Mini-Review:

Determination of Chlorpromazine Using Molecular Imprinting Polymers in Different Sample Matrices

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Abstract: *Antipsychotic drugs, including chlorpromazine, are frequently used to treat mental illnesses. However, prolonged exposure to even small amounts of the substance can accumulate and cause a potential human health risk. Thus, the selective and sensitive detection of these drugs is crucial. Molecularly imprinted polymers (MIPs) are receptors that are designed to have a highly specific molecular recognition ability, which is the primary and crucial function of receptors. The synthesis of chlorpromazine-imprinted polymers involves the polymerization of functional monomers and cross-linkers in the presence of chlorpromazine as a template, followed by the removal of the template to create cavities with complementary binding sites. Various strategies, including bulk polymerization, free radical polymerization surface imprinting, and nanoimprinting, have been employed to fabricate chlorpromazine-molecular imprinted polymers with high affinity and selectivity. Characterization techniques such as UV-vis spectroscopy, Fourier-transform infrared spectroscopy, and scanning electron microscopy are commonly employed to confirm the successful imprinting of chlorpromazine. The high selectivity of MIP toward templates enables them to be used in various applications like solid-phase extraction and chemical sensors, among others. The aim of this review is to present and highlight the various methods used to determine chlorpromazine based on molecular imprinting polymers in different samples.*

Keywords: *chlorpromazine; molecular imprinting polymers; applications*

■ INTRODUCTION

Chlorpromazine (CPZ) is a chemical molecule known as 2–chloro-10-(3-dimethylaminopropyl) phenothiazine (Fig. 1). It belongs to the class of phenothiazines and is commonly used as an antipsychotic medication [1]. Its mechanism of action involves the inhibition of dopamine receptors within the nervous system. CPZ can impede the activation of the emetic nerve, hence exerting a suppressive effect on the occurrence of vomiting. The recommended dosages for CPZ are typically between 25–50 mg/day as an injection or 100–200 mg/day as orally taken [2].

Nevertheless, the overutilization of CPZ of more than 2000 mg/day may lead to toxicity and depression of the central nervous system, while prolonged administration might result in hepatic impairment and adverse effects on human well-being, so the determination of CPZ in biological, food, and pharmaceutical samples using selective and sensitive is necessary [3-6]. Various methods have been reported for the determination of CPZ, including voltammetric methods [7-10], chemiluminescence [11], gas chromatography [12], liquid chromatography [13], capillary electrophoresis [14], spectrophotometric and spectrofluorimetric [15]

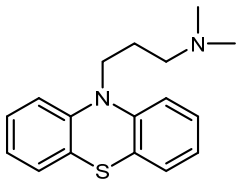


Fig 1. Illustrate the chemical structure of chlorpromazine

in different samples, such as pharmaceutical and biological samples. These samples require a pretreatment step due to the complicated composition that led to a series of matrix interference, poor selectivity and sensitivity. To overcome these drawbacks, we need novel, selective and rapid analysis methods to simplify the pretreatment step of samples that enhance the selectivity and sensitivity of detection, such as molecularly imprinted polymers (MIPs) [16]. MIPs are synthetic polymers formed by crosslinking the functional monomer around template molecules, leaving a complementary site that is similar to the template in shape, size, and chemical structure. When the template is removed, it represents one of the attractive techniques that is able to recognize target molecules specifically. This technique is utilized in a variety of molecular recognition-based applications, such as solid phase extraction [17-23] and sensors [24-27]. The superior features of this technique are its high selectivity and sensitivity towards the target molecules, potential reusability, long-term stability, low cost of preparation, and excellent ability to adapt to a variety of transducers [28-29]. Many scientists working in different fields have expressed interest in using these special properties of imprinted polymers for separation sciences and purification of drugs [30-33], elements [34], pesticides [35], contaminations [36] and others. The present review highlights the most recent progress in using the MIP technique for the determination of CPZ in various samples.

■ MIP

MIP is based on the formation of a three-dimensional polymer network between the functional monomer and the cross-linker in the presence of template molecules [37]. After the polymerization processes are done, the target molecules are removed, revealing recognition sites that are similar to the template in shape, size, and chemical function and that can be used to rebind the target molecules [38-39]. Consequently, the formed polymer exhibits the ability to specifically recognize and preferentially bind to the template molecules [40]. The non-imprinted polymers (NIPs) are usually prepared under the same conditions except for excluding the template. Nevertheless, NIPs that incorporate functional groups do not demonstrate a distinct capacity for template recognition, which plays a major role in the polymer's selectivity, as illustrated in Fig. 2 [32,41-43].

Molecular recognition phenomena are generally driven by covalent, semi-covalent, and non-covalent bonds. Non-covalent imprinting such as hydrogen bonds,

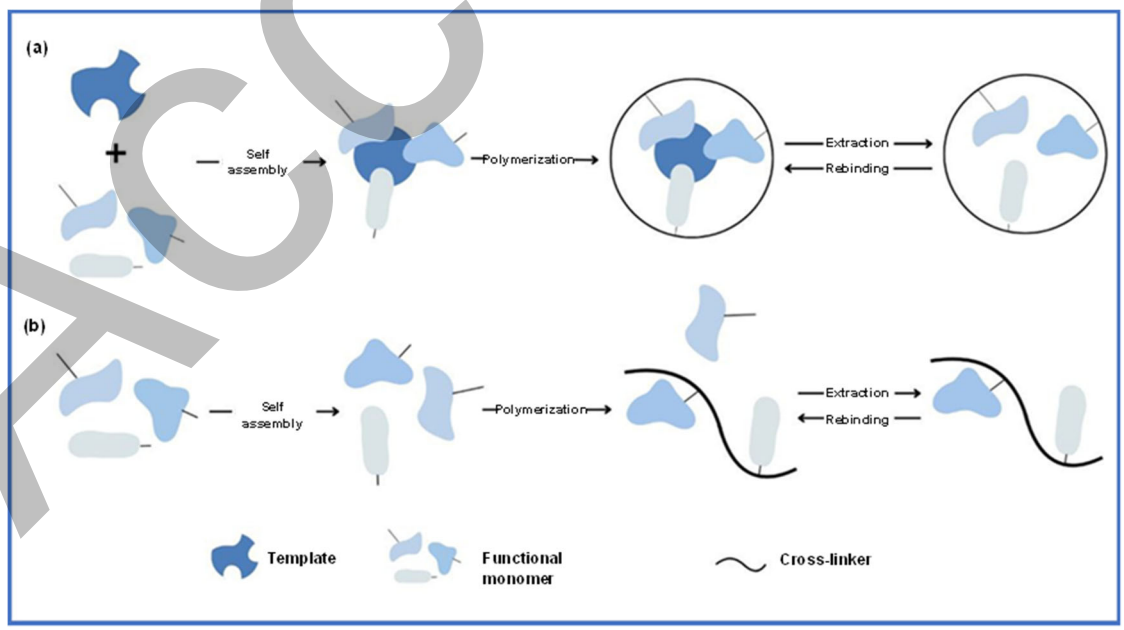


Fig 2. Illustration of the imprinting technique for (a) molecular imprinting polymer and (b) non-imprinting polymer [43]

dipole-dipole interactions, van der Waals interactions, and ionic interactions between the template molecule and functional groups found in the polymer matrix are preferred due to flexible type of interaction that leads to simple and fast binding and removal for a template than the covalent imprinting which leads to the rigid and durable type of interaction that make the processes for removal and rebinding of template slow [44-45]. Various polymerization methods have been reported for the preparation of MIP, including free radical polymerization, bulk polymerization, suspension polymerization, thermal polymerization, photopolymerization, electrochemical polymerization, precipitation polymerization, and emulsion polymerization [46-53].

Different techniques have been used for the characterization of MIP, including scanning electron microscope (SEM), atomic force microscope (AFM) and transmission electron microscope (TEM) that investigate the morphology, ultraviolet-visible spectroscopy (UV-vis), infrared spectroscopy (IR) and nuclear magnetic resonance (NMR) for characterize the structure and interaction between template and monomer [54]. MIPs have a wide range of applications like solid phase extraction [55-57], drug delivery [58-60], sensor [61-62], and catalyst [63-65] due to the feature of MIPs that represent by their selectivity, sensitivity, reusable, inexpensive, and easy manufacture processes [66].

■ APPLICATION OF MIPS FOR DETERMINATION OF CPZ

The detection of CPZ has been notably enhanced through the utilization of MIPs employing various detection modes, including electrochemical and optical methods, as illustrated in Table 1.

Table 1. A general summary of the preparation method for MIP for CPZ and its applications

MIP	analyte	Monomer	Cross-linker	Polymerization method	Porogen solvent	Ref.
1	CPZ	methacrylic acid, 2-vinylpyridine, 2-acrylamido-2-methyl-1-propanesulfonic acid	ethylene glycol dimethacrylate or trimethylolpropane trimethacrylate	free radical polymerization	MeOH, EtOH, AcN or THF	[67]
2	CPZ	methacrylic acid	trimethylolpropane trimethacrylate	suspension polymerization	chloroform	[68]
3	Dopamine and CPZ	nicotinamide		electrochemical polymerization		[3]
4	CPZ			electropolymerization		[38]
5	CPZ	nicotinamide		electropolymerization		[69]
6	CPZ as chlorpromazine hydrochloride	methacrylic acid	ethylene glycol dimethacrylate	free radical polymerization	chloroform	[70]
7	Phenothiazines and benzodiazepines including CPZ					[71]
8	Promazine and CPZ	methacrylic acid	ethylene glycol dimethacrylate	multi-step swelling and polymerization		[72]
9	CPZ and bromopromazine	methacrylic acid	ethylene glycol dimethacrylate	multi-step swelling and polymerization		[73]
10	CPZ	methacrylic acid	trimethylolpropane trimethacrylate	bulk polymerization	dichloromethane	[74]
11	Henothiazines, including CPZ	methacrylic acid	ethylene glycol dimethacrylate	free radical polymerization	chloroform	[75]
12	CPZ	methacrylic acid	ethylene glycol dimethacrylate	free radical polymerization	chloroform	[76]
13	Promazine derivative including CPZ	methacrylic acid	ethylene glycol dimethacrylate	multi-step swelling and polymerization		[77]

MIP	analysis technique	LOD (mol/L)	LOQ (mol/L)	Linear range (mol/L)	Recovery (%)	Real sample	Ref.
1	voltammetry	1.40×10^{-5} 1.00×10^{-5} 1.40×10^{-6}		1.00×10^{-4}–1.00×10^{-2}	99.00–104.00	fish samples	[67]
2	voltammetric methods	8.10×10^{-4}	2.7×10^{-3}	7.50×10^{-10}–2.50×10^{-7}	94.80–101.87	tablet and human urine	[68]
3	differential pulse voltammetry	2.50×10^{-10}		5.00×10^{-9}–2.00×10^{-6}	93.90–106.15	human serum, urine and pharmaceutical samples	[3]
4	cyclic voltammetry	7.00×10^{-8}		1.00×10^{-7}–1.00×10^{-4} and 1.00×10^{-4}–1.00×10^{-3}	92.05–95.09	human serum	[38]
5	cyclic voltammetry	2.5×10^{-8}		1×10^{-9}–4×10^{-5} and 4×10^{-5}–9×10^{-4}	98.11–100.81	biological samples	[69]
6	chemiluminescence	9.42×10^{-9}		3.14×10^{-8}–3.14×10^{-5}	95–102	urine and animal drinking water	[70]
7	ultra-performance liquid chromatography	3.14×10^{-12}–3.14×10^{-11}		1.25×10^{-10}–4.71×10^{-10}	63.5–94.1	pork samples	[71]
8	liquid chromatography	1.57×10^{-11}	6.28×10^{-11}	6.28×10^{-11}–6.28×10^{-8}	92–107	rat serum	[72]
9	liquid chromatography		1.75×10^{-11}	1.75×10^{-11}–1.75×10^{-8}	86–106	rat plasma	[73]
10	liquid chromatography	2.5×10^{-10}	6.2×10^{-10}	6.2×10^{-10} -6.2×10^{-8}	More than 73	pig urine	[74]
11	easy ambient sonic-spray ionization mass spectrometry (EASI-MS)		10^{-3}	1×10^{-6}–7×10^{-6}	96–106	urine sample	[75]
12	liquid chromatography		0.0942×10^{-6}	0.0942×10^{-6} to 1.099×10^{-6}	80–81	human plasma	[76]
13	liquid chromatography	studied the retention and molecular-recognition mechanisms of MIP for promazine derivative				____	[77]

Electrochemical Based Detection

Electrochemical sensors containing MIPs are a promising option for drug monitoring. The modified sensor has numerous advantages, including good chemical and physical stability, low fabrication process costs, high selectivity, sensitivity, and short time response. Due to these features, many research have been developed for the analysis of CPZ using various MIP-electrochemical sensors [78]. In 2011, Moreira and co-workers [67] prepared MIPs for the determination of CPZ, which is used as a sensor for ion-selective electrodes, by using methacrylic acid, 2-vinylpyridine, or 2-acrylamido-2-methyl-1-propanesulfonic acid as functional monomers, ethylene glycol dimethacrylic acid or trimethylolpropane trimethacrylate as cross-linker within the template molecule (CPZ). The sensing membrane was constructed by combining MIP with polyvinyl chloride (PVC) and *o*-nitrophenyl octyl ether (*o*NPOE) as a plasticizer in tetrahydrofuran (THF). The electrochemical sensor shows a high affinity for chlorpromazine with a calibration curve between 1.0×10^{-4}–1.0×10^{-2} mol/L. The obtained detection limit ranged from 0.46–3.90 μg/mL. The proposed method was applied for the determination of CPZ in fish samples with recoveries between (99–104%). This indicates the reliability of the suggested method for quantifying CPZ in real samples.

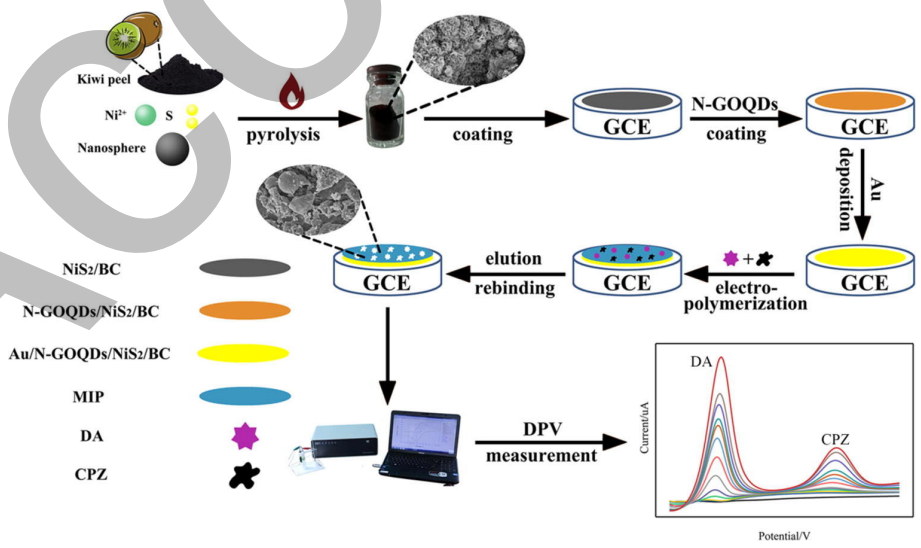
Motaharian and colleagues [68] introduced a new method for determining CPZ, representing a significant advancement in analytical chemistry. In their method, they make a nano-composite of MIPs and multiwall carbon nanotubes (MWCNTs). This makes the detection process more sensitive and selective. The new method includes the preparation of MIPs for drugs using functional monomers represented by methacrylic acid and trimethylolpropane trimethacrylate as a cross-linker. Utilizing these materials allows for the creation of highly specific binding sites within the polymer matrix,

improving the recognition and capture of CPZ molecules. The proposed method shows linearity between 7.50×10^{-10}–2.50×10^{-7} M, and the limit of quantification and limit of detection was found to be 2.58×10^{-10} and 8.60×10^{-10} μg mL^{-1}, respectively, based on the KSb/m equation, where k = 3 for LOD and 10 for LOQ. The Sb represents the standard deviation signal for the blank solution, and m refers to the slope of the linear dynamic range of the calibration curve. The suggested method is able to determine CPZ in complex sample matrices, including pharmaceutical and human urine samples, with recoveries between 94.80–101.87%. Overall, this method is a promising strategy for determining CPZ, with excellent sensitivity, compatibility with complicated sample matrices, and precise quantification. It could have implications for pharmaceutical analysis and clinical research.

In 2020, Lu et al. [3] used cyclic voltammetry to study electrochemical polymerization on the surface of a glass carbon electrode (GCE) that had been modified with a mix of gold nanoparticles (AuNPs), nitrogen-doped graphene oxide quantum dots (NGOQDs), and nickel sulfide nanoparticles (NiS_2) to make a MIP sensor as illustrated in Scheme 1. The electrochemical polymerization process used CPZ and dopamine as template molecules, with nicotinamide as the functional monomer. The designed MIP sensor selectively recognizes and binds CPZ and dopamine molecules. The prepared sensor shows a linear range between 0.005–2.000 μM for CPZ and a limit of detection equal to 0.25 nM. The method used for the determination of selected drugs in urine, human serum, and pharmaceutical samples had a recovery between 93.90–106.15%. This suggests the accuracy and reliability of the method for quantifying the concentrations of these drugs in real samples.

Chen et al. [38] developed an electrochemical sensor by interfacing a gold-copper bimetallic synergetic MIP on an acupuncture needle electrode. This design suggests a unique combination of materials for selective detection of CPZ. The sensor shows two linear ranges for CPZ 0.1–100.0 μM and 100.0–1000.0 μM, indicating its capability to detect a wide concentration range of the analyte. The detection limit achieved is equal to 0.07 μM. Utilized method for determining the chosen drug in human serum samples with recoveries in the range of 92.05–95.09%. The findings suggest its potential utility in clinical diagnostics and therapeutic monitoring of CPZ levels.

In a recent publication, Lu et al. [69] present a novel approach for quantifying CPZ. This method utilizes an electrochemical sensing platform prepared by



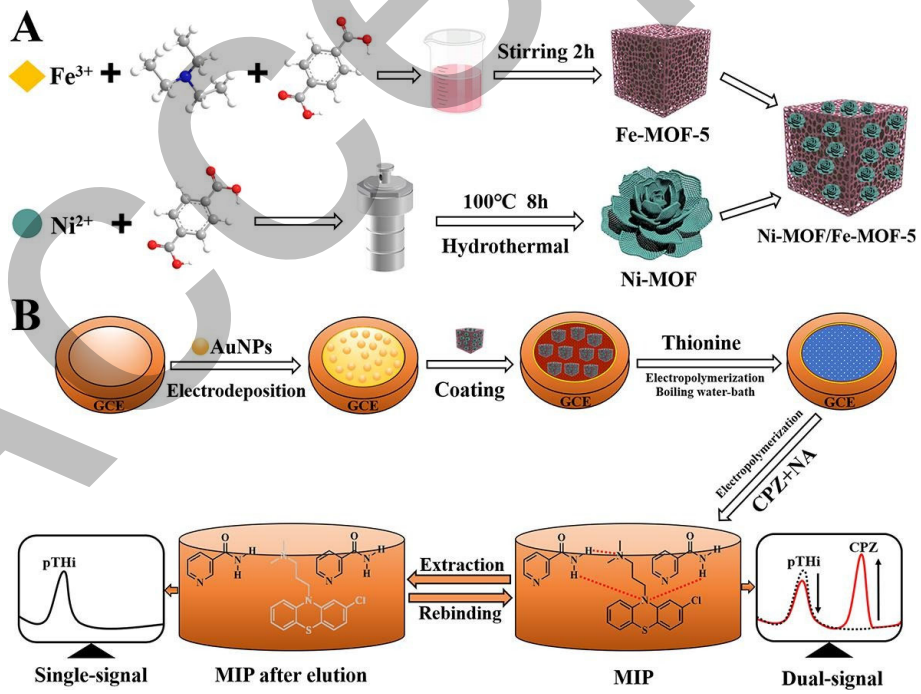
Scheme 1. Schematic of the preparation and electrochemical processes determination of the Au/N-GOQDs/NiS_2/BC/MIP/GCE composite. Figure reproduced with permission from Author (Lu et al.); copyright from Elsevier [3]

utilizing the high selectivity of the MIP technique and the strategy of ratio-metric quantification. The sensor consists of AuNPs, electrodeposited onto a glassy carbon electrode surface to provide a stable and conductive platform, nickel-metal organic framework (Ni-MOF), and iron-metal organic framework-5 (Fe-MOF-5). These materials are drop-coated onto the AuNPs to enhance the sensing properties and polythionine (pTHi) Electropolymerized to serve as an internal reference for ratiometric quantification. MIP membrane is created through *in-situ* electropolymerization, utilizing CPZ as the template molecule and nicotinamide as the functional monomer. This model combines the MIP membrane as a receptor for molecular recognition and pTHi as an internal reference probe. The integration of these components enhances the sensor's sensitivity and selectivity. The ratio-metric signals of peak current (ICPZ/IpTHi) exhibited a linear relationship with CPZ concentration within the range of 0.001–40.000 and 40.000–900.000 μM, under ideal conditions. The ultra-low detection limit was calculated based on signal-to-noise ratio, which was found to be 0.025 μM. The method utilized for the determination of CPZ in biological samples achieved recoveries between 98.11% and 100.81% (Scheme 2(a-b)).

Fluorescence-Based Detection

Combining fluorescence-based detection with MIPs constitutes a robust sensing strategy. This combination improves the precision of MIPs and the sensitivity of fluorescence, enabling specific identification of target analytes. Its applicability extends across various domains, including environmental monitoring, medical diagnostics, and food safety.

In a study introduced by Niu and co-workers [70] for the determination of phenothiazine medications, including CPZ as chlorpromazine hydrochloride, based on molecular imprinting-post-chemiluminescence, the MIP specific to chlorpromazine hydrochloride is synthesized using methacrylic acid as the functional monomer and ethylene glycol dimethacrylate as the cross-linker. This MIP is crucial for selectively capturing CPZ in samples for analysis. The method demonstrates linearity within the concentration range of 1.0×10^{-8} to



Scheme 2. Preparation procedure of (a) iron-metal organic framework-5 and nickel-metal organic framework and (b) MIP/pTHi/Ni-MOF/Fe-MOF-5/AuNPs on–off electrochemical sensor. Figure reproduced with permission from Author (Lu et al.); copyright from Elsevier [69]

1.0×10^{-6} g/mL, indicating a consistent relationship between analyte concentration and response, and the detection limit was found to be 3.0×10^{-9} g/mL as a result, depending on the signal to noise ratio. The proposed method has been used for the determination of chlorpromazine hydrochloride in urine and animal drinking water, with a recovery range between 95–102%. The study's findings suggest the potential applicability of molecular imprinting-post-chemiluminescence in the precise determination of CPZ and other phenothiazine medications. This method offers advantages such as selectivity, sensitivity, and accuracy, making it valuable for pharmaceutical and environmental analysis. Another interesting work conducted by Xia and co-workers [71] reported for the first time a MIP-based chemiluminescence array was susceptive to simultaneously determining phenothiazines and benzodiazepines, including CPZ, in pork samples. The obtained results showed that the reported method can effectively be used for the determination of four phenothiazines and five benzodiazepines with a calibration curve between 0.04–0.15 ng/mL for the nine drugs and recoveries in a range of 63.5–94.1% for the fortified blank pork samples. The detection limit based on signal-to-noise ratio was found to be 0.001–0.010 ng/mL (Fig. 3).

In another study introduced by Nishimura and Haginaka [72], the preparation of MIP for promazine and CPZ was done by using a functional monomer represented by methacrylic acid and a cross-linker represented by ethylene glycol dimethacrylate. The prepared MIP was used for the determination of promazine in rat serum samples using column-switching liquid chromatography with fluorescence detection. The method gives a linear dynamic range between 0.02 and 20.00 µg/mL with limits of quantitation and detection of CPZ were 0.02 and 0.005 µg/mL, respectively. The method utilized for determining the selected drug in rat serum with recoveries of 92–107%. A similar MIP was used to determine chlorpromazine and its metabolites by column-switching liquid chromatography in rat plasma. The results show linearity between 0.0056–5.600 µg/mL and 0.0056 µg/mL as a detection limit depending on the signal-to-noise ratio. The method was successfully applied for the determination of CPZ in rat plasma with recoveries of 86–106% [73]. Overall, these findings highlight the potential of molecular imprinting, post-chemiluminescence, and column-switching liquid chromatography with fluorescence detection in precisely determining chlorpromazine and other phenothiazine medications, offering valuable tools for pharmaceutical and environmental analysis.

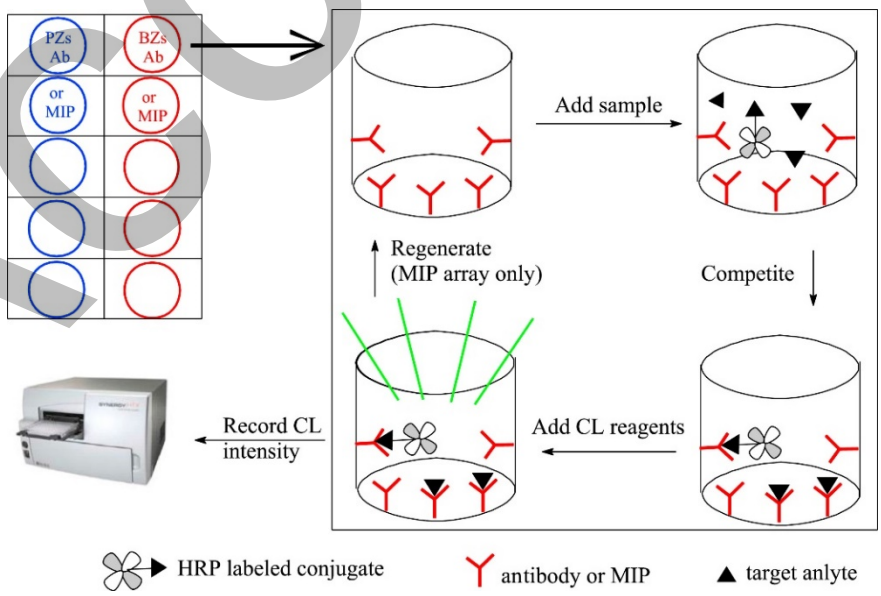


Fig 3. Two chemiluminescence arrays. Figure reproduced with permission from Author (Xia et al.); copyright from Elsevier [71]

Colorimetry-Based Detection

MIPs can effectively integrate with spectroscopic analysis due to their advantageous selectivity, leading to a straightforward, cost-effective, selective, and swift approach. The combination of MIP-SPE and high-performance liquid chromatography with spectrophotometric detection is used to analyze CPZ in different samples. Song and co-workers [74] reported a new MIP used as solid-phase microextraction to extract CPZ and compared the results obtained with conventional solid-phase extraction. The MIP was prepared by using CPZ, methacrylic acid, trimethylolpropane trimethacrylate, dichloromethane as a template, functional monomer, cross-linker, and porogen solvent, respectively. The linear dynamic range was found to be 0.2–20.0 µg/mL. The detection and quantitation limits were calculated based on 3 and 10 from signal to noise, yielding values of 0.08 and 0.20 µg/mL, respectively. The developed solid-phase extraction was applied for the determination of CPZ in pig urine with recoveries greater than 73.3%.

Figueiredo and co-workers [75] reported the use of MIP as a selective surface for easy ambient sonic-spray ionization mass spectrometry for the determination of five phenothiazines (CPZ, trifluprомazine, perphenazine, prochlorperazine, and thioridazine). The preparation of CPZ is done by using methacrylic acid, ethylene glycol dimethacrylate, and 2,2'-azobisisobutyronitrile. The chosen drug shows a linear range of 1–7 µmol/L, with 1 µmol/L as a limit of quantitation depending on the signal-to-noise ratio. The method utilized for the determination of CPZ in urine samples with recoveries of 96–106%.

In another study by de Oliveira Isac Moraes and co-workers [76] prepared a new restricted access based on MIP coated with bovine serum albumin (RAMIP-BSA). The synthesis processes involved the utilization of CPZ (the template) and functional monomer represented by methacrylic acid with ethylene glycol dimethacrylate as a cross-linker. The RAMIP-BSA was packed in a column coupled with high-performance liquid chromatography used for direct analysis of human plasma samples. The analytical method shows a linear concentration range between 30 to 350 µg/L with a quantitation limit equal to 30 µg/L and recoveries between 80–81% for real samples. Haginaka and co-workers [77] prepared MIP for promazine derivatives, including CPZ, by multi-step swelling and polymerization using the drug, methacrylic acid and ethylene glycol dimethacrylate, as a template, functional monomer and cross-linker respectively. This work studied the retention and molecular recognition mechanisms of MIP for promazine derivatives.

■ CONCLUSION

CPZ-imprinted polymers are appropriate for real-time monitoring in a variety of matrices, including pharmaceutical and biological materials, due to MIP properties that provide cost-effective, selective, sensitive detection, and reusable results. They can be used for a variety of applications, including electrochemical sensors and sorbents in solid-phase extraction. MIPs' adaptability permits their use in various industries, including medicines, food analysis, and environmental monitoring. Researchers and practitioners can increase sample preparation sensitivity, reproducibility, and cost-effectiveness by leveraging MIPs' unique features. As advances in MIP synthesis and characterization continue, the future holds great promise for the widespread use of MIP-based analytical chemistry, allowing for more precise and reliable detection of target molecules in various samples.

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■ CONFLICT OF INTEREST

The authors do not have a conflict of interest.

■ AUTHOR CONTRIBUTIONS

Eman Wajeh Ammen conducted conceptualization, writing, reviewing, and editing the original paper. Yehya Kamal Al-Bayati conducted

conceptualization and editing the original paper. Both authors agreed to the final version of this manuscript.

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