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Molecularly imprinted polymers: A closer look at the template removal and analyte binding

Abderrahman Lamaoui [a], Veerappan Mani [b], Ceren Durmus [b], Khaled Nabil Salama [b], Aziz Amine [a,*]

[a] Laboratoire Génie des Procedés & Environnement, Faculté des Sciences et Techniques, Hassan II University of Casablanca, B.P. 146, Mohammedia, Morocco
[b] Sensors Lab, Advanced Membranes and Porous Materials Center (AMPMC), Computer, Electrical, and Mathematical Science and Engineering (CEMSE) Division, King Abdullah University of Science and Technology (KAUST), Thuwal, 23955-6900, Saudi Arabia

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ABSTRACT

Molecularly imprinted polymers (MIPs), which first appeared over half a century ago, are now attracting considerable attention as artificial receptors, particularly for sensing. MIPs, especially applied to biomedical analysis in biofluids, contribute significantly to patient diagnosis at the point of care, thereby allowing health monitoring. Despite the importance given to MIPs, removal of templates and binding of analytes have received little attention and are currently the least focused steps in MIP development. This critical review is dedicated to a comprehensive analysis and discussion of cutting-edge concepts and methodologies in the removal and binding steps pertaining to various types of analytes, including ions, molecules, epitopes, proteins, viruses, and bacteria. The central objective of this review is to comprehensively examine and discuss a range of removal methods, including soxhlet extraction, immersion, microwave-assisted technique, ultrasonication, electrochemical approach, and proteolytic digestion, among others. Additionally, we will explore various binding methods, such as soaking, drop-casting, and batch sorption, to provide a comprehensive overview of the subject. Furthermore, the current challenges and perspectives in removal and binding are highlighted. Our review, at the interface of chemistry and sensors, will offer a wide range of opportunities for researchers whose interests include MIPs, (bio) sensors, analytical chemistry, and diagnostics.

1. Introduction

Biosensors have shown great importance in diagnostics devices because of their fast and cost-effective applications in healthcare, which could replace conventional clinical diagnosis methods (Li et al., 2021). These biosensors are typically based on biological recognition elements such as antibodies (Sun et al., 2021), enzymes (Rahimi and Joseph, 2019), or DNA (Yang et al., 2021) for the specific detection of a target analyte. Although these biosensors are substantially selective and sensitive, they present certain limitations mainly associated with biological receptors under non-physiological conditions (Xu et al., 2020).

Molecularly imprinted polymers (MIPs) are synthetic materials that contain specific recognition sites called imprints that selectively uptake molecules they were templated during preparation, mimicking the immune system through antigen–antibody affinity (BelBruno, 2019; Lamaoui et al., 2021a). MIPs, as artificial antibodies, have the potential to be employed as alternative recognition elements in diagnostic devices to overcome many issues faced with natural antibodies, including difficult production and handling, long-term stability, and loss of performance in organic media (Lamaoui and Amine, 2022). MIPs are known for their intrinsic stability in various media, cost-effectiveness, and extended shelf life (Xu et al., 2020). These properties have led to their widespread use in solid-phase extraction (Lamaoui et al., 2019, 2022b), sensors (Üzek et al., 2019), nanozymes (Zhang et al., 2019), and medical therapy (Bossi, 2020; Xu et al., 2021).

Furthermore, MIP can be prepared for different templates such as ions (Safran et al., 2019; Gerdan et al., 2022; Samandari et al., 2019), small molecules (Karim et al., 2022; Lahcen et al., 2019; Lamaoui et al., 2021c), epitopes (Torrini et al., 2023; Garcia Cruz et al., 2020), proteins (Chen et al., 2019; Sunayama et al., 2018), viruses (Lu et al., 2012; Siqueira Silva et al., 2021; Yang et al., 2017), and bacteria (Roushani et al., 2020; Tokonami et al., 2014; Yasmeen et al., 2021).

According to SCOPUS data, there is an increased growth in the number of publications in the period of 2010–2022 from 450 in 2010 to

* Corresponding author.
E-mail address: aziz.amine@fstm.ac.ma (A. Amine).

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more than 1300 publications in 2022 demonstrating the broad interest given by the scientific community to MIPs. Nowadays, several companies, mainly *"Sigma Aldrich"* and "*MIP discovery*", provide MIPs products, which can be used in sensors, lateral flow devices, sample preparation, protein enrichment, interference removal, and purification.

MIP is produced by polymerizing monomers in the presence of a template molecule, extracting the template molecule from the MIP to create molecularly imprinted cavities featuring recognition sites, and then exposing the resultant MIP to the target-containing sample, which uptakes the target molecule (Fig. 1). The appropriate monomer and porogen solvent are selected through in silico design to minimize time and cost. Various synthesis approaches, including bulk polymerization (Boitard et al., 2017), precipitation polymerization (Lu et al., 2019), sol–gel transition (Starosvetsky et al., 2012), self-polymerization (Lamaoui et al., 2023), solid-phase synthesis (Canfarotta et al., 2016), electrosynthesis (Beduk et al., 2020), stamping method (Ren et al., 2013), and lithography (Kavand et al., 2019) have been reported.

Although the synthesis of the MIPs, which involves the choice of functional monomer, cross-linker, solvent, and synthesis method, is an important process, the removal of the template and binding of analytes are undoubtedly key factors for the optimal functioning of the MIPs. Therefore, key issues to take into consideration when integrating the MIPs in sensing, especially for diagnostic applications, include the successful removal of the template from the MIP and the binding of analytes in the real sample. On the one hand, if the MIPs still contain the target analyte, fewer cavities will be available and errors will arise during the analytical applications, particularly for biomarkers sensing where the limit of detection must be extremely low. It is noteworthy that leakage of the target analyte from the MIP during measurement can also occur. Lorenzo et *al.* reported that the remaining template in the MIP would decrease the binding efficiency (Lorenzo et al., 2011). Moreover, the unsuccessful removal can lead to several problems on both the surface of the polymer such as its chemical modification (Lamaoui et al., 2021d), and on the imprinted cavity such as its distortion, collapse, and rupture during template removal (Lorenzo et al., 2011).

In a comprehensive analysis of existing literature on MIPs, it becomes evident that the section focusing on the removal of the target molecule receives notably less attention and lacks detailed discussion. Insufficient explanations are provided regarding crucial aspects such as the selection of the template removal method, choice of the employed solution, duration and temperature of extraction, and the underlying extraction mechanism. This oversight has had significant repercussions, rendering the removal step the least cost-effective and undervalued aspect in the overall development of MIPs. Addressing this gap in research is crucial to improving the efficiency and effectiveness of the MIP development process.

On the other hand, unsuccessful binding may increase the non-selective sorption which decreases the selectivity of the MIP-based diagnostics. Moreover, a few papers (Lamaoui et al., 2019, 2021c, 2022a) reported and discussed the sorption studies including isotherms, kinetics, and thermodynamics which are fundamental to answering several questions related to the binding mechanisms.

The primary focus of our review is to analyze and discuss the available data on the removal and binding steps in MIPs applied for diagnostics. Indeed, the review aims to provide an overview of the removal and binding of different substances used in diagnostics including ions, small molecules, epitopes, proteins, viruses, and bacteria. Rather than organizing the removal and binding sections solely based on the employed methods, we have chosen to categorize them according to the types of templates involved. This approach is designed to enhance readability and ensure ease of understanding for our readers. Furthermore, we will highlight the current challenges and perspectives in removal and binding.

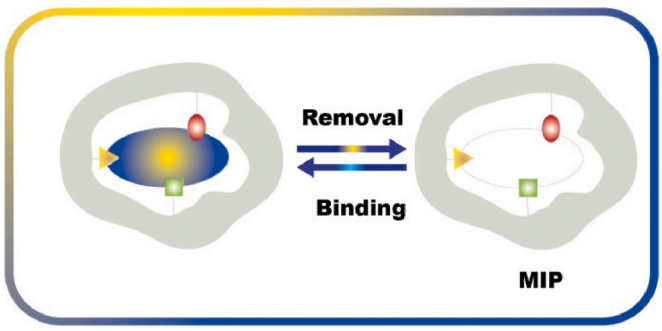

Fig. 1. Removal and binding.

2. General overview on the removal of templates

The removal is very important to ensure that no residual templates occupy the active sites and that all active sites in the MIP structure are available for the sorption of the target analyte from the sample (Lorenzo et al., 2011). We will present in the following subsections an overview of the removal approaches of different templates from the MIPs (Fig. 2). Through this section, we will learn about the different types of removal methods along with their discussion and mention the pros and cons of each one.

2.1. Removal of ions from ion-imprinted polymers

Ion-Imprinted Polymers (IIPs) offer distinct advantages over Ion-Selective Electrodes (ISEs) in ion sensing applications. IIPs excel in selectivity, as they are tailored to recognize specific ions with high precision, decreasing interference in complex sample matrices—a feat challenging for ISEs. Moreover, IIPs often prove more cost-effective in the long term, thanks to their reusability, while ISEs require ongoing maintenance and replacement of ion-selective membranes. IIPs demonstrate versatility and durability, are adaptable to diverse ion sensing needs, and are robust even in harsh environmental conditions. In contrast, ISEs are constrained by the specificity of their ion-selective membranes, which may deteriorate over time. Researchers frequently leverage IIPs to exploit these advantages, making them a preferred choice in ion sensing applications where selectivity, cost-efficiency, and resilience are paramount. ISEs utilize electrochemical sensors to detect variations in electrical potential resulting from alterations in ion concentration. In contrast, IIPs offer a broader range of detection methods beyond just potentiometric sensors. In fact, IIPs can be harnessed for diverse detection approaches, making them versatile in ions analysis.

The removal of target ions after complexation and polymerization is a key factor in the creation of ion-imprinted sites. It is crucial to find appropriate solvents that effectively remove the imprinted ions while preserving the structure of the polymer matrix. Several solvents have been investigated in this regard, each offering unique advantages and considerations.

One promising solvent for the removal of aluminum ions (Al^{3+}) from IIPs is sodium fluoride (NaF) solution. NaF forms a specific complex with Al^{3+}, most likely $Al(F)^{4-}$, effectively removing it from the polymer matrix (Carroll et al., 1993). This approach has been successfully applied by Krywko-Cendrowska to remove Al^{3+} ions from ion-imprinted nanofilms based on tannic acid and silver nanoparticles (Krywko-Cendrowska et al., 2021). The use of NaF resulted in the complete removal of Al^{3+} ions, as confirmed by X-ray photoelectron spectroscopy. These findings demonstrate the potential of NaF as a selective solvent for aluminum ion removal from IIPs (El-Wekil et al., 2018).

Another widely employed solvent for ion removal is ethylenediaminetetraacetic acid (EDTA). EDTA is known for its effectiveness in maintaining the characteristics of the internal pore structure of IIP films. It has been used for the removal of various ions, including calcium (Ca^{2+}) (AL-Maibd et al., 2021), cadmium (Cd^{2+}) and copper (Cu^{2+}) ions (Bali Prasad et al., 2014). Aslıyüce et al. successfully removed trapped

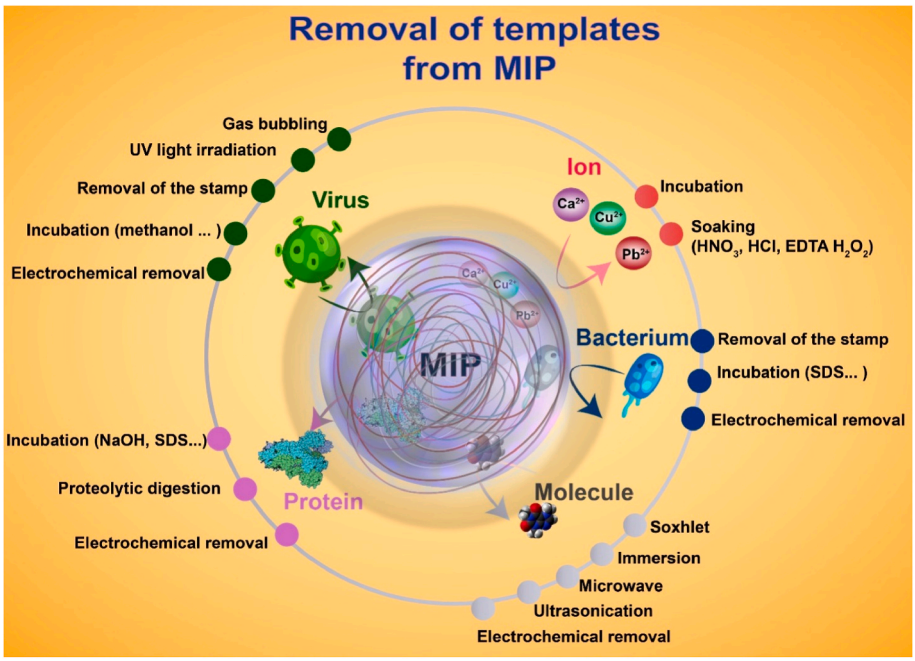

Fig. 2. Summary of selected removal approaches of templates from MIPs. EDTA: ethylenediaminetetraacetic acid; SDS: Sodium dodecyl sulfate.

iron (Fe^{3+}) ions from a polymer cryogel by pumping it with a 0.1 M EDTA solution (Aslıyüce et al., 2010). However, importantly, we should note that the complete removal of Fe^{3+} ions was not verified in this study. The application of EDTA as a metal-chelating agent offers a versatile approach for selective ion removal from IIPs.

Strong mineral acids, such as hydrochloric acid (HCl) and nitric acid, have also been explored for ion desorption from IIPs. HCl has been utilized to leach lead (Pb^{2+}) ions from IIPs combined with terpyridine complexing agents (Shamsipur et al., 2018) and 1-(2-pyridylazo)-2-naphthol (Tarley et al., 2017). Similarly, Sb^{+3}, Cd^{+2}, Pb^{+2} and Te^{+4} ions were successfully removed using HCl from an IIP based on ammonium pyrrolidine dithiocarbamate as a ligand and sodium carbonate, tetraethyl orthosilicate as a crosslinking agent (Jakavula et al., 2021). Yolcu and Çıtlakoğlu employed a 0.5 M HCl solution to remove Cd^{2+} ions from an organic polymer composed of methacrylic acid (MAA) and 1-vinylimidazole as monomers, and ethylene glycol dimethacrylate (EGDMA) as a crosslinker (Fig. 3A) (Yolcu and Çıtlakoğlu, 2021). These studies highlighted the potential of strong acids as effective desorption agents for specific ion removal from IIPs.

Hydrogen peroxide acting as an oxidant in a basic medium has been applied to remove metal ions such as Cr^{3+}(Alizadeh et al., 2017). Chemically, H_2O_2 reacts with transition metal ions to generate·hydroxyl radical which is a powerful oxidizing reagent with high oxidation potential and it exhibits a faster rate of oxidation reaction (Peng et al., 2019).

In addition, innovative approaches have been explored for ion removal from IIPs. Karrat et al. presented a novel method for eliminating chromium (Cr^{6+}) ions using a diphenylcarbazide solution (Karrat et al., 2023). The reaction between 1,5-diphenylcarbazide and Cr^{6+} resulted in the formation of a visible pink complex, enabling easy tracking of the analyte's extraction without specialized equipment (Fig. 3B). This approach offers a promising strategy for rapid and gentle rupture of covalent bonds between Cr^{6+} and the polymer, highlighting the potential for efficient ion removal. By exploring innovative techniques like this, researchers can expand the range of ion removal methods, thereby improving the selectivity and efficiency of IIPs.

Compared to others, the use of chelating agents such as the EDTA and diphenylcarbazide to remove ions from IIPs are highly recommended due to their high capacity and selectivity to remove ions without affecting the polymer structure. However, it should be ensured that chelating agent-ion interactions are stronger than monomer-ion interactions. Therefore, in silico-design such as density functional theory may help to calculate and compare the binding energies of monomer-ion and chelating agent-ion complexes before selecting the chelating agent. Table 1 summarizes the removal methods of different ions from IIP/MIP.

2.2. Removal of small molecules

MIPs designed for small molecules represent a common class of MIPs. In this section, we will discuss the reported methods for the removal of small molecules from MIPs, emphasizing their context, advantages, and limitations.

The removal of templates from MIPs can be achieved through various techniques. A common method involves immersing the MIP in a solvent, which takes advantage of the selective solubility of the template in a solvent or solvent mixture while keeping the polymer network insoluble and stable. The immersion in a solvent is a convenient and cost-effective approach that allows the extraction of template molecules without altering the surface of the polymers. Methanol and acetic acid (HAc) mixtures are widely employed for removing small molecules from MIPs due to their high extraction yield and ability to solubilize most template molecules and other residues. However, considering the toxicity of methanol, it is recommended to substitute it with ethanol (Lamaoui et al., 2021c). HAc, being more environmentally friendly and cost-effective, is an efficient solvent that enhances the removal of small molecules (Azman et al., 2020). Other solvents, such as acetonitrile and basic solutions (e.g., 0.1 M NaOH), are also used when the template molecules exhibit poor solubility in organic solvents (Madikizela et al., 2016; Elfadil et al., 2022). The immersion in a solvent is a simple and instrument-free protocol (Amatatongchai et al., 2019), but it can be time-consuming and requires a large amount of solvent to establish a concentration gradient, which limits its industrial applicability. Although the careful selection of solvents can minimize chemical injury to the polymer network, long immersion times may occasionally lead to topological changes in the MIPs. Notably, Karrat et al. (2023) developed a novel strategy utilizing aluminum ions to extract Rutin from MIPs within 40 s, forming a visually detectable yellow complex (Fig. 3C).

To overcome some limitations of conventional immersion -based

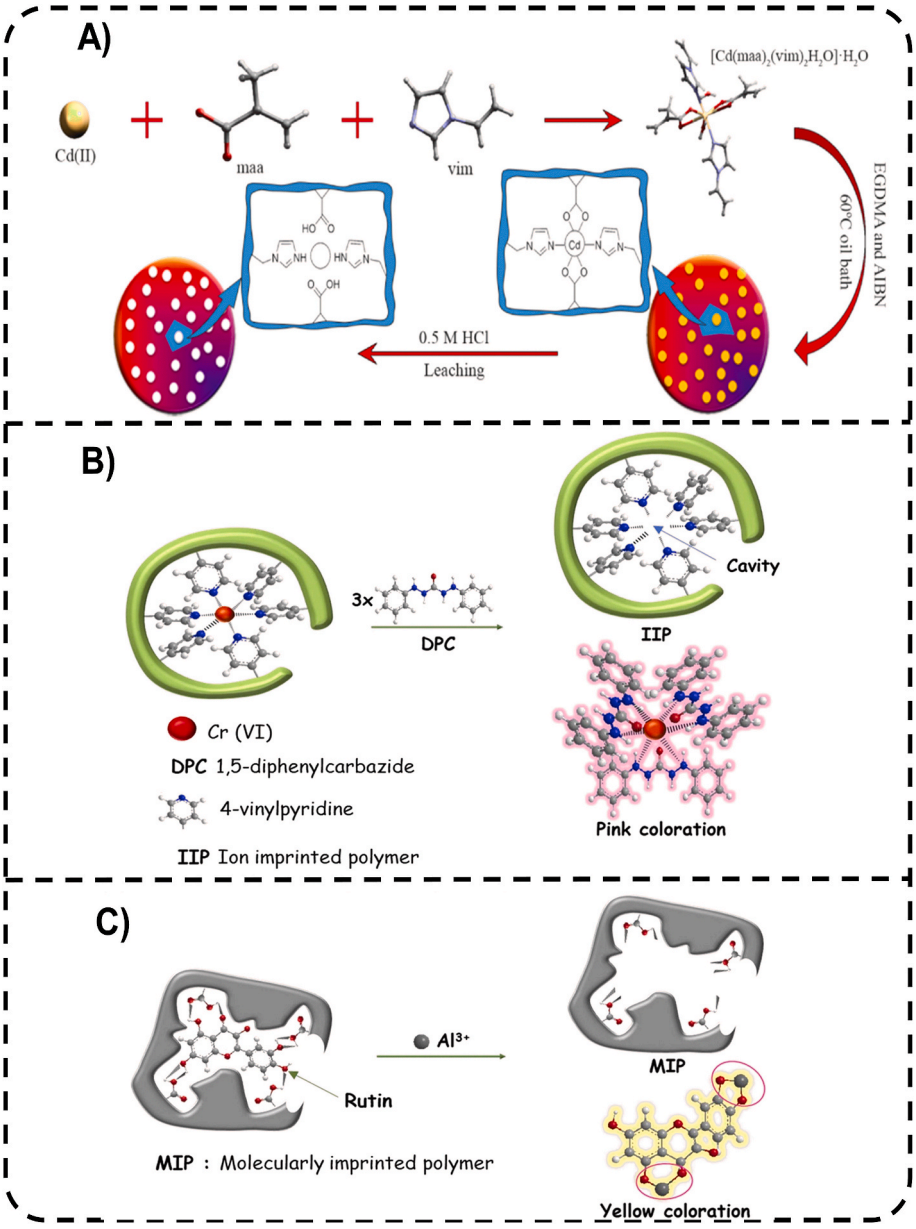

Fig. 3. A) Synthesis of Cd^{+2} imprinted polymer and removal of Cd^{+2} using HCl as a template removal agent. Reprinted from reference (Yolcu and Çıtlakoğlu, 2021) with permission of Elsevier. Removal mechanism of B) Cr^{6+} from IIP and C) Rutin from MIP. Reprinted from reference (Karrat et al., 2023) with permission of Elsevier. MAA: Methacrylic acid; VIM: 1-vinylimidazole; EGDMA: Ethylene glycol dimethacrylate; AIBN: Azobisisobutyronitrile.

removal, Soxhlet-based extraction was introduced. The selection of solvent, the solvent volume, and the extraction time are critical parameters in this method. Soxhlet extraction with methanol containing HAc (9:1 v/v) is the most widely employed method for the removal of small molecules from MIPs (Golsefidi et al., 2012). It has been successfully applied in various MIP systems, including those targeting p-hydroxybenzoic acid (Liu et al., 2019), cloxacillin (Ashley et al., 2017), 17ß-estradiol (Lee and Doong, 2012), L-phenylalanine methyl ester (Kupai et al., 2017), sarcosine (Tang et al., 2020; Mendes et al., 2017), dopamine (Mendes et al., 2017), butyric acid (Mendes et al., 2017), glucuronic acid (Caldara et al., 2021), cortisol (Villa et al., 2021), cholesterol (Pešić et al., 2020), and more. Soxhlet extraction is a simple and versatile method that does not require expensive instruments, and MIPs do not need additional filtration steps after extraction. However, the stationary position of MIP particles during solvent circulation can sometimes hinder efficient template removal. This method is characterized by its relatively slow pace and challenges in automation, and its widespread industrial application has not been extensively documented. Fundamentally, we should highlight that trace amounts of the template may persist encapsulated within the polymer matrix. However, studies have indicated that these residual templates do not have a significant impact on subsequent binding experiments (Ashley et al., 2017). Kupai et al. reported minimal leaching of the template, with concentrations falling below the detection limit of the analytical method (Kupai et al., 2017). To address some of the limitations of Soxhlet extraction, Eppler et al. proposed a novel extractor device called the "Ulm Extractor – ULEX" (Eppler et al., 2012). This device offers benefits such as the use of solvent mixtures, temperature-controlled extraction conditions, enhanced kinetics, and continuous control of the extraction, providing improvements over traditional Soxhlet extraction.

Microwave-assisted extraction is another effective method for template removal, which offers the advantage of being the fastest route compared to other techniques. The pH and polarity of the extraction solution are crucial parameters to consider when using microwave-

Table 1
Selected removal by extraction of ions and small molecules from IIPs and MIPs.

Type of templates	Type of ions/molecules	Type of monomer	Extraction method
Ions	Ca^{2+} (Alizadeh et al., 2016)	itaconic acid	1.0 M HCl
	Sb^{3+}, Cd^{2+}, Pb^{2+} and Te^{4+} (Jakavula et al., 2021)	(3-Aminopropyl)triethoxysilane	0.5 M HCl
	Cd^{2+} (Samandari et al., 2019)	methacrylic acid	4.0 M HNO_3
	Cd^{2+} and Cu^{2+} (Bali Prasad et al., 2014)	2-acrylamido ethyl dihydrogen phosphate	0.1 M EDTA
	Fe^{3+} (Aslıyüce et al., 2010)	poly(hydroxyethylmethacrylate-N-methacryloyl-(l)-cysteine methyl ester)	0.1 M EDTA
	Cr^{3+} (Alizadeh et al., 2017)	itaconic acid	3% w/w H_2O_2
	Cr^{6+}(Karrat et al., 2023)	4-Vinylpyridine	Diphenylcarbazide
Small molecules	Cholesterol (Pešić et al., 2020)	ethyleneglycol dimethacrylate without monomer	Soxhlet using chloroform
	Serotonin (Amatatongchai et al., 2019)	Phenyltrimethoxysilane	Immersion in ethanol
	Cortisol (Duan et al., 2022)	*o*-phenylenediamine	Electrochemical method in 0.1 M NaOH
	Cortisol (Daniels et al., 2021)	MAA	Ultrasonication of MIP particles in methanol
	Bisphenol-A (Chin and Chang, 2019)	Styrene and methyl methacrylate	Microwave-assisted removal method in methanol at 75 °C for 20 min
	Cortisol (Tang et al., 2021)	Pyrrole in the presence of Prussian blue	Over-oxidation of Polypyrrole- Prussian blue by CV in PBS
	Rutin (Karrat et al., 2023)	Methacrylic acid	Al^{3+}

assisted extraction (Zhang et al., 2005). Microwave irradiation has been successfully applied for the removal of templates such as bisphenol-A using methanol as a solvent at 75 °C for 20 min with repeated cycles (Chin and Chang, 2019). Factors such as extraction time, number of solvent exchanges, and the type of acid used influence the bleeding level of templates during microwave-assisted removal (Ellwanger et al., 2001). It has been observed that the application of stronger acids may lead to polymer hydrolysis, while milder acids like formic acid result in less material loss, indicating their gentler impact on the polymer matrix. The use of basic solvents, including amine bases and NaOH, has yielded mixed results in template removal investigations (Ellwanger et al., 2001). Generally, amine solvents performed poorly, but ethylenediamine showed some improvement compared to trimethylamine.

Ultrasound-assisted extraction is another alternative method for removing molecules from MIPs. This technique minimizes the removal time by dispersing the MIP particles in an extraction solution, creating an enhanced concentration gradient for molecules to diffuse from the MIPs into the extractant (Pooralhossini et al., 2017). Ultrasound induces cavitation, creating small bubbles with slightly elevated temperatures. MIPs are immersed in a suitable solution, and ultrasound irradiation is applied for a duration ranging from 3 to 60 min (Pirzada and Altintas, 2021). Continuous replacement of the solution is necessary to prevent extractant saturation. Cavitation facilitates solvent transport and penetration, while the elevated temperature enhances template diffusivity and solubility. Ultrasonication can be performed using an ultrasonic bath or probe. While the ultrasonic probe offers more localized treatment, it may cause damage to the polymers. The choice of solvent is critical when using the ultrasonic probe, as high-power ultrasonic waves strongly depend on the solvent properties (Lamaoui et al., 2019). Additionally, the duration and temperature of ultrasonication significantly influence the removal efficiency. For instance, chlorogenic acid templates were completely removed using ultrasonication at 40 °C for 10 min (Golsefidi et al., 2012). Ultrasonication has also been employed to remove cortisol from MIPs within 20 min using methanol as the solvent (Daniels et al., 2021). However, it should be noted that spectrophotometric measurements at 242 nm may not be sufficient to confirm the complete removal of cortisol. Upon verification of cortisol removal at the wavelength of 242 nm, it may appear that cortisol has been effectively removed. However, we should note that spectrophotometric measurements at this particular wavelength might not be sufficiently sensitive to detect low concentrations of cortisol. As a result, while the data might indicate successful removal based on the spectral response at 242 nm, it could potentially miss trace amounts of cortisol that remain within the polymer matrix. Therefore, relying solely on this wavelength for assessment may not provide a comprehensive confirmation of complete cortisol removal, especially at lower concentrations.

An emerging non-conventional method for template removal is electrochemical-based extraction. Successful removal of cortisol and other templates via electrochemical methods has been reported (Duan et al., 2022; Tang et al., 2021; Mugo et al., 2022). In this method, template molecules are eliminated from the MIPs through electro-elution by applying usually a positive bias voltage for a specific duration in an acidic medium (Fig. 4A) (Nguy et al., 2017), while a negative potential is avoided due to the potential reinforcement of

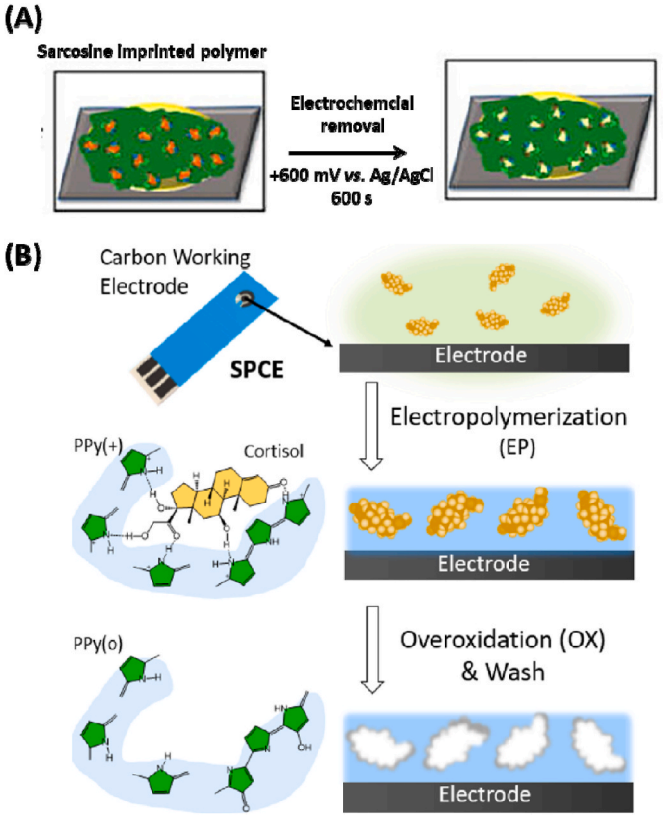

Fig. 4. (A) Electrochemical removal of sarcosine from sarcosine-imprinted polyaminothiophenol Reprinted from (Nguy et al., 2017) with permission of Elsevier. (B) Removal of cortisol templates via overoxidation of polypyrrole. Reprinted from (Dykstra et al., 2022) with permission of ACS. SPCE: Screen-printed carbon electrode.

binding interactions. The positive potential disrupts the hydrogen bonds between the protonated molecules and the polymer, facilitating template removal. One approach involves the overoxidation of polypyrrole, where carbonyl (C═O), hydroxyl (-OH), and carboxyl (COOH) groups are formed at the β-positions of the pyrrole ring due to the high potential, weakening the hydrogen bond and resulting in template removal (Fig. 4B) (Dykstra et al., 2022). Electrochemical methods offer the advantages of efficiency and gentle removal, but their applicability is limited to MIP-based electrochemical sensors. Table 1 summarizes selected removal methods of different small molecules from MIPs.

2.3. Removal of epitopes and proteins

From a scientific standpoint, the creation of protein-imprinted polymers presents challenges in preserving the structural properties of the protein, making it a costly process. To address this, researchers have successfully focused on imprinting specific portions of the protein, such as peptides or epitopes, rather than the full protein. The imprinting of epitopes offers a high binding affinity and specificity for the target protein since the synthesis approach is similar to low-molecular-weight labeling. The imprinted cavities of MIPs recognize the target protein when its epitope region binds to them.

The removal of epitopes and proteins from MIPs depends on their solubility characteristics. Acidic epitopes/peptides can be reconstituted in basic solutions, while basic epitopes/peptides can be removed using acidic solutions. Hydrophobic and neutral epitopes/peptides, containing hydrophobic or polar uncharged amino acids, can be removed using small amounts of organic solvents or surfactants. HAc is widely used to remove peptides/epitopes and proteins because it can play the role of acid and organic solvent. For example, it was applied to remove a peptide of glycoprotein 41 for human immunodeficiency virus (Lu et al., 2012), peptide hormone gonadorelin (Torrini et al., 2022), a peptide from death protein 1 ligand (Torrini et al., 2023), and cardiac troponin T (cTn-T) (Phonklam et al., 2020; Palladino et al., 2018). The addition of organic solvents into HAc enhances the removal of hydrophobic amino acids-containing peptides/proteins (Pu et al., 2022). Oxalic acid, a dicarboxylic acid, has been employed to remove peptides such as amyloid β-42 (Moreira et al., 2018), and proteins such as prostate-specific antigen (PSA) (Yazdani et al., 2019), cancer antigen 15-3 (Pacheco et al., 2018b), and cTn-T (Silva et al., 2016), and Galectin-3 (Cerqueira et al., 2021). HCl, on the other hand, is applied only for removing peptides from MIPs based on silica materials due to its strong acidity. Weak basic solutions like ammonia and strongly basic solutions are used for removing specific peptides (Ren et al., 2022; Tchinda et al., 2019). Organic solvents, such as trimethylamine (Bartold et al., 2022) and ethanol (Lee et al., 2020; Ma et al., 2019; Santos et al., 2018; Piloto et al., 2018; Shumyantseva et al., 2018; Lahcen et al., 2021), have also shown effectiveness in removing epitopes and proteins (Iskierko et al., 2019; Shumyantseva et al., 2018; Tang et al., 2018). Indeed, triethylamine has the role of organic solvent and basic medium, thus can selectively extract acid and hydrophobic peptides. Salts, such as NaCl, are utilized to break electrostatic interactions between the polymer and the template such as $A\beta_{42}$ peptide (Özcan et al., 2020), carcinoembryonic antigen (Yu et al., 2016), and PSA (Mazouz et al., 2020).

Surfactants play a significant role in the removal. Sodium dodecyl sulfate (SDS), when combined with acetic acid (HAc), is commonly used to remove proteins such as carcinoembryonic antigen (Qi et al., 2019; Wang et al., 2019), α-fetoprotein (Sun et al., 2019), neuron-specific enolase biomarker (X. Wang et al., 2018), human epidermal growth factor receptor 2 (Pacheco et al., 2018a), myoglobin (Moreira et al., 2015), and bovine serum albumin (W. W. Zhao et al., 2019), but caution must be taken as it can modify certain polymer surfaces (Fu et al., 2008; Lamaoui et al., 2021d). SDS was also combined with organic solvents such as methanol to remove proteins including carbohydrate antigen 125 (Rebelo et al., 2019).

Proteolytic digestion, using enzymes like Proteinase K or trypsin, provides an alternative approach for removing epitopes and proteins while preserving the polymer structure and imprinted cavities. The preeminent site of cleavage is on the peptide bond adjacent to the carboxyl group of aliphatic and aromatic amino acids (Yarman et al., 2017). Proteinase K has been applied successfully to remove peptides, such as amyloid β-42 (Ribeiro et al., 2022) and proteins such as carcinoembryonic antigen (Carneiro et al., 2021) and myoglobin (Moreira et al., 2014). Trypsin is highly active and stable with low cutting selectivity and it exhibits wide cleavage selectivity to remove peptides such as amyloid β-42 (Pereira et al., 2020) and proteins such as PSA (Rebelo et al., 2014, 2016). One issue arises from the possibility of retaining certain template fragments within the MIP after proteolytic digestion. This presence of template fragments or reagent remnants can subsequently result in binding difficulties. Consequently, an additional and thorough washing step with oxalic acid becomes necessary to address this concern (F. Zhang et al., 2018). Electrochemical methods offer also a soft approach for removing epitopes and peptides from MIPs without deteriorating the polymer film (Tchinda et al., 2019; Pirzada et al., 2020; Ribeiro et al., 2018; Pirzada et al., 2020, 2020).

Unlike traditional extraction methods which are based on the extraction of templates from MIPs, the MIP is extracted from the template in the solid phase synthesis method. Indeed, this synthesis method involves the immobilization of a template on solid support followed by a polymerization process to construct a polymer around the template. Then the resulting polymer is eluted from the solid-template (Fig. 5). This approach was applied to remove epitopes (McClements et al., 2022; Garcia Cruz et al., 2020; Betlem et al., 2020). This method does not require hazardous chemical treatments to remove the template from the polymer. Table 2 summarizes the various removal methods for different epitopes, peptides, and proteins from MIPs, providing a comprehensive overview of the techniques discussed above.

2.4. Removal of viruses

In this section, we provide an overview of various techniques used for removing viruses from MIPs. While these techniques have been extensively employed in the field, importantly, we should provide context for their application and highlight their significance in practical settings.

The most commonly applied approach for removing viruses from MIPs is the immersion of the MIP in a washing solution. Typically, a combination of organic solvent and protonic acid is used for the elution of viruses. For instance, methanol/HAc has been widely used to remove viruses such as *H5N1* (Chen et al., 2022), *Japanese encephalitis virus* (Liang et al., 2016; Yang et al., 2020), *hepatitis A virus (HAV)* (Liu et al., 2017) (L. Wang et al., 2021a), and *hepatitis B virus (HBV)* (S. Chen et al., 2021). Additionally, the use of surfactants like SDS with HAc has proven successful in removing the *dengue type 1 virus* (Navakul et al., 2021), *HAV* (Yang et al., 2017) (X. Zhang et al., 2018), and *HBV* (L. Wang et al., 2021c).

Cai's group introduced a novel method to simplify elution. They used UV light (365 nm) to remove *Enterovirus 71* from the MIP without additional reagents (Fig. 6A) (L. Wang et al., 2021b). They incorporated a light-responsive functional monomer, 4-(4′-Acryloyloxyphenylazo) Benzoic acid, into the MIP. Under visible light, the monomer adopts a trans configuration, but under UV light (365 nm), it changes to a cis configuration. This structural change breaks down the carboxyl groups responsible for binding to the virus surface, resulting in decreased binding ability of the imprinted cavities and virus release. Another technique for template removal without the use of reagents involves gas bubbling. Cai's group employed N_2 bubbling in a work focused on removing HBV from a MIP composed of a CO_2-sensitive functional monomer, dimethylamino ethyl methacrylate (L. Wang et al., 2022). The progressive deprotonation of the protonated ammonium cation through N_2 bubbling transforms it into an uncharged amine group, considerably weakening the binding strength between the imprinted

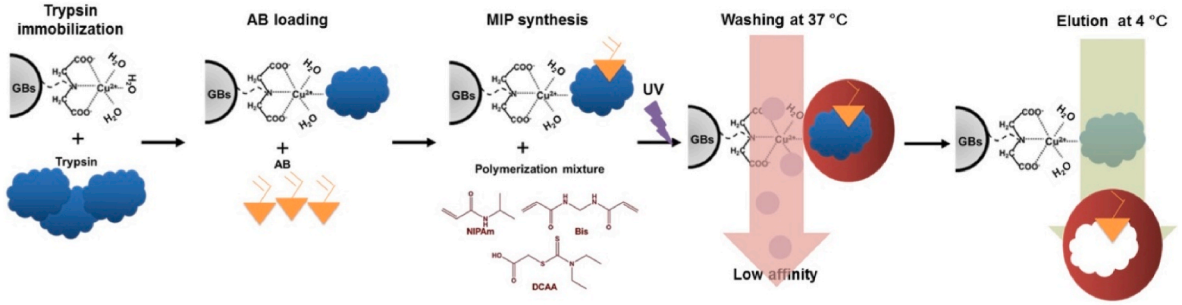

Fig. 5. Solid-phase synthesis of MIP and its elution from solid-phase with immobilized template Reprinted from (Xu et al., 2018) with the permission of Elsevier. Trypsin was immobilized onto glass beads (GBs) functionalized with Cu^{2+}-iminodiacetic acid, primarily targeting its surface histidine residue. A fluorescent functional monomer 4-acrylamidophenyl(amino)methaniminium chloride (AB) was next added. Subsequently, the MIP was synthesized using N-isopropylacrylamide, N, N'-methylenebis(acrylamide), and a water-soluble iniferter called diethylthiocarbamoylsulfanyl acetic acid through UV polymerization around the trypsin. Then, unreacted reagents and low-affinity polymers were removed through washing, ultimately isolating high-affinity MIP nanoparticles by lowering the temperature.

Table 2
Removal methods of epitopes/peptides/proteins from MIPs.

Templates	Type of epitope/peptide/protein	Type of monomer	Removal methods
peptides/ epitopes	benzoylation-modified peptides (SGRGKbz) (Pu et al., 2022)	deep eutectic solvents monomer and zinc acrylate	3:3:4 v/v/v Acetonitrile/water/HAc
	amyloid β-42 (Moreira et al., 2018)	aniline	Washing with 0.5 mol/L oxalic acid for 2 h
	phosphopeptide sequence with different phosphorylation forms (Angiotensin II angiotensin II mutant analogs) (Ren et al., 2022)	Ureidopropyltriethoxysilane (UPTES) and TEOS	10% $NH_3{\cdot}H_2O$ for 50 min
	epitopes of matrix metalloproteinase-1 (MMP-1) protein biomarker of idiopathic pulmonary fibrosis (MIAHDFPGIGHK) (Bartold et al., 2022)	triphenylamine rhodanine-3-acetic acid	0.5 mM triethylamine for 30 min
	PQQPFPQQ Gluten Epitope (Iskierko et al., 2019)	p-bis(2,2′-bithien-5-yl)methylbenzoic acid, 2,2-(cytosin-1- yl)ethyl and p-bis(2,2′-bithien-5-yl) methylbenzolate	10 mM NaOH and ethanol mixture at the volume ratio of 1:2 for 3 h
	A peptide from triplication in the α-synuclein (for Alzheimer's disease) (Lee et al., 2020)	Poly(hydroxymethyl 3,4- ethylene dioxythiophene)	5% Ethanol
	amyloid β-42 (Özcan et al., 2020)	pyrrole	1.0 M NaCl for 15 min
	Nonapeptide (epitope of Bovine serum albumin) (Li et al., 2017)	o-phenylenediamine	5% Tween-20 in 0.1 M PBS
	amyloid β-42 (Pereira et al., 2020)	PEDOT and *O*-phenylenediamine	Trypsin solution for 1 h
	amyloid β-42 (Ribeiro et al., 2022)	acrylamide	500 μg/mL Proteinase K
	Epitope of insulin (Garcia Cruz et al., 2020)	N-(3-Aminopropyl) methacrylamide hydrochloride	Removal of the MIP from the immobilized epitope on the solid phase (Elevated temperature, 60 °C)
	cysteine-modified epitopes neuron-specific enolase (Pirzada et al., 2020)	scopoletin	Electrochemical removal
Proteins	Cancer antigen 15-3 (Ribeiro et al., 2018)	Toluidine Blue	Electrochemical removal (0.1 NaOH)
	Myoglobin (Moreira et al., 2014)	O-aminophenol	500 μg/mL Proteinase K prepared in PBS, pH 7.4)
	Cardiac Troponin T (Phonklam et al., 2020)	Aniline	500 mM HAc
	Galectin-3(Cerqueira et al., 2021)	Aminophenol	0.5 M oxalic acid
	Carcinoembryonic antigen (Qi et al., 2019)	Dopamine	SDS/HAc (1% HAc and 1.0 g/L SDS)
	Cardiac Troponin T (Lin et al., 2021)	O-phenylenediamine	NH_4OH/ethanol
	Cancer antigen 15-3 (Santos et al., 2018)	Pyrrole	Ethanol

cavity and the virus.

The solid-phase synthesis technique immobilizes the template onto a solid phase, and the MIP is formed around it. Subsequently, the resultant MIP particles are eluted from the solid phase. This method eliminates the need for hazardous chemical treatments to remove the template from the polymer. The elution of MIP particles is achieved through heating at 60 °C (Poma et al., 2013). Cai's group successfully applied this protocol to elute the MIP from solid-phase immobilized HAV and HBV (Fig. 6B) (Cai et al., 2023). The heating enhances the exchange rate between the particles and the template phase, facilitating efficient elution. In summary, the removal methods of different viruses from MIPs have been summarized in Table 3.

2.5. Removal of bacteria

In this section, we discuss various techniques for removing template bacteria from MIPs. Significantly, we should consider the challenges associated with imprinting microorganisms, particularly their large size, which poses difficulties in removing bound cells from the template-like cavities. While these techniques have been previously reported in the literature, we aim to provide context for their application and highlight their significance in the field of MIPs.

One common approach to remove or destroy bacteria from MIPs involves the use of SDS in an acidic medium. The acidic environment helps to break down the external cell wall of bacteria, while the surfactant disrupts the bacterial cell membrane. This disruption leads to the release of intracellular contents and ultimately bacterial death. Additionally, the acidic medium protonates the SDS molecules, increasing their solubility and effectiveness in removing bacteria. For example, Roushani et al. employed a solution mixture of 0.01 M SDS and 10 mM HNO_3 in water for 2 h to remove *Acinetobacter baumannii* from a MIP based on polydopamine grafted on a glassy carbon electrode (Roushani

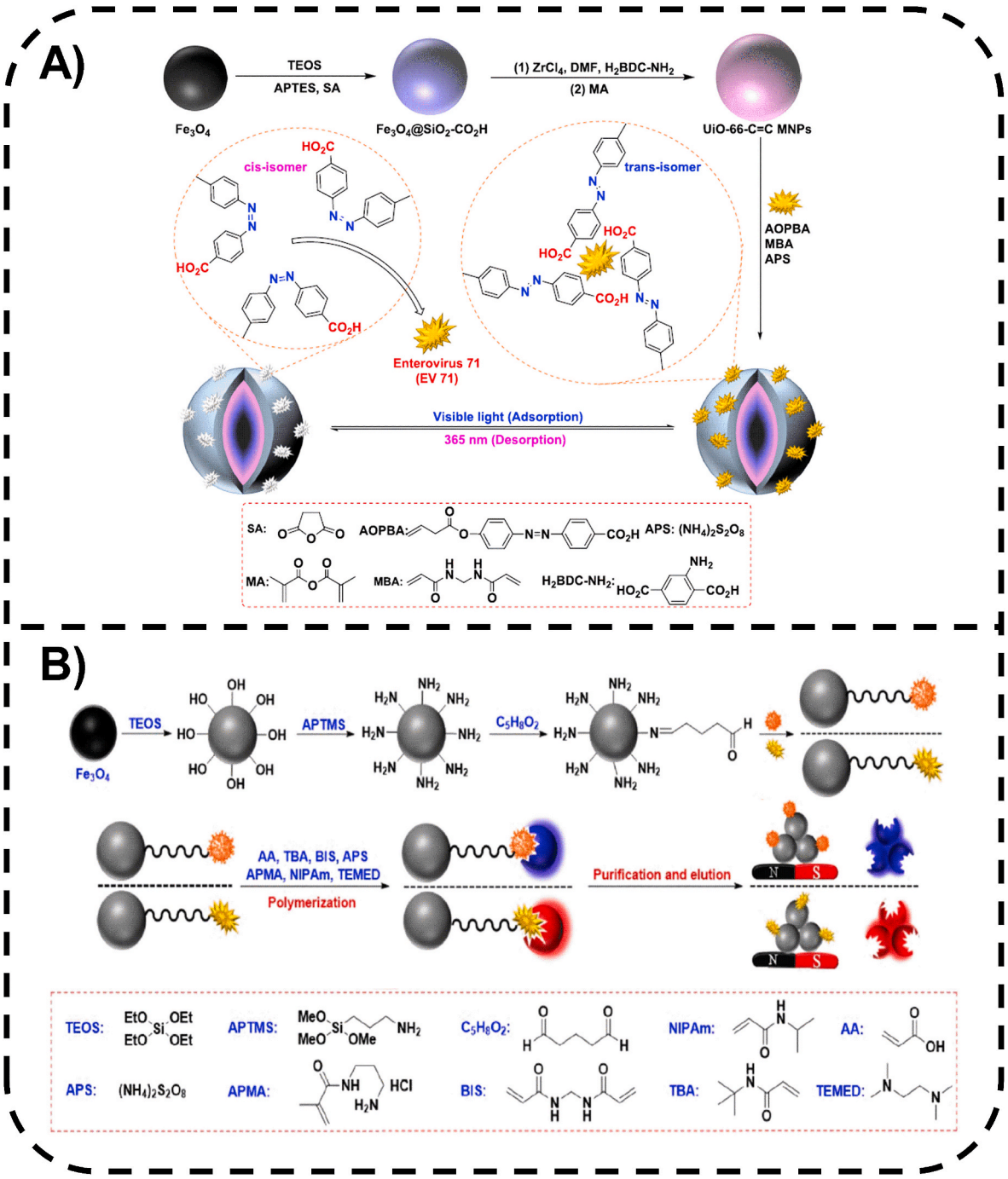

Fig. 6. A) Schematic illustration for the preparation of virus imprinted MIP: UV-light irradiation-based approach was used for the template removal. Reprinted from (L. Wang et al., 2021b) with permission of Elsevier. (B) Solid-phase synthesis of MIP particles for simultaneous determination of HAV and HBV. Reprinted from (Cai et al., 2023) with permission of Elsevier. AA: acrylic acid; AOPBA: 4-(4′-Acryloyloxyphenylazo) Benzoic Acid; APMA:N-(3-aminopropyl) methacrylamide hydrochloride; APTMS:3-aminopropyltriethoxysilane; APS: Ammonium persulfate; BDC: 1,4-benzenedicarboxylate; BIS: N,N-methylene bisacrylamide; *EV 71*: *Enterovirus 71*; MBA: N,N′-Methylenebisacrylamide; NIPAm: N-isopropylacrylamide; SA: Succinic anhydride; TBA: N-tert-butylacrylamide; TEMED:N,N,N′,N′-tetramethylethylenediamine.

et al., 2020). Shen et al. washed polymer beads containing sphere-shaped *Micrococcus luteus* and rod-shaped *Escherichia coli (E. coli)* bacteria six times with water 10% HAc and 1% SDS, followed by six washes with water (Shen et al., 2014). Wang et al. utilized SDS/HAc (5%, w/v) at 37 °C for 2 h under constant shaking (400 rpm) for the in-situ elution of *Staphylococcus aureus* from a MIP (R. Wang et al., 2021). It is noteworthy that soft approaches, such as soaking the MIP film in an acidic or alkaline solution, have proven ineffective in removing bacteria, necessitating the adoption of multistep removal protocols.

Enzyme-based removal of bacteria involves the use of specific enzymes that target and break down components of bacterial cells, leading to their removal or inactivation. Lysozyme is a common enzyme that is responsible for breaking the intermolecular binding of boronic acid moieties of MIP to glycoproteins on the surface of bacteria. Since the enzyme only degrades sugars in bacterial cells, treatment with a surfactant such as Triton X is necessary to remove the fragments of the bacteria membrane and the excess of the enzyme from the MIP film.

Table 3
Removal methods of viruses and bacteria from MIPs.

Type of templates	Type of virus/ bacteria	Type of monomer	Removal methods
Viruses	*Influenza A virus* (Wangchareansak et al., 2013)	AM, MAA, MMA and NVP	Removal of the stamp followed by washing with 10% HCl and then with water for 3 h
	Influenza A H5N1 virus (Wangchareansak et al., 2014, p. 1, p. 1)	AA, MAA, MMA and NVP	Removal of the stamp followed by washing with 10% hydrochloric acid for 3 h
	H5N1 (Chen et al., 2022)	AAM, acrylic acid, methyl acrylate	Washing with 9:1 v/v methanol and HAc
	Japanese encephalitis virus (Yang et al., 2020)	Zinc acrylate	Washing with 9:1 v/v methanol and HAc
	HBV (S. Chen et al., 2021)	TEOS	Washing with 9:1 v/v methanol and HAc
	Japanese encephalitis virus (Luo et al., 2019)	APTES and TEOS	Washing with 5% v/v HAc and 5% v/v methanol
	Dengue type 1 virus (Navakul et al., 2021)	AM/MAA/MMA and NVP	Washing with 10% v/v HAc and 0.1% w/v SDS
	HAV (Yang et al., 2017)	Dopamine	Washing with 5% v/v and 10% w/v SDS
	HBV (L. Wang et al., 2021c)	APTES and TEOS	Washing with 0.1 mol L^{-1} HAc and 10% w/v SDS
	HAV and *HBV* (Cai et al., 2023)	*N*-isopropylacrylamide, acrylic acid and *N*-tert-butylacrylamide	Removal of the MIP particle from the template phase by shaking at 60 °C for 30 min
	HBV (L. Wang et al., 2022)	AM and dimethylaminoethyl methacrylate	N_2 bubbling
	Enterovirus 71 (L. Wang et al., 2021b)	4-(4′-Acryloyloxyphenylazo) Benzoic Acid	UV light irradiation for 30 min
Bacteria	*Staphylococcus aureus* (R. Wang et al., 2021)	Poly(3-thiopheneacetic acid)	Washing with 5% w/v SDS and HAc at 37 °C for 2 h
	Acinetobacter baumannii (Roushani et al., 2020)	Dopamine	Washing with 0.01 M SDS and 10 mM HNO_3 for 2 h
	Salmonella typhi (Razavilar et al., 2019)	MAA	Washing with 5% w/w SDS and 0.6 M NaOH for 30 min at 85 °C
	Listeria monocytogenes (X. X. Zhao et al., 2019)	*N-Acrylchitosan*	Washing with 1% w/v SDS, 10% HAc, and methanol
	Enterococcus faecalis (Erdem et al., 2019)	N-methacryloyl-(L)-histidine-methylester	Washing with 0.1 M NaCl
	Bacillus subtilis, Staphylococcus aureus, Escherichia coli and *Pseudomonas aeruginosa* (Tokonami et al., 2014)	Pyrrole	Electrochemical removal in aqueous 0.1 M NaOH solution and treatment of the film with lysozyme
	Pseudomonas aeruginosa (Tokonami et al., 2013)	Pyrrole	Washing with 10 mg/ml lysozyme and 10% Triton X for 2 h at 4 °C Then electrochemical treatment in aqueous 0.1 M NaOH
	Salmonella paratyphi (Perçin et al., 2017)	N-methacryloyl-L-histidine methyl ester-Cu^{2+} complex	Removal of the stamp followed by simple washing with 10 mg/ml lysozyme solution (in 10 mM PBS, pH 7.40) for 30 min

AM: Acrylamide; MAA: methacrylic acid; MMA: methylmethacrylate; NVP: N-vinylpyrrolidone; APTES: (3-Aminopropyl)triethoxysilane; TEOS: Tetraethyl orthosilicate.

While lysozyme is commonly used for its antibacterial properties, it is not typically used to directly remove bacteria from MIPs. Enzyme-based approaches offer advantages such as specificity, efficiency, and the potential to target a broad range of bacterial species.

Electrochemical removal is another soft method widely employed to remove bacteria from MIPs. Tokonami et al. utilized a combination of electrochemical removal and lysozyme treatment to remove Gram-negative bacteria (*E. coli* and *Pseudomonas aeruginosa*) by applying a constant potential in a basic medium (Tokonami et al., 2014). This electrochemical process not only enables the removal of bacteria but also facilitates the overoxidation of polypyrrole. While electrical overoxidation alone can be used to remove small molecules (Shiigi et al., 2005), the interaction between bacteria and polypyrrole is stronger due to the larger size of bacteria. Therefore, this method allows for the creation of accurate bacterial templates by transferring the chemical structure of the bacterial surface to the molecular level. The overoxidation was also applied with treatment using lysozyme and Triton X to break the strong interactions between the polymer surface and the polysaccharides on the bacterial cell wall (Tokonami et al., 2013).

Lithography enables easy removal of template bacteria by removing the stamp. Yilmaz et al. effectively eliminated *E. coli* from polymeric film-coated sensors by washing them with ethyl alcohol and a lysozyme solution (Yilmaz et al., 2015). Similarly, Idil's group removed the *E. coli* bacteria stamp followed by washing with sodium phosphate buffer and a lysozyme solution (Idil et al., 2017). Givanoudi's group removed bacteria by removing the stamp, but further washing with an SDS detergent was necessary (Givanoudi et al., 2021).

In summary, various techniques have been developed and applied to remove template bacteria from MIPs. These techniques include the use of surfactants in acidic media, electrochemical removal combined with lysozyme treatment, and the removal of the stamp in lithography-based approaches. Each method offers advantages and considerations depending on the specific MIP system and the target bacteria. Understanding and selecting the appropriate removal technique is crucial for the successful application of MIPs in bacterial determination and sensing. In summary, the removal methods of different bacteria from MIPs have been summarized in Table 3.

2.6. Methods for confirming template removal completeness

Ensuring the thorough removal of the template molecule is fundamental to the functionality and reliability of MIPs. To confirm the completeness of template removal, several methods can be employed. One common approach is utilizing analytical techniques such as UV-Vis spectroscopy (Liu et al., 2016), liquid chromatography–tandem mass spectrometry (D. Elfadil et al., 2022), or electrochemical methods (Ben Messaoud et al., 2018) to directly detect the presence of the template in the eluent or wash solution. The absence of any signal or peak corresponding to the template indicates successful removal. Another

approach involves the direct detection of the presence of a template on the MIP surface, often through colorimetric (Lamaoui et al., 2022a) or electrochemical methods (Beduk et al., 2020; Seguro et al., 2022). X-ray photoelectron spectroscopy is also a valuable technique to provide insightful data regarding the removal of the template from the MIP structure (Bai et al., 2021). It's noteworthy that the choice of confirmation method should align with the specific nature of the template molecule and the overall objectives of the MIP. Selecting an appropriate method for assessing template removal completeness is crucial in ensuring the reliability and effectiveness of MIP-based applications.

3. Summary and current challenges of the template removal

The successful creation of imprinted cavities featuring recognizing sites in IIPs relies on the efficient removal of target ions after complexation and polymerization. Various techniques have been developed for this purpose. Chemical solutions like NaF and EDTA are commonly used to remove metal ions, while strong acids such as HCl and nitric acid can also be effective without causing polymer deterioration. The selection of solvents and mixtures is crucial, with Soxhlet extraction being simple but slow, microwave-assisted extraction being faster but requiring optimization, and ultrasound-assisted extraction offering improved efficiency. Electrochemical methods are efficient for MIP-based electrochemical sensors. Enzymatic digestion is an efficient approach for removing epitopes, peptides, and proteins. UV irradiation and N_2 bubbling are innovative techniques for virus removal. Methods like SDS treatment, multistep protocols, electrochemical removal with lysozyme, and lithography are used for bacterial removal. The choice of method depends on the specific application, type of template, and MIP characteristics.

The removal of templates from MIPs is a challenging task due to several factors. One of the major challenges is that the templates embedded in the core of MIPs particles cannot be removed easily as the solvent cannot penetrate inside. As a result, these templates remain inside the MIPs particles even during the analytical application, which can affect the accuracy of the results. Another challenge is the return of molecules to the cavities when the extraction solution is changed to water or buffer, leading to incomplete removal. The elimination of the solvent used in the extraction is also difficult, as it contains traces of molecules that tend to return to their cavities when water or buffer is added, making it difficult to achieve complete extraction. Additionally, the harsh conditions used in the removal can lead to the distortion, collapse, and rupture of the cavities, resulting in the loss of selectivity of the MIPs. In some cases, the components of the removal solution can interact with the surface of the polymer, leading to its modification and causing high non-specific sorption (NSS), which is another challenge for the removal of templates from MIPs. Last but not least, the evaluation of the complete removal of templates from MIPs is typically assessed through analytical methods. However, it is crucial to note that these methods often lack a low detection limit. This means that it can be difficult to accurately determine the complete removal of templates from the polymers. Therefore, it's essential to carefully consider the limitations of these methods when analyzing the effectiveness of template removal from the MIPs and we recommend the use of ultrasensitive methods.

In the development of MIPs, the choice of cross-linking conditions is a critical factor that significantly influences their performance. The degree of cross-linking, ranging from minimal to maximal, plays a pivotal role in determining the structural integrity of the resulting MIPs. At the lower end of the spectrum, a loose and elastic polymer network is achieved, which helps preserve MIP integrity and prevent collapse during template removal. This level of cross-linking facilitates template removal by enabling efficient template diffusion. Conversely, at the higher end of cross-linking, a rigid polymer network is formed. While this offers mechanical stability, it necessitates effective template release into the solution through diffusion (Ellwanger et al., 2001; Lorenzo et al., 2011). Striking the right balance between these extremes is essential to design MIPs that are both structurally sound and capable of facile template removal. The Table 4 offers a convenient reference for comparing and contrasting the various removal techniques discussed in the manuscript.

4. General overview on the binding of analytes

The binding of the target analyte within the cavities is a crucial aspect of MIP development. Evaluating the binding potential of MIPs, compared to non-imprinted polymers (NIPs), is essential. The assessment of binding performance involves various studies such as isotherm sorption, sorption kinetics, sorption thermodynamics, and selectivity analysis for both MIPs and NIPs. Additionally, factors like solvent effects and pH are critical in achieving high-performance MIPs. Depending on the analyte type, different binding approaches have been reported, including techniques such as electrochemistry, gas-bubbling, UV-visible irradiation, and more. In the following subsections, we will provide a detailed description and discussion of the binding methods corresponding to the type of analyte.

4.1. Binding of ions (analytes)

The binding of ions onto IIPs entails reintroducing the target ion(s) onto the polymer surface after it has been extracted or isolated from a sample. The selection of a suitable binding method depends on the specific application and its requirements. In the following section, we will explore a range of techniques used for the efficient binding of ions onto IIPs, providing valuable insights into their respective applications.

Table 4
Removal methods and their merits and disadvantages.

Removal methods	Merits	Disadvantages	Application
Soxhlet	Simple, versatile and does not require expensive instruments	Slow pace, challenges in automation, and trace amounts of the template may persist encapsulated within the polymer matrix	Molecules
Incubation/ immersion	Simple, efficient and instrument-free protocol	Time-consuming and requires a large amount of solvent to establish a concentration gradient	Ions, molecules, epitopes, proteins, viruses and bacteria
Removal of the stamp	Easy to remove bacteria	Limited to the removal of bacteria from MIP prepared via lithography approach	Viruses and bacteria
Proteolytic digestion	Preserves the polymer structure and imprinted cavities	Requires an extra intensive washing with oxalic acid after removing the template	Epitopes, epitopes and proteins
Removal of the MIP	No need for hazardous chemical treatments	Limited to MIP prepared vis solid-phase synthesis	Viruses
Gas bubbling	No need for hazardous chemical treatments	Limited to gas-sensitive mips, constructed with functional gas-sensitive monomers.	Viruses
Microwave	Fast	Potential damage to the polymer	Ions and molecules
Ultrasonication	Fast	Potential damage to the polymer	Ions, molecules, and bacteria
Electrochemical	Efficient and gentle removal	Limited to MIP-based electrochemical sensors	Ions, molecules, epitopes, proteins, viruses and bacteria

The simultaneous binding and determination of target ions onto IIPs has emerged as a prominent area of research. Denizli and colleagues pioneered the utilization of a plasmonic sensor in phosphate buffer at different pH values for the simultaneous binding and determination of Cu^{2+} ions (Safran et al., 2019; Gerdan et al., 2022). Their groundbreaking work showcased the feasibility of real-time monitoring without the need for separate binding steps. Nevertheless, the simultaneous binding and determination approach employed in real-time monitoring of target ions onto IIPs may present challenges in achieving high selectivity. This is due to the absence of a specific step that allows for the elimination of interferents, potentially impacting the selectivity of the IIPs.

Therefore, Krywko-Cendrowska et al. (2021) and Shamsipur et al. (2018) achieved successful binding of target ions by a simple immersion of the IIP-modified electrodes in solution without stirring. This immersion-based approach simplified the binding while ensuring efficient ion capture. To further enhance the binding efficiency, Tarley et al. employed magnetic stirring during the immersion (Tarley et al., 2017). This innovative technique offered improved mass transfer and facilitated the binding of target ions onto the IIPs. The utilization of IIP columns has demonstrated promising results for the extraction of target analytes from real samples. Aslıyüce et al. effectively employed an IIP column to flow a plasma sample with beta-thalassemia under moderate pressure using a peristaltic pump over a specific period (Aslıyüce et al., 2010). This column-based method not only enabled efficient extraction but also facilitated the purification of the target analyte. Collectively, these techniques represent valuable contributions to the IIPs, providing practical solutions for monitoring target ions onto IIPs and opening up new avenues for their application in diverse domains.

Sonication was also employed to bind analytes onto the IIP or MIP. Jakavula et al. carried out the sorption of Sb^{3+}, Cd^{2+}, $Pb^{2+,}$ and Te^{4+} onto multi-ion imprinted silica materials within 22 min (Jakavula et al., 2021). The drawback that can be found with sonication is the destruction of the polymer (Liu et al., 2021). Therefore, we should consider the potential risk of polymer destruction when applying sonication. In the case of Jakavula et al.'s study, the use of silica materials helped maintain the mechanical integrity of the IIP.

Electrochemical binding offers a powerful method to accumulate target ions onto the surface of IIP-modified electrodes. This technique involves applying a potential to the electrode with or without stirring the solution. Samandari et al. immersed the IIP-modified electrode in a solution containing Cd^{2+} ions and applied a negative potential for a specific duration under stirring conditions (Samandari et al., 2019). The Prasad group also utilized a similar approach to bind Cd^{2+} and Cu^{2+} ions onto IIP-modified electrodes (Bali Prasad et al., 2014). The same group demonstrated also that this method is useful to bind Ce^{4+} and Gd^{3+} (Prasad and Jauhari, 2015, p.). It is noteworthy that the choice of electrochemical potential is an important parameter in optimizing the accumulation process (Ghanei-Motlagh et al., 2016). Prasad & Jouhari studied the effect of different potentials and determined the optimal value for their system (Prasad and Jauhari, 2015, p.). Potential values outside the optimal range may result in the reduction of hydrogen ions and the formation of hydrogen bubbles.

In summary, the choice of binding method depends on the specific requirements of the application. Different techniques offer diverse options for achieving effective binding of ions onto IIPs. These techniques offer researchers a spectrum of approaches tailored to their particular requirements and experimental conditions.

4.2. Binding of small-molecules (analytes)

The binding of molecules to MIPs involves the formation of stable complexes between target molecules and the functional groups within the polymer matrix. Several factors influence the binding, including the size and shape of the target molecule, the density and distribution of binding sites within the MIP, and the affinity of the binding sites to the target molecule. Additionally, the presence of other molecules in the environment can affect the binding as they may compete for binding sites within the MIP. In light of these considerations, various binding methods have been reported in the literature.

One commonly used method to investigate the sorption properties of MIPs and calculate sorption parameters is batch binding (Z. Wang et al., 2018). The choice of the binding solution is critical, and different media have been investigated, such as nonpolar hexane and polar methanol-water mixtures (Pešić et al., 2020). The highest imprinting factor was observed with a methanol-water mixture. While batch binding is useful for determining kinetic, isotherm, and thermodynamic parameters, it requires subsequent filtration or centrifugation to separate the MIP particles from the liquid. To overcome this drawback, alternative approaches have been explored. These include incorporating magnetic nanoparticles as core materials and modifying them with the MIP (Lamaoui et al., 2021c, 2022b; Lamaoui et al., 2021a), as well as using other binding approaches, such as direct drop-casting of molecules onto the surface of MIP-based sensors (Mugo et al., 2022) or passing a solution containing the target analyte through columns under gravity (Daniels et al., 2021).

In some applications, a touch-based sensor approach has been developed to measure analytes, such as fingertip sweat cortisol Fig. 7 (Tang et al., 2021). In this method, the cortisol from accumulated finger sweat diffuses through a hydrogel onto the MIP electrode by touching. Optimal conditions for the touching time (30 s) and immersion time (2 min) were determined for the cortisol to interact with the MIP electrode.

The binding performance of MIPs is influenced by various synthesis parameters. The synthesis time significantly affects the binding capacity of the MIP, with an increase observed up to a certain point. The progressive increase in the degree of polymer network crossing and the production of more imprinted sites during the polymerization process contribute to this effect. However, once the monomer and cross-linker fully react, the binding capacity plateaus. The self-assembly time for hydrogen bond formation before the synthesis of MIP is another important factor affecting the binding performance of MIP. Extending the self-assembly time has been shown to enhance the selectivity of MIPs (Lamaoui et al., 2019).

The synthesis temperature also plays a crucial role in binding efficiency (O'Shannessy et al., 1989; Parlak et al., 2018a). High synthesis temperatures can decrease the stability of the monomer-template complex and the recognition ability of the MIP toward the target molecule, while low temperatures generally exhibit good binding properties (Lamaoui et al., 2021b, p. 4). Comparing synthesis at room temperature with that at 4 °C revealed higher imprinting factors at 4 °C (Parlak et al., 2018a). However, excessively low temperatures may lead to incomplete polymerization and a decrease in the creation of binding sites, particularly with thermal heating and microwave methods. Optimal temperature conditions vary depending on the specific system (Lamaoui et al., 2021c).

The choice of solvent during synthesis significantly impacts the morphology of the polymer. Porogenic solvents with high vapor pressure, such as dichloromethane, facilitate the formation of a highly porous structure with a larger internal surface area, allowing for enhanced access of molecules to the molecular cavities within the polymer. This increased porosity contributes to improved binding properties of MIPs (Parlak et al., 2018b). Additionally, other solvents such as acetonitrile, isopropanol, and chloroform have been tested for their impact on the binding. A study conducted by P. Pešić et al. concluded that isopropanol exhibited the most effective binding (Pešić et al., 2020).

As the field of MIPs continues to advance, it becomes essential to address the specific scenario involving the use of surrogate or dummy templates that differ from the target analyte. This situation arises when structurally analogous templates are selected, albeit distinct from the intended analyte. The use of dummy templates offers several advantages. First, it allows for the creation of MIPs in cases where the target

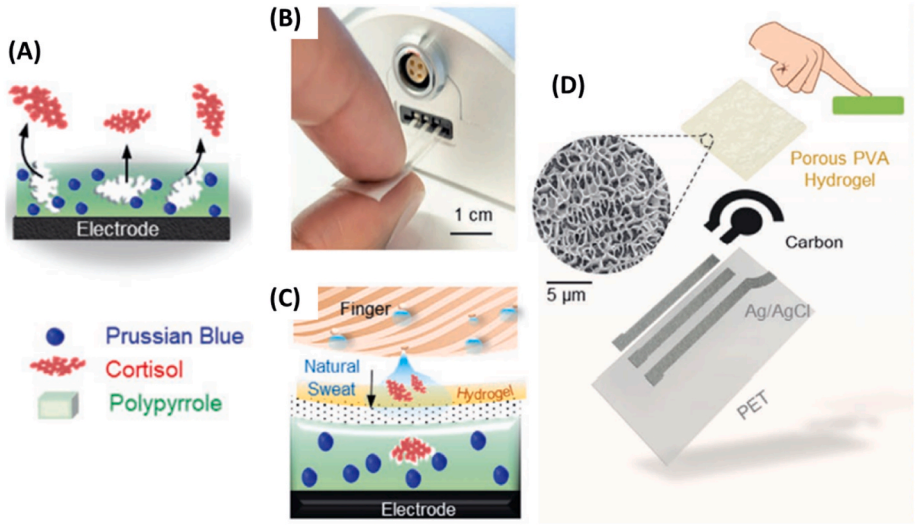

Fig. 7. The touch-based fingertip cortisol sensor with (A) schematic illustration of the MIP-based sensor, (B) photo demonstrating the single-touch sensor application (C) illustration of the sensing mechanism, where the cortisol from the accumulated finger sweat diffuses through the hydrogel onto the MIP electrode, and (D) structural illustration of the fingertip cortisol sensor, with the cryogenic scanning electron microscopy (cryo-SEM) image of the porous PVA hydrogel (inset). Reprinted from with (Tang et al., 2021) the permission of Wiley Online Library. PET: poly(ethylene terephthalate); PVA: polyvinyl alcohol.

analyte is scarce, hazardous, or expensive, making the research more accessible (Wang et al., 2023). Second, it avoids template leaking and decreases interference in trace detection (Zheng et al., 2023).

Once the surrogate template has been successfully removed, the MIP sites become available for binding the intended analyte (Leibl et al., 2020; Xu et al., 2013). Understanding and optimizing the binding dynamics between the MIP and the analyte in these scenarios is essential. This involves characterizing the specificity, selectivity, and affinity of MIPs for the desired analyte.

4.3. Binding of epitopes and proteins (analytes)

The binding of epitopes and proteins to MIPs encompasses several important factors that contribute to their efficient recognition and binding. One crucial factor is the conformational geometry of the analyte, which is highly influenced by the pH of the binding solution. Understanding the pH-dependent behavior of analytes is essential for optimizing binding conditions. For instance, Harijan et al. found that the optimal binding of an epitope on MIPs occurred at pH = 7.0 (Harijan et al., 2022). Similarly, Chen et al. demonstrated that the maximum binding capacity for glycoprotein onto MIPs was achieved at pH = 7.4 (W. Chen et al., 2021). Conversely, the binding capacity of MIPs to horseradish peroxidase decreased at pH = 9.0 due to protein denaturation under alkaline conditions.

Electrostatic interactions are a pivotal factor in the binding of peptides onto the MIPs, as demonstrated through zeta potential measurements as reported by Dechtrirat et al. (2012). The presence of these interactions enhances the binding capacity of MIPs compared to NIPs. However, it is important to note that these electrostatic interactions can increase non-specific binding, particularly for basic peptides.

Protein imprinting can be accomplished through whole protein or epitope imprinting techniques (Ansari and Masoum, 2019). Zhang et al. observed that the binding of whole proteins to epitope-imprinted polymers relies not only on specific binding but also on non-specific binding (Zhang et al., 2021). The dissociation constants (Kd) typically range in the nanomolar range for peptide binding on epitope-printed polymers, while the binding of the corresponding proteins shows values in the micromolar range. Achieving and reproducing pM or fM sensitivity often demands complex optimization and may not be necessary or feasible in routine scenarios. Therefore, while recognizing the existence of ultra-sensitive MIP-based sensors, we emphasize the importance of considering the trade-offs between sensitivity, complexity, and cost-effectiveness based on the intended application.

Kinetic modeling is commonly employed to describe the sorption kinetics of proteins onto MIPs. The pseudo-second-order kinetic model has been successfully applied to describe the sorption of glycoprotein, with MIPs exhibiting a faster half-life ($t_{1/2}$) of 3.6 min compared to NIPs ($t_{1/2}$ = 10.7 min) (W. Chen et al., 2021). Temperature variations between 15 and 35 °C did not significantly influence the recovery of the protein, indicating that the interactions between phenylboronic acid (used for glycoprotein immobilization) and the glycoprotein are temperature-insensitive (W. Chen et al., 2021).

Various isotherm models have been tested for different peptides and proteins. The Scatchard model demonstrated the best fit for the sorption of phosphopeptides (Ren et al., 2022). The Langmuir model was found to be suitable for the sorption of benzoylation-modified peptides and glycoproteins on MIPs formed with Zinc acrylate and deep-eutectic solvents monomers (Pu et al., 2022) and magnetic-graphene oxide--based MIPs (W. Chen et al., 2021). Additionally, the Langmuir-Freundlich isotherm fitting provided particularly spectacular results in a recent study (Lamaoui et al., 2019). The Freundlich model was also investigated for the sorption isotherms of certain peptides (Kushwaha et al., 2019) and proteins (Ribeiro et al., 2018).

By providing a comprehensive understanding of the binding mechanisms and optimizing the experimental conditions, the context of these techniques can assist researchers in the MIP field to better design and develop efficient MIP systems for peptides, epitopes, and proteins recognition.

4.4. Binding of viruses (analytes)

The binding techniques discussed in this section provide valuable insights into the context of the binding of viruses to the MIPs. By understanding the specific techniques and their applications, researchers in the MIP field can gain a deeper understanding of their everyday work.

The combination of different functional monomers in MIPs offers a diverse range of groups that facilitate binding to target viruses while decreasing the NSS (Chen et al., 2022). In aqueous media, viruses carry a surface charge that is pH-dependent (Michen and Graule, 2010). This electrostatic charge plays a crucial role in the sorption of viruses. For instance, Navakul et al. reported that a MIP-based composite prepared with acrylamide, MAA, methyl methacrylate, and N-vinylpyrrolidone

exhibited a zeta potential of +9.90 mV at pH = 7.40, enabling the binding of positively charged dengue virus particles that possess a zeta potential of +42.2 mV (Navakul et al., 2021). The zeta potential was also utilized to explain the high binding of *HAV* onto the MIP at pH = 6.2 (Yang et al., 2017).

Kinetic studies have demonstrated the optimal binding time for specific viruses. For instance, the binding of the Japanese encephalitis virus onto MIPs reached its maximum within 40 min (Liang et al., 2016). By employing magnetic microspheres as core materials, the binding time was decreased to 20 min (Luo et al., 2019). The binding process is also influenced by temperature, with room temperature yielding the most favorable results for the *Japanese encephalitis virus* (Liang et al., 2016). Sorption isotherms have shown significantly higher fluorescence for MIPs compared to NIPs. To enhance selectivity and eliminate non-selective binding of viruses, Cai's group utilized polyethylene glycol as a blocking agent (Yang et al., 2020).

Innovative approaches have been explored for virus binding onto the MIPs. The visible light irradiation has been employed to bind viruses onto the light-sensitive MIPs. Indeed, Cai's group applied this approach to successfully bind *enterovirus 71* onto the MIP (L. Wang et al., 2021b). Furthermore, Gong et al. applied also the visible irradiation to induce the *cis* to *trans* isomerization leading to the uptake of 4-ethylphenol (Fig. 8A) (Gong et al., 2019). Gas-sensitive MIPs, constructed with functional gas-sensitive monomers, enable the binding of viruses through gas bubbling. Cai's group utilized CO_2 bubbling to bind *HBV* to a MIP composed of dimethyl aminoethyl methacrylate as the CO_2-sensitive functional monomer (L. Wang et al., 2022). CO_2 introduction alters the electrical properties of the imprinted cavities, resulting in the protonation of amino groups, which in turn strongly attract negatively charged viruses as shown in Fig. 8B.

4.5. Binding of bacteria (analytes)

The binding studies of bacteria (analytes) offer valuable insights into the selectivity and potential applications of MIP beads. For example, the binding of sphere-shaped *Micrococcus luteus* and rod-shaped *E. coli* demonstrated the high selectivity of MIP beads towards specific bacterial shapes (Shen et al., 2014). However, the level of precision achieved in bacterial imprinting is lower compared to small molecule imprinting.

To overcome the challenges posed by the active movement of living bacteria, researchers have explored techniques such as dielectrophoresis for rapid and sensitive determination (Tokonami et al., 2014). This technique concentrates and captures the target bacteria on the sensor surface, enabling determination by techniques like quartz crystal microbalance and surface plasmon resonance (Fig. 8C) (Yilmaz et al., 2015). By applying this approach, researchers were able to successfully attract *E. coli* in aqueous solutions and bind them to the surface of poly N-methacryloyl-(L)-histidine methyl ester (Özgür et al., 2020). Dielectrophoresis can effectively manipulate and separate bacterial populations, DNA, proteins, mammalian cells, and viruses (Zaman et al., 2021). The application of dielectrophoresis forces in the presence of *Pseudomonas aeruginosa* led to their selective capture in the MIP array (Fig. 8D) (Tokonami et al., 2013). Before the application of the dielectrophoresis voltage, *Pseudomonas aeruginosa* cells moved actively in random directions within the solution; however, once dielectrophoresis forces were applied to the electrode, they sought for cavities, were

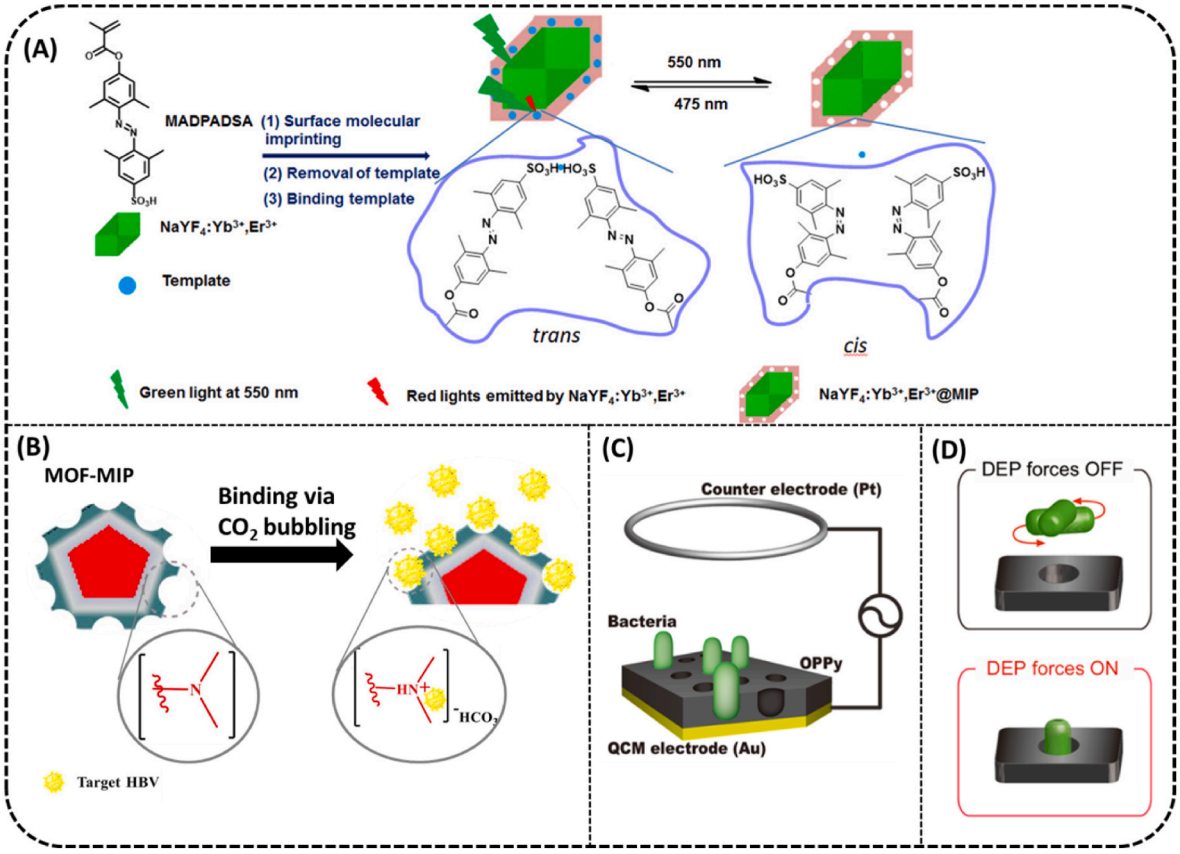

Fig. 8. (A) Irradiation at 475 nm induced cis to trans isomerization, resulting in the uptake of 4-ethylphenol. Reprinted from (Gong et al., 2019) with the permission of Elsevier. (B) Binding of HBV onto a gas-responsive molecular imprinting biosensor based on zeolite imidazole ester material (ZIF-8) through CO_2 bubbling. Reprinted from (L. Wang et al., 2022)with the permission of Elsevier. (C) Schematic illustration of electrode arrangement for bacterial binding with MIP film. (D) Binding of *Pseudomonas aeruginosa* by MIP under dielectrophoresis excitation. Reprinted from (Tokonami et al., 2013)with the permission of ACS. DEP: dielectrophoresis; HBV: hepatitis B virus; MADPADSA: 4-[(4-methacryloyloxy)-2,6-dimethyl phenylazo]-3,5-dimethyl benzenesulfonic acid; OPPy:overoxidized polypyrrole; QCM: quartz crystal microbalance.

vertically entrapped to the film.

The molecular interactions between the boronic acid residues of the MIP and the surface glycoproteins of bacteria play a crucial role in the reversible binding of bacterial cells during electropolymerization. These covalent interactions enable the capture of bacteria within the MIP array. Yasmeen et al. successfully applied this concept for the binding and determination of *E.coli K-12* using a capacitive impedimetric method (Yasmeen et al., 2021, p. 12). To control the binding of cells within specific patterns and prevent unwanted populations outside these patterns, surface modification of the imprinted surface of cells based on polydimethylsiloxane with Cr/Au was reported (Kavand et al., 2019).

By highlighting the contextual significance of these techniques, researchers in the MIP field can gain a deeper understanding of the challenges and potential solutions for bacterial binding.

In summary, while the binding techniques discussed in the previous section provide valuable insights into the diverse approaches used in the field of MIPs, it is essential to consider the context in which these techniques are applied. Understanding the factors influencing the binding, such as synthesis parameters, solvent choice, and environmental conditions, is crucial for designing and optimizing MIP-based systems. By considering these contextual aspects, researchers can gain a deeper understanding of the practical implications and potential applications of binding techniques in their everyday work.

Table 5 provides a useful point of reference for comparing and differentiating the diverse binding techniques discussed in the manuscript.

5. Current challenges in the binding of analytes

5.1. Regeneration and reusability of MIP

The regeneration and reusability of MIPs have a crucial role in developing reliable, economic, and sustainable analytical applications. While reusability is focused on using MIP again, regeneration involves bringing MIP back to its original state. Regeneration must be taken into consideration in flow injection methods whereas reusability is crucial in MIP-based wearable biosensors. Nonetheless, regeneration studies in the literature are limited to a few sorption-desorption cycles (Jakavula et al., 2021) (S. Wang et al., 2022) and no assessment of several cycles of MIPs has been reported. The regeneration of the cavities of MIPs involves removing the bound target molecules from the polymer matrix, which restores the binding sites for future use. Washing the MIP with a solvent is the typical method that can remove the bound target analyte from the polymer matrix. The choice of solvent depends on the nature of the target analyte and the polymer matrix used in the MIP (Wu et al., 2020). The group of Szekely reported that regardless of the degree of cross-linking, divinylbenzene-based polymers showed the most robust behavior compared to methacrylate and acrylamide-based polymers (Kupai et al., 2017). They can be regenerated more than 100 times without loss of performance. A few studies have investigated the reusability of MIP. Tang et al. developed a MIP-based wearable sensor for continuous cortisol monitoring in sweat. The reusability of MIP enabled the semi-continuous binding of cortisol without the regeneration of imprinted cavities (Tang et al., 2021).

Table 5
Binding methods and their merits and disadvantages.

Binding methods	Merits	Disadvantages	Applications
Soaking	Straightforward	Slow binding	Ions, molecules, proteins, viruses and bacteria
Drop-casting	Simple and easy	Limited to MIP-based film	Molecules
Batch sorption	Versatile	Rapid binding	Ions, molecules, proteins
Flow injection	Efficient, enables monitoring of target analytes	Limited to column	Ions
Dielectrophoresis	Non-destructive, rapid and efficient in binding bacteria	Requires careful experimental design, optimization of electric field conditions	Bacteria
Visible irradiation	No need for solvent	Limited to light-sensitive MIPs	Viruses
Gas bubbling	No need for solvent	Limited to gas-sensitive MIPs, constructed with functional gas-sensitive monomers.	Viruses
Ultrasonication	Fast	Destruction of the polymer	Ions and molecules
Electrochemical	Soft	Limited to MIP-based electrochemical sensors	Ions, and molecules

5.2. Non-specific binding of analyte

The mechanism of the sorption of the target analyte by the MIP is very important. Zhongbo and Hu proposed a model to explain the interactions between the MIP and the target molecule “Estradiol” (Zhongbo and Hu, 2008). As illustrated in Fig. 9A, three types of interactions are presented, including (a) specific sorption, (b) semi-specific sorption, and (c) NSS. Specific sorption takes place only by the sorption of the template molecule through the specific binding sites that are created during polymerization. The specific sorption is dependent on the nature of binding between the template and the polymer. For example, hydrogen bonding and electrostatic interactions are stronger than *Van der Waals* and hydrophobic interactions and lead to the preferential sorption of the template over competing compounds. The semi-specific binding is assigned to the use of excess functional monomers in the non-covalent imprinting approach, which is randomly distributed on the polymer surface. NSS results from hydrophobic interactions of *Van der Waals forces* or hydrogen bonding interactions localized mainly at the polymer surface.

The application of MIPs for recognition is experiencing a persistent challenge regarding the NSS which appeared when the NIP, also known as a reference of MIP adsorbs a high amount of the template. The non-specific interactions dilute the contribution of imprinting in the sorptions and thus dramatically decrease the imprinting factor value. Therefore, the presence of NSS sites may decrease the selectivity of the MIP.

In natural biosensors based on natural antibodies, NSS leads to raised background signals that cannot be distinguished from specific binding (Pan et al., 2017). These false-positive signals affect the reproducibility, dynamic range, limit of detection, selectivity, and sensitivity. Different approaches including passive and active methods have been reported to decrease or suppress the NSS in natural biosensors (Lichtenberg et al., 2019). However, it remains a challenge in the development of biosensors based on plastic antibodies. Hence, it is imperative to acknowledge the NSS of MIPs as a fact and report different investigations aimed at comprehending the underlying causes of this phenomenon. Once the factors contributing to this issue are well-understood, resolving it will become more feasible. Zhang et al. proposed the dimerization of functional monomers resulting in high imprinting efficiencies in terms of selectivity and low NSS while sacrificing some binding capacity (Zhang et al., 2010). The number of untemplated sites is significantly lower in polymers formed from monomers that can form dimers (Fig. 9B). Besides, Chin and Chang suppressed the NSS of the MIP by coating it with SiO_2 before the removal of the template “Bisphenol-A” (Chin and Chang, 2019). This coating not only decreases the NSSs but also prevents the polymer from the effects of organic solvent during template extraction. The SiO_2 was selected to modify the MIP because it insignificantly sorbs

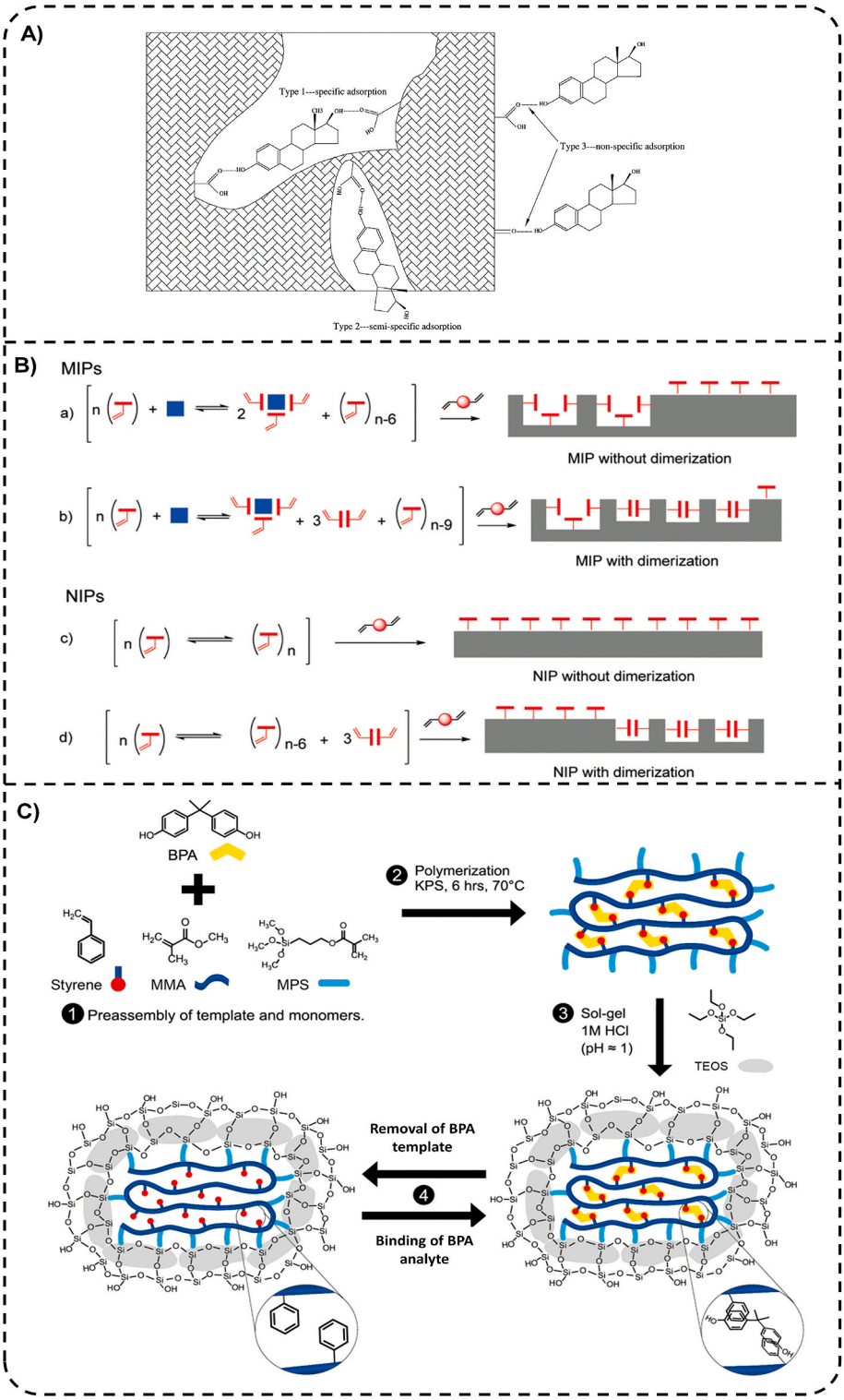

Fig. 9. A) Specific, semi-specific, and non-specific adsorptions of estradiol by MIP. Reprinted from (Zhongbo and Hu, 2008) with permission from Elsevier. B) Comparison between MIP (a and b) and NIP (c and d) prepared from functional monomers that can or cannot be dimerized. Reprinted from reference (Zhang et al., 2010) with permission of ACS. C): Preparation of MIP and its coating with SiO_2. Reprinted from reference (Chin and Chang, 2019) with permission of ACS.

Bisphanol-A. The procedure involves the synthesis of MIP, then the formation of the SiO_2 layer onto the MIP followed by the removal of templates (Fig. 9C). This approach demonstrated a very high imprinting factor "14", high sorption capacity "14.3 mg/g" and fast sorption "20 min". Nevertheless, the use of 1 M HCl in the process of forming SiO_2 on the MIP may jeopardize the polymer and/or lead to the removal of templates.

5.3. Other challenges

One of the current challenges in the binding of the target analyte by MIPs is the optimization of binding kinetics. MIPs typically exhibit slow binding which can limit their practical applications. Researchers are exploring various approaches to improve kinetics, including the incorporation of functionalized nanoparticles. The current challenges also

encompasse the scalability and reproducibility of the MIP synthesis. The synthesis of MIPs is often a complex and time-consuming process, and there is a need to develop more efficient and reliable methods for large-scale production. The reproducibility of MIPs is also a concern, as slight variations in the synthesis conditions can lead to significant differences in the binding properties of the resulting MIPs. Furthermore, the reusability of MIPs poses several challenges. Firstly, the binding sites of the polymers may become saturated after repeated use, leading to a decrease in selectivity and binding capacity. Secondly, the washing and regeneration steps required to reuse the polymers can cause damage to the polymer structure, affecting their performance. Overall, while MIPs offer high selectivity, their reusability remains a challenge that requires further research and development.

Measurements using MIP-based sensors in biological samples, such as blood, present challenges due to the high abundance of proteins typically in the g/L range, like serum albumin and immunoglobulin. Conversely, protein markers for diseases like cancer, diabetes, or heart failure are typically found in the μg/L to mg/L range. Given the common cross-reactivity, the MIP is expected to saturate or reach its maximum binding capacity when interacting with abundant proteins in blood serum. Despite reported cases of certain MIP-based sensors successfully conducting measurements even in the presence of highly abundant proteins, it remains a persistent challenge. Consequently, some research papers detail the development of MIPs tailored to selectively eliminate these abundant proteins before commencing the analysis of the specific targeted proteins and biomolecules (Liu et al., 2014; Lu et al., 2021).

6. Research outlook

6.1. Template removal

One of the key areas of current research in MIPs is focused on developing improved methods for template removal. Efforts are being made to explore chemical reagents that can selectively react with the template molecule, facilitating its efficient removal from the polymer matrix. Researchers are actively investigating different chemical agents and conditions that can achieve selective template removal without adversely affecting the binding sites of the MIP. Additionally, physical removal methods such as ultrasonication and microwave are being explored as promising approaches. Novel physical methods and optimized conditions are being investigated to enhance the efficiency and selectivity of template removal from MIPs. Characterizing and preventing potential distortion, collapse, or rupture of the imprinted cavities after removal is a critical concern in the development of functional MIPs. Ensuring the structural integrity of the imprinted cavities is essential for maintaining the desired selectivity and binding affinity of the polymer.

To tackle these issues, multi-faceted approaches to evaluate the preservation of small imprinted cavities after removal have been adopted. Indeed, binding tests of MIP and NIP, coupled with selectivity assessments, emerge as valuable techniques for comparatively characterizing potential imprinted cavity concerns (Pesavento et al., 2019). These methods prove particularly fitting for the intricate structures of all kinds of templates. Besides, additionally, combining these strategies with scanning electron microscopy (Dejous et al., 2016) and atomic force microscopy (Mazouz et al., 2017) can furnish essential insights into the imprinted cavities of large templates such as viruses and bacteria. This comprehensive approach ensures a thorough understanding of the integrity of small imprinted cavities and their suitability for targeted applications.

To mitigate distortion, collapse, or rupture of the imprinted cavities after templatre removal, careful attention should be paid to the selection of removal solvents, conditions, and methods. Employing solvents that do not significantly swell or shrink the polymer matrix, and optimizing the removal conditions to minimize mechanical stress, are crucial steps. Furthermore, incorporating crosslinking agents during the polymerization process can enhance the mechanical stability of the polymer, minimizing the risk of structural changes during removal.

6.2. Binding of target analytes

Insights into the mechanisms of molecular recognition between MIPs and target analytes are being actively pursued. Researchers are striving to gain a deeper understanding of the complex interactions that govern the binding, to enhance the selectivity and efficiency of MIPs. Special emphasis is being placed on decreasing the NSS to improve the selectivity of MIPs for target analytes.

6.3. Reusability of MIPs

The reusability of MIPs is a topic of ongoing research in the fields of polymer science and sensors. Researchers are dedicated to finding ways to improve the efficiency and effectiveness of these polymers, particularly for applications such as flow injection and wearable sensors. The development of strategies to regenerate MIPs and restore their original binding properties is of great interest, as it would contribute to their practical and economic viability.

6.4. Integration of computational and AI-assisted approaches

The future of MIPs in biosensor applications will likely witness a synergistic integration of traditional experimental methodologies with computational and artificial intelligence (AI) approaches. This innovative fusion aims not only to streamline MIP synthesis but also to enhance their performance in template removal and analyte binding.

Researchers are increasingly exploring the potential of computational chemistry and machine learning algorithms to design MIPs with optimized binding sites. Computational modeling plays a crucial role in constructing template-monomer complexes in solution. Indeed, it lies in the theoretical selection of the most appropriate functional monomers for the given template. The choice of porogenic solvent is a critical factor in MIP synthesis (Lamaoui et al., 2022b; Marć et al., 2018). Computational modeling aids in the selection of the most appropriate porogen solvent which does not prevent the creation of the pre-polymerization complex (Alizadeh and Amjadi, 2017). Computational modeling allows us to elucidate the prediction of MIP selectivity, as outlined by (Whitcombe et al., 1998; Wang et al., 2005), and to understand the influence of buffer media on target analyte recognition, as studied by (Lai and Feng, 2003). This deepens the understanding of MIP selectivity and paves the way for rational design.

By employing computer simulations and AI-driven molecular modeling, scientists can predict and fine-tune the binding affinity of MIPs for specific target analytes. This not only expedites the development of highly selective MIPs but also minimizes the need for extensive trial-and-error experimentation.

6.5. Stimuli-responsive MIPs

Stimuli-responsive MIPs are at the forefront of template removal technology, providing meticulous control over the release of template molecules. These MIPs are designed to react to specific environmental cues, like pH, temperature, or analyte presence, resulting in highly selective analyte binding. Their distinctive feature is the ability to release the template molecule on-demand, synchronized with application needs. This feature finds utility in diverse fields, from targeted drug delivery to environmental monitoring and clinical diagnostics.

However, designing stimuli-responsive MIPs requires in-depth knowledge of the template and the triggering conditions. Ensuring stability and reproducibility under variable conditions remains a significant challenge. Looking ahead, future developments might encompass integrating multiple responsive elements into a single MIP, enabling even more sophisticated behavior. Furthermore, coupling stimuli-

responsive MIPs with advanced sensor technologies, such as microfluidics and wearables, promises groundbreaking applications in biosensing and personalized medicine. In summary, stimuli-responsive MIPs herald a new era in achieving precision template removal, offering unparalleled control over analyte binding and driving innovation in biosensor technologies.

7. Conclusions

While MIPs have been extensively studied for their applications as artificial receptors in sensors and biosensors, the discussions of the crucial steps of template removal and analyte binding have been relatively neglected. This review article aimed to address this gap by analyzing and discussing advanced concepts and ideas of the template removal and analyte binding in MIP development. This comprehensive review highlighted the crucial significance of the removal and binding in the field of MIPs, emphasizing the need for researchers to dedicate considerable attention to these aspects.

Through this review, it becomes evident that there are common removal methods among all types of templates, such as the immersion and electrochemical approaches. However, we also find that each type of template possesses a unique removal method that sets it apart from others. For example, proteolytic digestion is applied for the removal of proteins. Besides, the removal is difficult for spore bacteria due to their large sizes. Therefore, collaborative efforts are necessary to achieve satisfactory results.

Application of the template removal to both MIP and NIP using a consistent methodology is mandatory to ascertain that the disparities in analyte binding capacity between MIP and NIP are a direct result of the cavities formed in MIP. Hence, a comparison between the binding capacity of MIP and NIP is always important to confirm the successful creation of imprinted cavities.

The NSS usually decreases the selectivity of the MIP. Therefore, special emphasis is being placed on decreasing NSS to improve the selectivity of MIPs for target analytes. On the other hand, future orientations will be devoted to the application of in-silico designs such as density functional theory to investigate the template-monomer and template-cavity mechanisms.

This review is poised to serve as a pivotal milestone in the realm of MIP-based (bio)sensors, to encourage their wide commercialization. By contributing to the advancement of precise MIPs, it will instill greater confidence and reliability, ultimately propelling the field forward and facilitating widespread adoption.

Declaration of competing interest

I confirm on behalf of all authors that there are no conflicts of interest associated with this publication.

Data availability

Data will be made available on request.

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