibl et al. 2021).

1.4.3 Applications of MIPs

In the realm of analytical procedures, it is typically required to possess the capability of selectively and sensitively detecting the target analyte. These requirements have been addressed by employing natural antibodies, receptors, or enzymes (Justino et al. 2015). Regrettably, the utilization of biomolecules is constrained to moderate circumstances due to the susceptibility of protein denaturation at severe temperatures, pH levels, and exposure to organic solvents. Furthermore, the process of immobilization is characterized by its demanding nature and the subsequent obstacles it poses in terms of coating surfaces, such as transducers. Moreover, it is commonly observed that they tend to possess a significant cost or require a substantial investment of time for their production. Artificial receptors have been designed in order to overcome these constraints (Wackerlig and Schirhagl 2016). MIPs have garnered significant interest and have emerged as a compelling choice in various domains, including separation, chemosensing, biosensing, drug delivery, catalysis and degradation. This interest stems from the distinctive features exhibited by MIPs, such as specificity in recognizing target structures and universality of application. These polymers are highly physically stable, can be easily prepared, exhibit remarkable robustness, and are cost-effective when compared to other recognition systems (Chen et al. 2016). The aim of this part is to offer a concise overview of MIP-based composite systems and the specific investigations conducted in this domain, focusing on research papers published after 2020.

Sensing Applications

Sensor systems combine a physical transducer (i.e., electrochemical, optical or piezoelectric) with a sensing component. This integration allows for the translation of interactions between the target and recognition molecules into a signal that can be measured. The utilization of sensor systems facilitates the expeditious and precise detection of labeled or label-free substances, hence diminishing the duration of assays and minimizing the requirement for preliminary sample pre-processing procedures. Therefore, these systems serve as robust alternatives to conventional analytical methodologies (Saylan et al. 2020a). The integration of sensors with MIPs has been successfully achieved for the purpose of screening in several fields, such as medical diagnostics (Ayankojo et al. 2020; Kidakova et al. 2020; Li et al. 2022; Raziq et al. 2021), food safety (Caldara et al. 2022; Işık et al. 2021; Wang et al. 2023b; Xu et al. 2020b) and environmental applications (Arabi and Chen 2022; Singh et al. 2020).

A recent study focused on the synthesis of MIPs that exhibit a high selectivity towards lactate and the key interaction sites between the MIPs and the lactate-monomer complex was also investigated. For the purpose of rapid detection of variations from established “normal” lactate levels (1 mM), a linear range of 0.1–1.7 mM was selected in this study. Furthermore, in order to assess the selectivity capabilities of synthesized MIPs, malic acid and sodium 2-hydroxybutyrate were employed as competitive interferents owing to their chemical similarity to the target compound. The thermal characterizations provided confirmation of interactions occurring between the template-monomer complex. Additionally, these characterizations indicated that lactate could be integrated into the polymer matrix without causing substantial changes to the thermal characteristics of the material. The analysis of surface area provided evidence for the effective incorporation of lactate cavities, as indicated by a 1.3-fold increase in comparison to the MIP relative to the NIP. Additionally, the analysis revealed the presence of interconnected networks and potential merging of cavities, which may impose constraints on the binding capacity of MIPs. The results indicate that the MIP possesses a notable capacity to recapture lactate molecules, with an efficiency reaching up to 63.5%. Furthermore, the selective properties were examined by studying structurally analogous compounds such as malic acid and sodium 2-hydroxybutyrate, which acted as interfering substances in lactate-containing cavities (Mustafa and Leese 2023). The development of a non-invasive, material-based electrochemical sensor that provides continuous monitoring of fenamiphos (FMS) levels in vegetable samples is of great importance for the regulation and management of agricultural products. The present study involved the fabrication of an electrochemical sensor utilizing gold stabilization on sensitive MIP/metal-organic framework/graphite carbon nitride (MIP-Au@MOF-235@g-C₃N₄). This sensor was designed for the purpose of continuous examination of the FMS level in real samples, exhibiting a notable degree of sensitivity. The MIP-Au@MOF-235@g-C₃N₄ composite had a significantly enhanced specific surface area and catalytic performance. Moreover, the sensor demonstrated a remarkable sensitivity of 1.07 $\mu\text{A}/\mu\text{M}$ and a wide linear range spanning from 0.01 to 16.4 μM . Furthermore,

the technique that has been put out demonstrates recoveries that are deemed satisfactory, ranging from 94.7% to 107.9% (Mehmandoust et al. 2023). *Pseudomonas aeruginosa* (*P. aeruginosa*) is a widely distributed bacteria that exhibits resistance to multiple drugs, and has the potential to induce severe infections. Another study was carried out with the objective of developing a thermal sensor for the indirect detection of *P. aeruginosa* contamination utilizing MIPs. The developed sensor was based on the utilization of MIPs for pyocyanin recognition, which acts as the predominant toxin produced by *P. aeruginosa*. Phenazine was employed as a mimic template to assess various polymeric compositions in order to develop a specific MIPs for the recognition of pyocyanin. Based on the findings derived from the UV–vis study conducted to evaluate the sensitivity of MIPs, the synthesized MIPs had an imprinting factor of 1.59 and a rebinding capacity of 30 $\mu\text{mol/g}$. The immobilization of MIPs onto planar aluminum chip was carried out using an adhesive layer in order to conduct thermal resistance tests at pyocyanin concentrations that are clinically relevant (ranging from 1.4 to 9.8 μM). This immobilization process allowed for the achievement of a limit of detection (LOD) of $0.347 \pm 0.027 \mu\text{M}$. In order to assess the practicality of utilizing the MIP-based sensor in clinical diagnostics, saliva samples spiked with pyocyanin were used, resulting in the successful detection of the target analyte at a detection limit of $0.569 \pm 0.063 \mu\text{M}$. The sensor that has been developed is capable of detecting the presence of toxins, even at low concentrations (Frigoli et al. 2023). Insulin is a peptide hormone responsible for the regulation of blood glucose levels and serves as a marker for diabetes. A novel electrochemical insulin sensor was fabricated by employing a gold electrode that was surface-modified with carboxylated multiwalled carbon nanotubes (f-MWCNTs) and MIP cryogel. The MIP exhibited distinct binding sites for insulin, whilst the macroporous structure of the cryogel facilitated the efficient transport of insulin molecules towards these binding sites (Fig. 1.1). The utilization of f-MWCNTs resulted in an increase of the sensor's effective surface area and conductivity, while concurrently weakening the potential necessary for insulin oxidation. The oxidation of insulin was quantitatively assessed in a continuous flow system with the application of square wave voltammetry. The cryogel/f-MWCNTs sensor demonstrated a linear range spanning from 0.050 to 1.40 pM, exhibiting an exceptionally low LOD of 33 fM. The sensor demonstrated a notable level of selectivity and maintained its stability for an extended duration of 10 weeks during dry condition at ambient temperature. The findings of insulin quantification in human serum utilizing the sensor shown a strong concordance with the outcomes obtained from the Elecsys insulin assay. The created sensor presents a potentially advantageous option for the diagnosis and management of diabetes (Wardani et al. 2023).

Sharma et al. outlines a method to detect cortisol in biological samples and aqueous solutions. It involves the use of MIPs-coated graphite electrodes that have been modified by silver nanoparticles through the technique of differential pulse voltammetry (DPV). The imprinted graphite electrode features an expanded surface area due to the incorporation of silver nanoparticles, resulting in enhanced electroactivity. The responses of DPV, with its exceptional electrical conductivity, was elucidated. The study applied different cortisol concentrations (between 0.395 and 3.96 nM) to the MIPs-coated graphite electrodes, and the DPV method yielded signal responses with

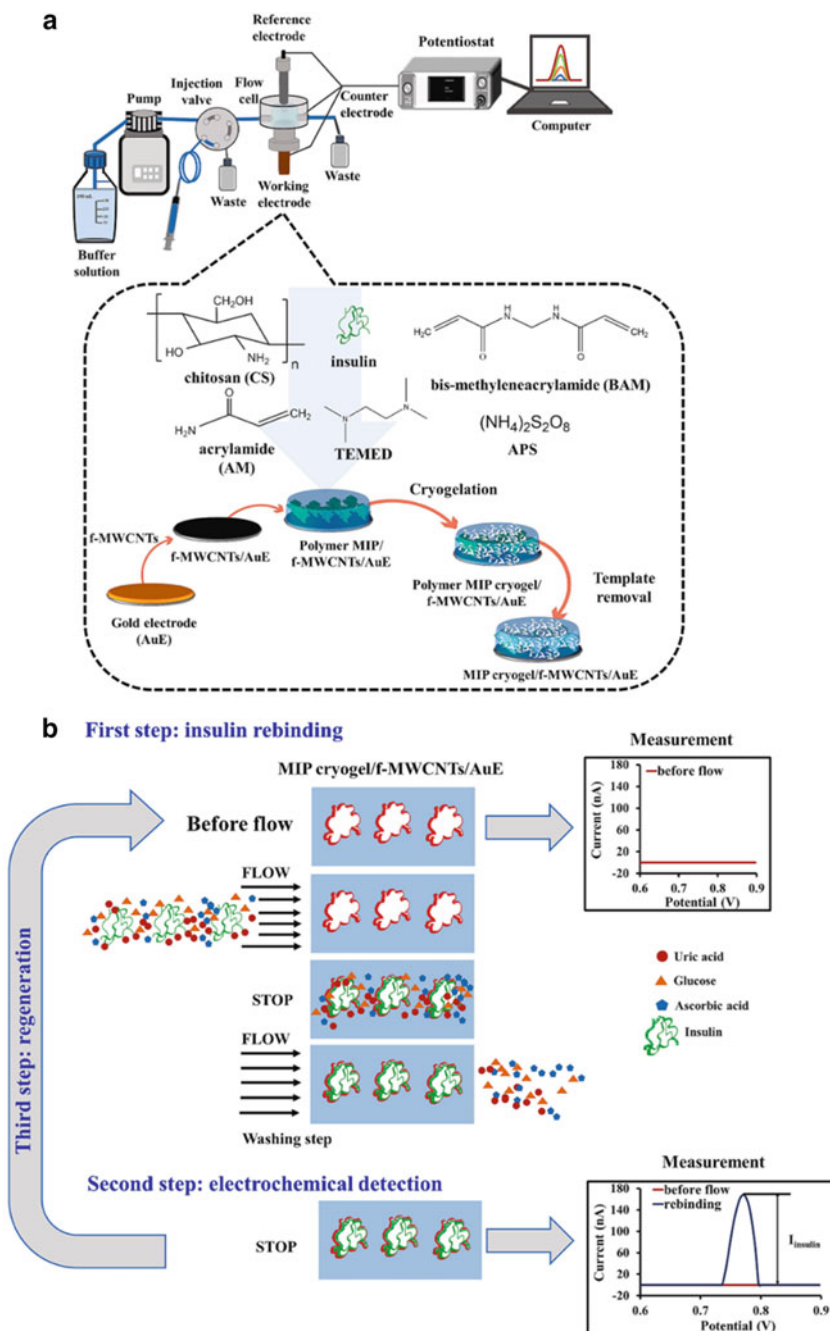


Fig. 1.1 Scheme of the MIP cryogel/f-MWCNTs modified gold electrode preparation and its use as a working electrode in a flow system (a) and steps of the insulin detection (b) (Wardani et al. 2023)

a high regression R^2 value of 0.9951. The tailored electrode exhibited strong electrocatalytic activity with a low LOD recorded at 0.214 nM. These results underscore the significant potential of this sensor for the determination of cortisol in biological samples (Shama et al. 2023). In this study, Saylan introduces the development of a MIPs-based optical sensor designed to detect *Enterococcus faecalis* (*E. faecalis*), a fecal contaminant found in water. The optical sensor employs an imprinted nanofilm produced with combining gold nanoparticles. Thorough characterization results were conducted to assess the sensor's performance, encompassing aspects such as kinetics, reusability, selectivity, and real sample analysis for *E. faecalis* detection. The results indicate that the optical sensor shows exceptional determination capabilities, boasting a low LOD of 6.6×10^3 cfu/mL and a high correlation coefficient ($R^2 = 0.9886$) over the concentration range of 5×10^4 – 1×10^8 cfu/mL. Crucially, the sensor's effectiveness is not confined to buffer solution but extends to water solutions, underscoring its suitability for environmental applications. According to the findings, it is reasonable to conclude that the developed optical sensor holds substantial promise for other bacteria detection, giving a cost-effective solution with heightened sensitivity (Saylan 2023). Saylan et al. also synthesized magnetic nanoparticles which are combined with optical surfaces for detecting a clinically significant biomarker, interferon- α , in both buffer and artificial plasma sample solutions. Initially, they synthesized the magnetic nanoparticles and conducted a thorough characterization of their properties and then scrutinized potential external factors affecting these magnetic nanoparticles to establish a benchmark for detection performance (Fig. 1.2). Upon identifying the optimal conditions, they modified the optical sensor surface with these magnetic nanoparticles for detection of interferon- α . The kinetic performance of the sensor, enhanced by magnetic nanoparticles, exhibited a high correlation coefficient ($R^2 = 0.99$) and a low LOD (41 IU/mL) across a wide interferon- α concentrations range. As a result, this sensor demonstrates significant potential for the highly sensitive and interference-free detection of other biomolecules. It could serve as an alternative method for biomarker detection across various applications (Saylan et al. 2022).

As an updated study, Erdem et al. designed a micro-reactor for real-time and continuous synthesis of an exceptionally large quantity of MIP nanoparticles that carry the unique characteristics of bovine serum albumin. This synthesis process is accomplished rapidly, typically within a short time frame of 5–30 min. They first employed COMSOL simulations to assess the mixing efficiency by adjusting flow rates and then conducted practical experiments to validate the micro-reactor's performance in generating nanoparticles with 52–106 nm sizes. They also delved into the molecular interactions between monomers and protein by employing molecular docking and dynamics simulations. Following these steps, they assessed the micro-reactor's parameters by evaluating the uniformity and concentration of the molecularly imprinted polymers, utilizing principal component analysis. The sensory capabilities of these MIPs were then put to the test on a metamaterial sensor, yielding an impressive precision rate of 81%, along with a notably high level of selectivity (4.5 times greater than alternatives), all while maintaining usability over three consecutive cycles. The micro-reactor distinguishes itself through its remarkable productivity, offering a significant reduction in assay time (48–288 times faster) and a substantial

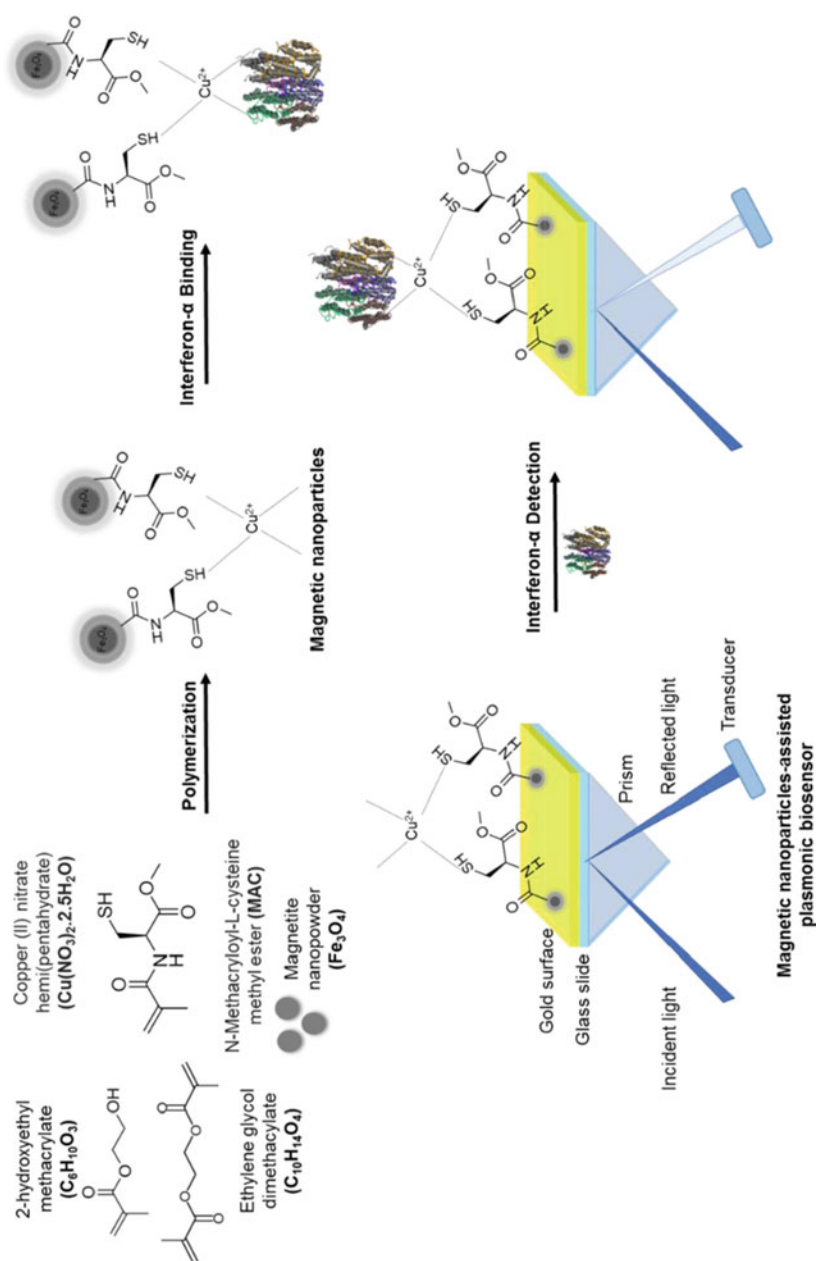


Fig. 1.2 Scheme of magnetic nanoparticles preparation and interferon- α detection with magnetic nanoparticles-assisted optical sensor (Saylan et al. 2022)

decrease in reagent volume (2 times less) when compared to conventional methods. This enables the production of 1.4–1.5 times more MIPs in a single step, ensuring a continuous and efficient production process (Erdem et al. 2023).

Adsorption and Separation Applications

The selective cavities of MIPs possess the ability to separate between target analytes and analogs because of their size, shape, and functional groups. These materials also exhibit significant potential in the isolation of biomacromolecules, small organic molecules, metal ions, and other substances (Bagheri et al. 2021). Their versatile nature allows for extensive utilization across various domains, including pollutant separation and treatment (Decompte et al. 2020; Diab et al. 2021; Sun et al. 2019; Vargas-Berrones et al. 2023; Villar-Navarro et al. 2017).

Quercetin, a highly physiologically active natural flavonoid, is abundantly present in a diverse range of plants. In a recent study, quercetin-MIPs were created using surface molecular imprinting method and the sol–gel polymerization on SiO₂. Synthesized MIPs were analyzed for characterization using scanning electron microscopy (SEM), Fourier transform and infrared spectroscopy (FT-IR) in order to confirm its functionality, surface morphology and structure. SEM scans showed that MIPs exhibited rough and spherical structure, measuring 260 nm diameter size and the FTIR spectra of MIP show bands N–H and C–H groups (Fig. 1.3). A static adsorption experiment was assessed quercetin-adsorbing MIP. The results showed that adsorption equilibrium could be attained in 90 min and that 35.70 mg/g was the maximum capacity. Following the pseudo-second-order kinetics and Freundlich isotherm model, chemical adsorption and heterogeneous surface with multilayer adsorption governed the MIP adsorption kinetics and isotherm for quercetin. Unlike NIPs, MIPs showed strong selectivity and precise detection for quercetin, with 1.61 selectivity coefficient over biochanin A. MIP's adsorption capability remains above 90% after five adsorption–desorption cycles, demonstrating excellent reusability and promise for selective quercetin adsorption (Zhi et al. 2023).

There is a strong demand for cost-effective and efficient alternatives to high-priced ethanol fractionation and affinity chromatography techniques for the extraction of IgG from human plasma. MIPs designed for IgG molecules exhibit promise as prospective candidates. However, these polymers encounter significant challenges, including the laborious removal of templates and inadequate printing efficiency. In particular research, a novel approach was implemented in order to address the aforementioned challenges. In the process of producing MIPs, poly (L-glutamic acid) (PLGA) peptide cross-linkers were employed as an alternative to conventional cross-linkers like *N,N*-methylenebisacrylamide (BIS). The expansion of imprinting cavities in polymers can be achieved using the pH-induced helix–coil transition and accurate folding of peptide segments. By altering the pH from 5.0 to 7.0, the cavities can be extended, but their original size and shape can be recovered by readjusting the pH. Hence, it is possible to obtain complete elution of the IgG template using mild conditions, leading to a notable enhancement in imprinting efficiency. In comparison

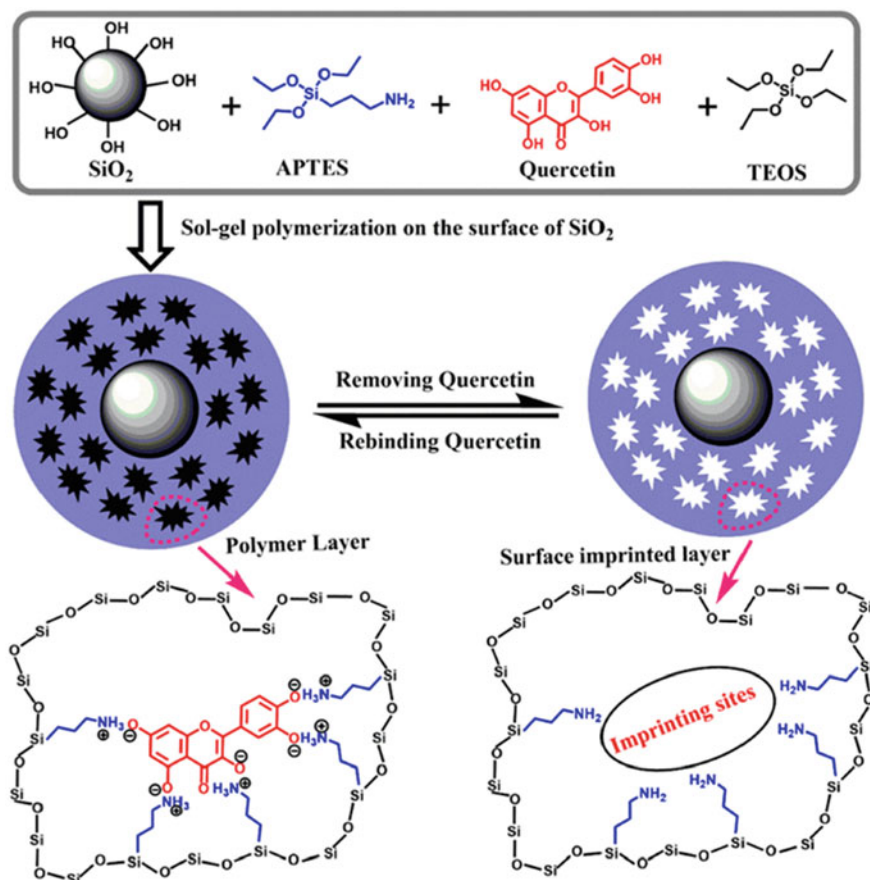


Fig. 1.3 Scheme of MIP preparation (Zhi et al. 2023)

to BIS cross-linked MIPs, it was observed that molecular imprinting of PLGA cross-linked MIPs resulted in the creation of 8.6 times more binding sites. According to the results, the synthesized MIPs exhibited notable characteristics, including a substantial adsorption capacity of 612.5 mg/g, a high imprinting factor of 4.92, and a remarkable level of selectivity. The study suggests that the MIPs developed in this research possess a high adsorption capacity and selectivity, which may enable the effective separation of IgG from human serum, hence facilitating the production of high purity products (Dong et al. 2023). Apurinic/aprimidinic endonuclease 1 (APE1) is a multifunctional DNA repair protein that is found in various subcellular locations. The precise mechanisms underlying the tightly controlled subcellular localization and interactomes of this protein remain incompletely explained, however they are intricately related to post-translational modifications occurring in diverse biological scenarios. In recent research, a bio-nanocomposite possessing antibody-like characteristics was successfully created. This bio-nanocomposite was able to

effectively capture APE1 from cellular matrices, thereby facilitating a thorough investigation of this particular protein. At first, the APE1 template was immobilized onto the surface of silica-coated magnetic nanoparticles that had been modified using avidin. In the present experimental setting, the initial step involved the addition of 3-aminophenylboronic acid, serving as the functional monomer, to facilitate a reaction with the glycosyl residues present in avidin. Subsequently, 2-acrylamido-2-methylpropane sulfonic acid was introduced. In order to improve the affinity and selectivity of the binding sites, a secondary imprinting process was conducted utilizing dopamine as a functional monomer. The bio-nanocomposite based on MIPs exhibited notable characteristics such as strong affinity, specificity, and capacity towards template APE1. This enabled the efficient APE1 extractions from cell lysates, resulting in high recovery (78–92%) and purity levels. The highest binding capability of MIP for APE1 was observed to be 90 ± 4 nmol/g. Moreover, the bio-nanocomposite has the ability to efficiently release protein that is tied to specific cavities (Xie et al. 2023). The potential problem of water contamination resulting from the discharge of toxic heavy metals by diverse industrial sectors has emerged as a prominent concern for environmentalists. Mercury in the form of Hg (II) is widely recognized as a highly hazardous heavy metal owing to its capacity to induce carcinogenicity and several adverse health effects. In light of the adverse impacts of mercury on both the environment and human health, a study was undertaken to develop a MIP/nanoporous carbon (NC) nanocomposite that is environmentally sustainable. This nanocomposite was synthesized with the specific purpose of effectively adsorbing Hg (II) from aqueous solutions. Various characterizations, such as morphological analysis, thermal degradation analysis, functional analysis, and surface area analysis, were conducted on the synthesized nanocomposite. The efficacy of a MIP/NC nanocomposite, possessing a substantial specific surface area of 884.9 m²/g, was assessed in terms of its ability to adsorb and remove Hg (II) from aqueous solution. Analyzes showed that a maximum adsorption efficiency of 116 mg/g Hg(II) was achieved at pH 4. Furthermore, the equilibrium sorption result complied with the Freundlich model, indicating its suitability for pseudo-second order kinetics. The adsorption effectiveness of the MIP/NC was assessed through a comparative analysis with a real condensate sample derived from the oil and gas sector. The results revealed that Hg(II) was successfully recovered at a rate of 87.4%. The synthesized MIP/NC has demonstrated potential as an adsorbent for Hg(II) in contaminated settings. This implies that a range of composite absorbents including diverse precursors should be considered for the assessment of heavy metal and pharmaceutical removals (Abubakar et al. 2023). Beyond the essential task of comprehending and elucidating protein functions, there is a growing demand in protein purification for methods that are both cost-effective and efficient. This need is particularly pronounced in the context of enzyme production. In response to this demand, an innovative method has been demonstrated by Özbek et al. for the thrombin purification, a protein critical in the hemostatic process. This method leverages thrombin-imprinted microcryogels, which offer the advantages of reusability and high selectivity. The microcryogels were subjected to comprehensive characterization studies, utilizing techniques. Through an exploration of various parameters

influencing thrombin adsorption, the maximum adsorption capacity ($Q_{\max}$) was determined to be 55.86 mg/g. Additionally, the microcryogels' selectivity was assessed through competitive agent testing, and their reusability was evaluated. The purity of the thrombin was confirmed using the fast performance liquid chromatography method. The experimental results revealed that the adsorption of thrombin by the microcryogels adhered to the Langmuir isotherm ($Q_{\max}$: 55.86 mg/g, R^2 : 0.9505) and followed the pseudo-second-order kinetics for various thrombin concentrations (Özbek et al. 2023). Öztürk et al. developed MIP-based magnetic silica microspheres that are incorporated into cryogels to create a novel composite for the tyrosine adsorption (Fig. 1.4). Tyrosine is a vital chemical involved in numerous cellular processes, including brain regulation, stress reduction, mood control, melanin pigment production, and the regulation of thyroid functions. Through the characterizations, they optimized the conditions for tyrosine adsorption on these composite cryogels, achieving a maximum adsorption capacity of 62.27 mg/g in a pH 8.0 buffer solution. The reusability of the composite cryogel carrier was assessed through multiple adsorption and desorption cycles using 0.1 M NaCl, and it demonstrated the ability to be used more than 8 times without a decline in performance. Additionally, competitive tests with various amino acids revealed the high selectivity of the cryogel. The Langmuir isotherm provided an excellent fit to the adsorption data, highlighting the efficiency of the adsorption process (Öztürk et al. 2021).

Lastly, Saylan et al. engineered magnetic bacterial cellulose nanofibers serving as a new adsorbent with the capability for thymidine adsorption. The process involved silanizing magnetic bacterial cellulose nanofibers with 3-(trimethoxysilyl) propyl methacrylate, followed by polymerization with a monomer to template thymidine through metal chelate coordination. These modified nanofibers were subjected to various characterization methods, and their effectiveness in thymidine recognition was assessed to optimize adsorption conditions. During this evaluation, several factors were considered, and the maximum adsorption capacity was 431.3 mg/g, observed under pH 9.0 and at a temperature of 25 °C. Furthermore, the selectivity of these magnetic bacterial cellulose nanofibers was evaluated by conducting competitive experiments with other nucleosides. Impressively, these nanofibers exhibited high selectivity, with adsorption levels for thymidine being 4.13 and 3.80 times higher compared to other nucleosides (cytidine and uridine) at equal concentrations. The nanofibers also displayed a strong reusability capacity after multiple adsorption–desorption cycles. This innovative approach, combining molecular imprinting with magnetic bacterial cellulose nanofibers, demonstrates excellent potential for nucleoside adsorption and holds promise for various applications (Saylan et al. 2020b).

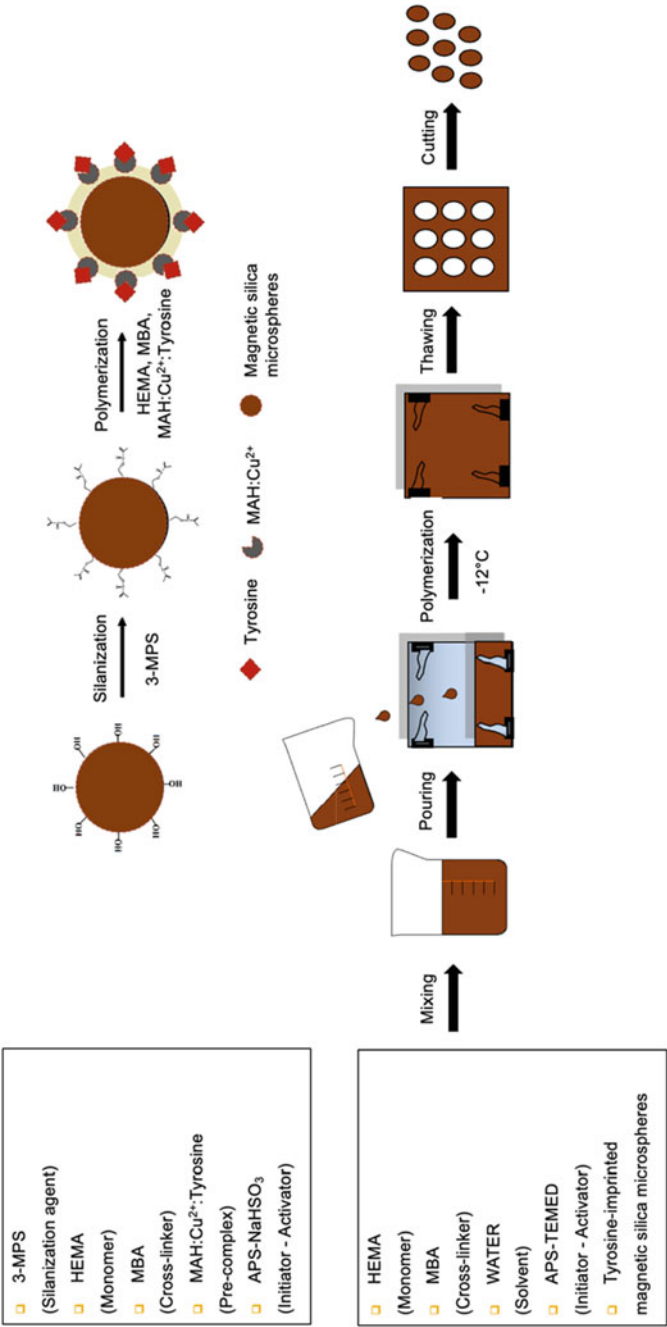


Fig. 1.4 Scheme of composite cryogels preparation (Öztürk et al. 2021)

1.5 Conclusion and Future Perspectives

In the realm of molecular recognition and molecular imprinting, significant progress has been made, leading to the development of highly specialized and selective materials for molecular detection and separation. This technology has allowed for the precise targeting and binding of molecules of interest, offering a broad range of applications in several fields, including chemistry, biology, and medicine. The studies and research presented here demonstrate the effectiveness of molecular imprinting in creating tailored recognition sites within polymers, nanoparticles, and other materials. These molecularly imprinted polymers have shown remarkable potential in selective adsorption, catalysis, sensing, and separation processes. The ability to design materials with specific binding sites for target molecules has opened up avenues for improved analytical techniques, drug delivery systems, and environmental remediation. However, challenges still exist in optimizing molecular imprinting techniques, such as enhancing the selectivity and stability of these materials and broadening their applicability across a wider range of molecules and conditions. Advances in nanotechnology, computational modeling, and novel imprinting strategies are likely to address these challenges and further propel the field. The future of molecular recognition and molecular imprinting holds exciting prospects. As technology continues to advance, several key developments can be anticipated. For instance, the integration of molecular imprinting with cutting-edge nanomaterials will lead to the creation of highly efficient and versatile recognition systems. These materials will offer enhanced selectivity, sensitivity, and reusability in various applications. The development of responsive and adaptive molecularly imprinted polymers, capable of adjusting their recognition properties in response to environmental changes or stimuli, will enable dynamic molecular recognition with broader applicability. In addition, the use of machine learning and computational modeling will accelerate the design and optimization of molecularly imprinted materials, reducing the trial-and-error process and increasing their specificity. Molecular imprinting will continue to play a crucial role in drug delivery, diagnostics, and targeted therapies, offering more precise and personalized medical treatments. The use of molecular imprinting for selective removal of pollutants and contaminants from the environment will become more prevalent, contributing to cleaner water, air, and soil. Molecularly imprinted polymers will be integrated into sensor technologies, enabling rapid and accurate detection of target molecules, with applications in fields like food safety, environmental monitoring, and security. Also, collaborations between chemists, biologists, materials scientists, and engineers will drive innovation in molecular imprinting, leading to the development of multifunctional materials with a wide range of applications. In conclusion, molecular recognition and molecular imprinting are poised to make significant contributions to diverse scientific and technological domains. With ongoing research, technological advancements, and cross-disciplinary collaborations, this field promises to revolutionize our ability to selectively manipulate and harness molecular interactions, addressing complex challenges in the modern world.

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