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Review

Electrochemical Methods Based on Molecularly Imprinted Polymers for Drug Detection. A Review

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Molecular imprinting of polymers is a state of the art procedure for producing artificial biomimetic receptors with high selectivity towards the selected molecules. Compared to the biological receptors, molecularly imprinted polymers are more stable, easy to prepare, and can be used under harsh conditions, these being the main reasons why their use in chemical and bioanalytical applications has been gaining in interest in the last decades. The main steps in molecular imprinted polymer synthesis from the selection of the reagents to the choice of the polymerization method are summarized. Furthermore, the binding mechanisms between the analyte and the molecules of the monomer during the electrochemical polymerization process and the molecularly imprinted polymer during the detection process, as well the detection techniques are discussed. All discussions present a critical point of view of the authors and are focused on drug detection.

Keywords: molecular imprinted polymers; electrochemical sensors; drug analysis

1. INTRODUCTION

Molecular imprinting of polymers is a technique pioneered more than thirty years ago [1] which offers an alternative way to the traditional biorecognition methods (e.g. the use of antibodies for the elaboration of immunosensors) due to the dedicated architecture of the tridimensional cavities embedded within the polymer [2]. Therefore, the commonly referred to as “plastic antibodies”, molecularly imprinted polymers (MIPs) are capable to bind a certain analyte from a complex matrix with high selectivity [1] since they can act as receptors for the target molecule recognition [3].

The standard polymerization reaction for MIP synthesis takes place within a complex mixture which contains a proper functional monomer along with a cross-linker, an initiator, and the target molecule, all blended in an appropriately chosen solvent or mixtures of different solvents. Firstly, a

pre-polymerization complex is formed, where the template is bounded to the monomer by different types of interactions, through covalent, semi-covalent, non-covalent or metal coordinated associations.

Depending on the type of bonding, the energy required for removing the template is different, being the highest in case of covalent bonds and the lowest in case of non-covalent ones. Therefore, non-covalent bonding is more versatile, which allowed it to become the preferred strategy for MIPs preparations [1]. Upon removal of the template molecule from the polymeric matrix, complementary cavities result, with specific shape, structure and functional groups, which will act as specific binding sites for the molecules previously removed [4]. The schematic representation of MIP synthesis is presented in Figure 1.

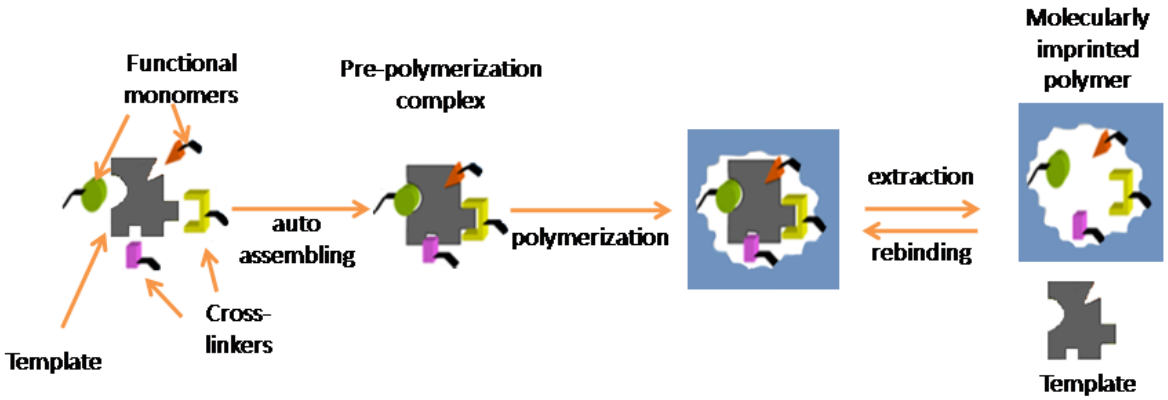


Figure 1. Molecular imprinting of a polymer

Due to their numerous advantages, among them being noticed the low costs, high stability and affinity towards the target molecule, as well as easily to integrate in standard fabrication processes, MIPs have drawn attention within the scientific world [6]. Hence, a multitude of applications involving MIPs have been developed, such as solid phase extraction, affinity separation, chemical sensors, immuno-like assay, or controlled (targeted) drug delivery. Even if the majority of applications which involves MIPs are correlated with affinity separation techniques, the development of MIP based sensors has been intensively studied [6]. MIPs could be used to gather qualitative and quantitative information for analytes from many classes, including: biomolecules (proteins, amino acids, and enzymes), drugs from pharmaceutical dosage forms or biological samples, along with pesticides which can also be traced in food [7]. However, traditional strategies (e.g. bulk synthesis) used for MIP fabrication present some drawbacks, such as leakage or incomplete removal of the template, random distribution of binding sites, slow mass transfer, and irregular morphology [8]. Different imprinting strategies, such as *in situ* polymerization or core shell MIP synthesis, were applied in order to minimize these shortcomings.

Since the presence of drugs in nowadays living has become a habitual pattern in the majority of people's lives, their detection and analysis has become utterly important. Whether it is about therapeutic drug monitoring, doping, recreational drugs, and quality control in pharmaceutical industry, clinical toxicology, forensics or environment, analytical testing is an important key for

discovering the presence of unrelated or incidental substances. Using MIPs in drug analysis has been studied for a couple of decades now, as they can be used to extract only the desired molecule [9]. Sensitivity could be also substantially improved by using electrochemical techniques as detection methods for MIPs based sensors, these types of procedures coming with the outstanding possibility of miniaturizing the devices, obtaining hand-held or even point-of-care devices [10].

Although over the last couple of years a multitude of reviews and books were published on molecularly imprinted polymers, there is only a scarcity among them that particularly treat the subject of electrochemical based ones. Moreover, this review presents a critical general view over the molecularly imprinted polymers used in electrochemical detection of drugs. Additionally, the synthesizing constituents as well as the interactions between them, the polymerization techniques and electrochemical detection methods reported in literature in the last years are summarized.

2. SYNTHESIS METHODS FOR MOLECULARLY IMPRINTED POLYMERS

2.1. Molecularly imprinted polymers constituents

Depending on the nature of the template molecule, the elements for the polymerization mixture are selected: the monomer, the cross-linker, the initiator and the appropriate solvent which facilitates the binding of the components. Each ingredient added within the polymerization blend has its particular influence over the properties and performances of the final MIP.

2.1.1. Monomers

The monomer interacts with the template molecule due to their functional groups, leading to the development of the pre-polymerization complex, this being a crucial step in the MIP synthesis. Within its structure, two types of elements can be identified: the ones capable of recognizing and interacting with the template and the polymerizable unit [11].

Methacrylate [12-23] and vinyl [14, 24, 25] based monomers are often used for MIPs synthesis through a free radical mechanism [6]. Besides these, silane based monomers [26-29], pyrrole derivatives [30-34] and *p*-aminothiophenol [35-37] are also frequently used, being exploited for the benefits brought by their functionalities.

There are numerous publications in the literature that cover this subject, some of them being cited herein [2, 11, 38-40].

2.1.2. Cross-linkers

A cross-linker is an organic (rarely inorganic) compound which is added within the polymerization blend, with the main purpose of fixing the molecules of the monomer around the ones of the template.

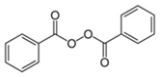
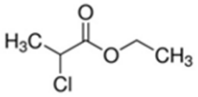
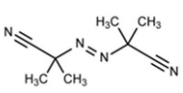
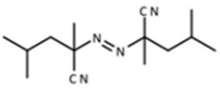
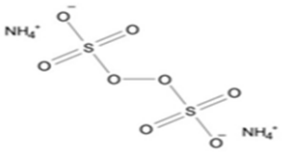
The cross-linkers that are most oftenly encountered in MIP development are methacrylate based ones [41-45], followed by thiophene ones [46, 47], silanes [26, 48] and also glutharaldehyde

[49] and *N,N'*-methylene bis-acrylamide [12]. The cross-linker has a crucial role in the stability of the polymer, which is why is added in almost all mixtures for MIP fabrication [11, 39, 40, 44].

2.1.3. Initiators

Polymerization is a chain reaction that starts with the activation of a single monomer's molecule that becomes the active center of the entire reaction. The triggering of the reactive species is generally due to the presence of an initiator in the polymerization mixture. The initiators can be classified in three major classes: thermal initiators (the most commonly used being benzoyl peroxide and azo-*bis*-isobutyronitrile [11]), redox initiators and photo-initiators, respectively. In Table 1, the most used initiators for MIP synthesis are mentioned.

Table 1. Commonly used initiators for MIP synthesis

Initiators	**Chemical structure**	**Ref.**	**Initiators**	**Chemical structure**	**Ref.**
Benzoyl peroxide		[11]	Ethyl 2-chloro-propionate		[25]
Azo-*bis*-isobutyro nitrile		[13, 16, 50]	2,2'-Azo-*bis*-(2,4-dimethyl valeronitrile)		[51]
Ammonium persulphite					[52]

2.2. Preparing strategies for MIP

Over the years, various polymerization techniques have been studied for the synthesis of MIP. Among them, the most used methods are the ones which follow a free radical mechanism (free radical polymerization): bulk polymerization, suspension, emulsion or precipitation polymerization and sol-gel methods [10, 53]. Given the fact that the previously mentioned methods have been repeatedly explained and discussed in the last years' literature [11, 54-57], only a brief comparison between these ones has been centralized in the Table 2.

Table 2. Advantages and disadvantages of polymerization methods for MIP synthesis

Method used for MIP synthesis		Benefits	Drawbacks
Free radical polymerization	**Bulk polymerization**	- The compounds in the blend are in liquid state - No additional solvent is needed - The easy control over the size of the MIP particles - Low cost - Easy in preparation	- The obtained MIP requires grinding - Some irregularities in the shape of the particles - Requires high amount of porogen agent - Binding sites can be destroyed during the MIP elaboration protocol
	Suspension	- Regular shape MIP microspheres are obtained - A MIP film with high porosity is obtained	- A reaction mixture that contains both aqueous and organic phases is required - The presence of a stabilizer and a surfactant is mandatory - The monomer and the initiators are hydrophobic
	Precipitation polymerization	- Regular shape MIP beads are obtained in good yields - The polymeric chains are growing individually to microspheres -The presence of porogen agents in the reaction mixture is not necessary -Easy procedure and less time consuming	- Precipitation only takes place when the polymeric chains are large enough to be insoluble in the reaction mixture
	Emulsion polymerization	-It is not necessary to add any stabilizer or surfactant to produce monodisperse MIP beads by using this technique	-A hydrophilic initiator, a hydrophobic monomer and an emulsifier agent needed
Sol-gel polymerization		- Easy controllable pores size - High mechanical stability - High thermal stability	- Low sensitivity -Slow kinetics -Low response time
Seed polymerization		- Sub-micron sized particles are used - The polymerization takes place at the surface of the particles - The thickness of the polymeric layer can be easily controlled - Largely, equal in size and shape particles are obtained	

***In situ* polymerization**	- Monolithic MIPs are obtained - The imprinted polymer is created on the surface of the transducer or is immobilized after its preparation -Easy control of the MIP layer density and thickness -Homogenous and controlled polymer coatings are generated -The mass transfer is facilitated during analysis -Fast response to template is assured	- Harsh conditions are often needed to remove the template molecule -Slow kinetics for the removal and rebinding of the template

The polymerization process includes not only the optimal composition of the polymerization mixture (pre-polymerization), but also the selection of the polymerization technique and the experimental parameters, along with the most efficient method of extraction for the template molecule. Easy, quick and cheap methods that lead to reproducible results are represented by electrochemical polymerization techniques, an increasing interest in engaging these methods for MIP preparation being observed [2]. The polymeric film can be directly obtained onto the surface of the electrode through CV or other electrochemical technique, followed by the extraction of the template performed either by chemical, with different solvents, or by electrochemical methods. Hence, for the detection of warfarin, a MIP based sensor was electrochemically obtained through CV, starting from resorcinol as a monomer. After the polymerization, an electrochemical extraction for the molecules of warfarin was also chosen, using a 0.1 M NaOH solution along with CV scanning, the extraction process being monitored through UV-Vis tests [58]. The template extraction through CV is probably governed by the changes in the functionalities in both the target and the polymer due to the electrochemical oxidation/reduction processes that occur during the scanning of the potential range. By changing the template and the solvent for extraction (using H_2SO_4), a MIP for metronidazole was developed [59]. Another electropolymerization using *o*-phenylenediamine as monomer for a MIP for acetaminophen detection was followed by an ethanol extraction using DPV for checking the progress of the extraction [60].

Within the electrochemical polymerization methods, an important factor is represented by the applied potential along with the number of cycles. If the last factor influences the growth in thickness of the polymeric film, the applied potential has a crucial role in the mechanism of polymerization, constituting a border between the desired reaction and the physical process of adsorption at the surface of the working electrode. Moreover, the functional groups within the monomer structure play a role in the polymerization outcome. Hence, the presence of amino or hydroxyl groups favors the formation of the polymer [61]. The functional group that is firstly prone to oxidation is the amine one, forming a radical cation, which will be involved in radical-radical interactions with another molecule of monomer with the formation of a dimmer structure. The mechanism pursues in the same manner,

leading to the growth of the polymeric film [62]. The hydroxyl groups, present within the monomer structure, promote the link between the monomer and the template molecule through hydrogen bonds. During the electropolymerization, the analyte diffuses toward the working electrode surface, passing through the polymer matrix, interacting with the monomer units and hence creating specific recognition sites [63].

The amount of monomer added within the polymerization mixture, as well as the ratio between the monomer and cross-linker, influence the sensitivity of the sensor. For example, by using a 0.5:1 ratio of methacrylic acid: ethyleneglycol dimethacrylate instead of an 1:1 ratio, the sensitivity toward a 0.5 M chloramphenicol solution of the sensor based on MIP increased by more than 100%. An explanation could be the MIP rigidity determined by the higher quantity of cross-linker, which preserves the formed cavities for the analyte rebinding [64].

Another strategy that can be taken into consideration when developing a MIP sensor is whether the template should be added within the polymerization mixture or previously attached to the surface of the working electrode, before the polymerization occurs. An example cited in literature is a MIP based sensor for vancomycin, where the antibiotic was immobilized on glass beads prior to the polymerization. The polymeric film then covered the empty spaces between the template molecules [65].

Over the years, several studies have been performed for the optimization of the electrodes surface and implicitly for the sensitivity enhancement. Hence, various nanomaterials have been used in association with MIPs, along them being present: metal or magnetic nanoparticles, carbon nanotubes, graphene oxide, or even biomolecules like enzymes for signal amplification [66].

Several studies mention the use of multi-walled carbon nanotubes (MWCNTs) in association with Fe_3O_4 magnetic nanoparticles as a support for MIPs which are used to detect different drugs: kanamicin [6, 15], ciprofloxacin [67]. By using both of the above materials, the electron transfer, electrocatalyst properties and the sensor sensitivity were improved [67]. Moreover, the use of MWCNTs provides the sensors strength, flexibility and high thermal and electrical conductivity [27]. M. Lütfi *et al.* [68] described a 2-aminoethanethiol functionalized MWCNTs associated with Fe@Au nanoparticles used as a platform for the fabrication of an imprinted polymer for the detection of cefexime, whereas another study reports the association of MWCNTs with Au nanoparticles (AuNPs) as a support for a MIP for the detection of ampicilin [69]. A different study shows the use of *N*–Co-doped reduced graphene oxide along with silver, as a support for the MIP electrochemically synthesized with salbutamol as template molecule [70].

Within the last years, the association between MIPs and some fluorescent materials has got scientists attention, quantum dots (QD) being the ones with many advantages, like: small and symmetric emission spectrum and a high signal to noise ratio. In association with MIP, a higher sensitivity and selectivity towards the template molecule is observed [26].

2.3. Types of physico-chemical interactions during the imprinting process

A MIP can form with the template molecule several types of bonds: covalent, semi-covalent, non-covalent or metal coordinated, as shown in Figure 2 [71]. The imprinting of polymers through

covalent bonds (pre-assembly method) is applied especially in the case of compounds without functionalities. Covalent bonds can be strong or readily reversible, the first ones being represented by carboxylic ester groups, whereas the second ones imply Schiff's base, boronate esters or ketal/acetal chains [72]. The further polymerization process allows the formation of cross-linking polymers, and the extraction of the template molecules after the breaking of the covalent bonds leads to the formation of the recognition cavities [73].

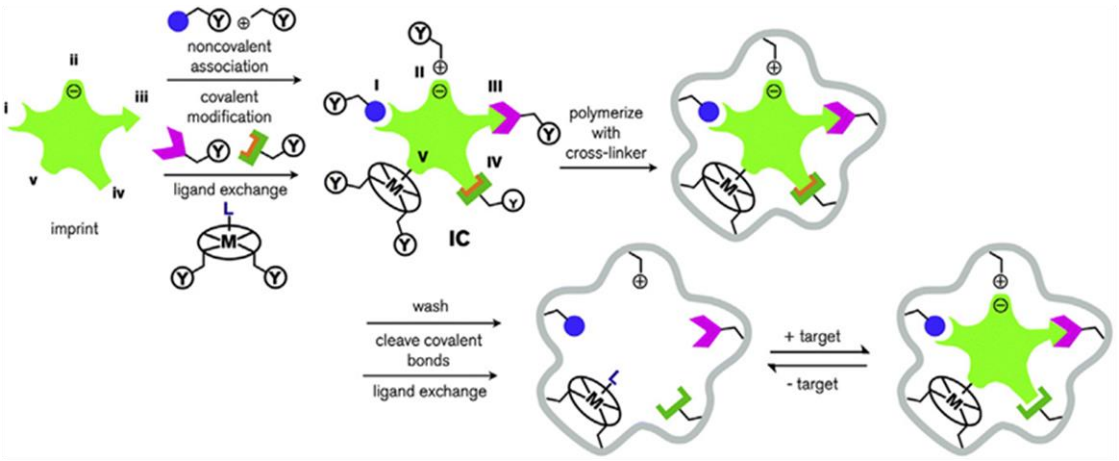


Figure 2. Types of interactions between the template (target molecule), the monomer and the MIPs: (i) noncovalent (nonionic), (ii) noncovalent (electrostatic/ionic), (iii) covalent, (iv) semicovalent and (v) metal coordination "Reprinted with permission from [71]. Copyright (2018) John Wiley and Sons"

This method is not often used due to the strong covalent bonds which hinder the template extraction from the MIP layer. Semi-covalent imprinting implies the covalent bonding of the template molecule to the monomer in the pre-polymerization stage (through an amidic bound or by the formation of an ester), followed by the non-covalent rebinding of the analyte. Moreover, this method is known for the possibility of using sacrificial spacers [56]: compounds that are removed along with the analyte ones. Among the compounds that can play the role of sacrificial spacer, the ones with carbonyl group are taken into account as well as salicylate and molecules with silyl groups.

Recent studies led to the discovery of custom designed monomers for specifically targeting a certain template and also to the development of inclusion complexes, mostly using cyclodextrin derivatives as monomers [72]. Molecular imprinting in association with metal ions leads to the expansion of MIPs applications. Metal ions are used with the purpose of facilitating the interactions between the monomer and the template molecule during the pre-polymerization stage, creating ionic bonds instead of the significantly weaker hydrogen ones [74].

When choosing a functional monomer or a cross-linker, the possible interactions with the template molecule have to be taken into consideration, the final goal of this process being its efficient entrapment within the polymeric layer. Moreover, a crucial step that has to be considered before the polymerization is the possibility of efficiently removing the template from MIP by easily neutralizing these interactions. Another aspect includes the fact that the intermolecular forces between the analyte

and the polymer should be strong enough to assure the affinity of the rebinding in order to assess the selectivity for the target in complex matrices. The presence of a cross-linker usually leads to a stable and rigid film, avoiding the deformation of the cavities after the template extraction [19].

The most often used strategy is to form initially a complex between the monomer, cross-linker and template based on non-covalent interactions such as hydrogen bonds, π- π* or van der Waals interactions, hydrophobic and electrostatic forces. For example, in case of MIP for fluoxetine, the use of methacrylic acid as monomer allows the formation of hydrogen bonds between the carboxyl group, which is an H donor and the secondary amine and fluorine centers of the analyte. Contrary, the presence of vinyl benzene leads to a self-assembled complex formation with the target molecule based on π-π interactions between the benzene rings. The interactions between itopride hydrochloride (ITOH) as template, methacrylic acid (MAA) as functional monomer, ethylene glycol dimethacrylate (EGDMA) as a cross-linker and dimethyl sulfoxide (DMSO) as porogen agent are presented in Figure 3 along with SEM characterization of the polymeric film [4].

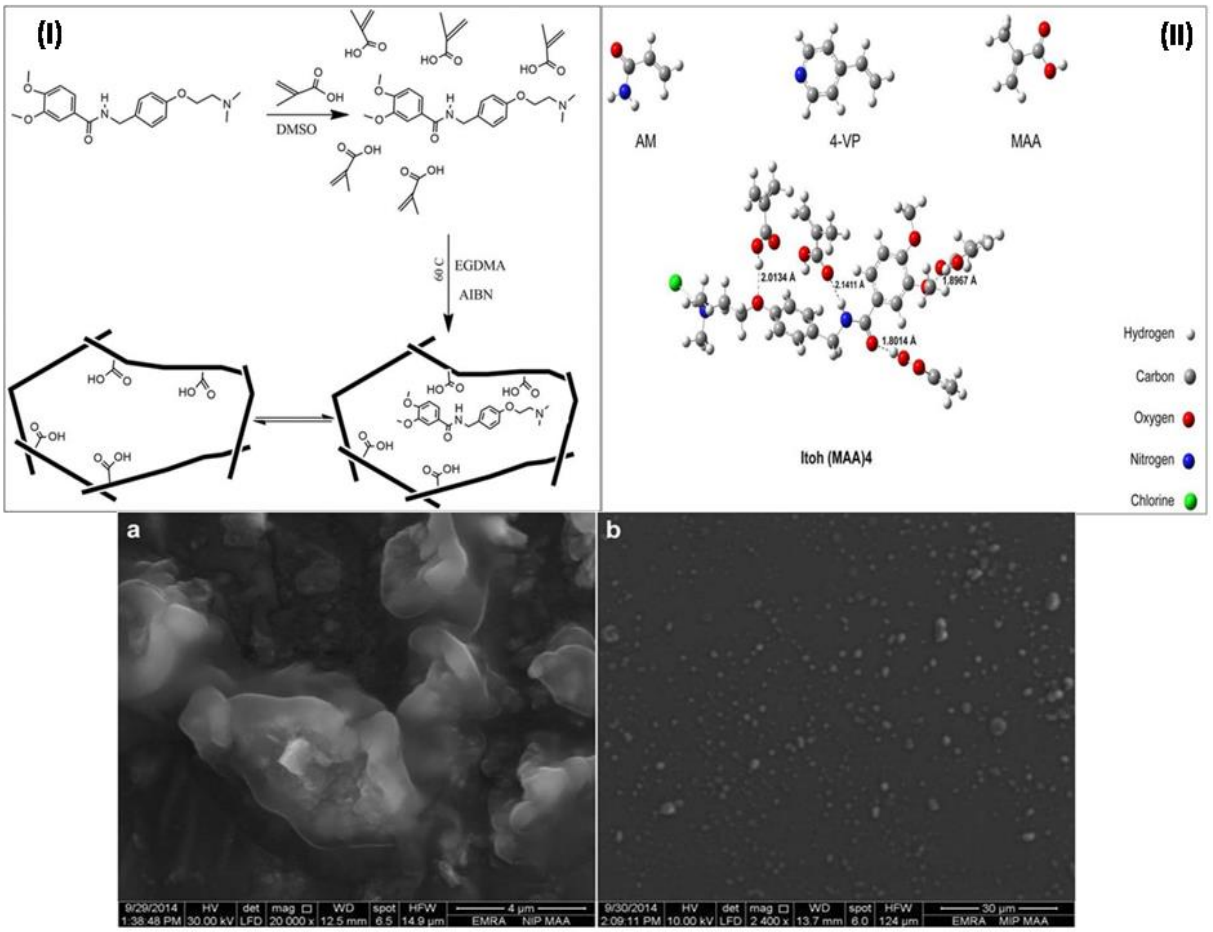


Figure 3. Schematic representation of the MIP synthesis procedure (I); optimized conformation of self-assembly complex of itopride hydrochloride (II) SEM images of PVC membrane containing 1% NIP (a) and PVC membrane containing 1% MIP. "Reprinted with permission from [4]. Copyright (2018) John Wiley and Sons"

The rebinding process is mainly influenced by the spatial structure complementation of imprinting cavities to the template molecules and the interactions between the analyte and the residual functional groups in the polymeric matrix. For almost all the examples, hydrogen bonding is responsible for the molecular immobilization during the rebinding and it seems that other analytes and possible interferents do not match with the template imprinted cavities, this providing the so-called anti-interference capability, a very important property when detecting analytes in multicomponent samples [59].

In the case of MIP sensors, low concentrations of analyte in samples determines the preferential occupancy of the high affinity cavities on polymer surface, while those with lower affinity, situated in the film depth, will be occupied only after the contact with concentrated solutions. Thus, it is very important to study and clarify the response of the sensor at different concentrations of analyte, including the ones at molecular level [75].

The preconcentration of template molecules onto the electrode surface is achieved through the interactions with the monomer or/and the cross-linker that occurred before polymerization. Due to this step, a higher number of template molecules are immobilized later in the MIP film, increasing the amount of imprinted sites and thus increasing the sensitivity of the sensor [76]. The optimum ratio between monomer and template in the polymerization mixture has to be also found in order to access a good quantity of recognition binding sites [77].

3. APPLICATIONS OF ELECTROCHEMICAL MIPs BASED SENSORS IN DRUG DETECTION

Electrochemical detection techniques represent rapid and cost-effective drug detection methods due to their sensitivity, selectivity and the possibility of using biological or environmental samples without any complex, time consuming pretreatment. Moreover, the prospect of miniaturizing the devices while maintaining the previously mentioned proprieties enriches the list of advantages, this technique being well suited for the quality control of drugs.

3.1. Electrochemical methods for characterization of MIPs and drugs detection

One of the most important and extensively used electrochemical technique is CV, which implies the monitoring of the current while reversibly varying the potential applied on the working electrode at a certain scan rate. Due to the inaccurate measurement of the peak currents, CV is not suited for quantitative determinations, but rather for qualitative ones, specifically the characterization of the imprinted surface [78].

An enhanced sensitivity and accuracy is achieved by using small-amplitude pulses which lay the ground for differential pulse voltammetry (DPV), a widely used method for quantitative measurements [78]. Another technique with an outstanding versatility is square wave voltammetry (SWV), which is considered one of the most advanced voltammetric methods due to its faster scan

rates, higher signal to noise ratio and better sensitivity than DPV, which makes it the best tool for quantitative determinations [79, 80].

Electrochemical impedance spectroscopy (EIS) is a technique that has the advantage of not damaging the analyzed surface or perturbing the studied system and has been increasingly used in the past few years for the characterization of various electrochemical systems. This high sensitivity method consists of applying an alternative current on the tested molecularly imprinted surface in order to determine the changes in the mass transfer resistance. EIS can be successfully applied for the characterization of biosensing surfaces or for evaluating bioanalytical signals, as it provides quantitative information about processes that take place at the electrode surface [81].

3.2. MIPs applied in pharmaceutical drugs detection

Drug detection and quantification is crucial in many areas, among them being pharmaceutical industry (where the quality of a drug is assessed throughout the fabrication process in order to assure the proper efficacy and safety), environment (for example in the waste waters), clinical toxicology or forensics. This topic involves not only financial and public health aspects, but it can also be found in the political agendas at international level. Hence, developing sensitive, rapid, low-cost methods is currently undergoing intense studying [82]. In Table 3 there are enlisted examples of MIP platforms for the electrochemical detection of drugs.

As it can be observed in Table 3, many different strategies were adopted for MIP fabrication in order to obtain electrochemical sensors especially customized for the sensitive and selective detection of drugs. The association between different monomers, cross-linkers, and/or initiators, together with the rigorous choice of the polymerization method, has helped to achieve this goal and allowed the detection of the target analytes from real samples, such as commercial drugs, serum, blood, urine, and food (Table 3).

DPV, as shows the data in Table 3, is the unanimously used method for the detection of paracetamol with MIP-based sensors. This is mainly due to the fact that paracetamol exhibits electrochemical activity and thus its detection can be done directly based on its own electrochemical signal. Comparing the results obtained in different experimental setups used for MIP construction, it can be noticed that the analytical performances of the sensors are comparable (teens and hundreds of nM, respectively), best sensitivity being registered for the MIP based on poly(*p*-aminobenzene sulfonic acid)/*o*-phenylenediamine [60].

In the case of the widely used anticoagulant warfarin, electrochemical detection seems to be influenced by the nature and by the properties of the modifiers included in the reaction mixture used during polymerization. Thus, a detection limit in pM range was obtained for warfarin in rabbit plasma by using a MIP sensor based on resorcin monomer polymerized onto a three-dimensional nanoporous surface consisting in Au-Ag alloy micro wire [58].

Table 3. MIP platforms for the electrochemical detection of drugs

Pharmacological class	Analyte	MIP film composition	Detection Method	LOD/M	Samples	Ref.
Analgesic/ Antipyretic	Paracetamol	poly(*p*-aminobenzene sulfonic acid)/ *o*-phenylenediamine	DPV	$4.3\cdot10^{-8}$	tablets human urine	[60]
		aniline/poly(2-acrylamido-2-methyl-1-propanesulfonic acid/styrene) micelles	DPV	$5\cdot10^{-8}$	paracetamol samples	[83]
		dimethylamino ethylmethacrylate/2-hydroxy ethylacrylate/2-ethylhexyl acrylate/styrene	DPV	$3.3\cdot10^{-7}$	tablets	[84]
		Polypyrrole	DPV	$7.9\cdot10^{-7}$	tablets syrup	[85]
Anticoagulant	Warfarin	resorcin monomer/Au–Ag alloy micro wire with a 3D nanoporous surface	DPV and CV	$8\cdot10^{-12}$	rabbit plasma	[58]
		AuNPs/*o*-phenylenediamine/multiwall carbon nanotubes with carboxylic functional group	SWV	$7.8\cdot10^{-11}$	human serum	[86]
Antibiotics	Streptomycin	poly(pyrrole-3-carboxy acid)/ electrochemically reduced graphene oxide	DPV	$5\cdot10^{-10}$	porcine kidney honey (spiked samples)	[87]
		tetraethoxysilane/polyethylen eglycol/ mercaptoacetic acid-modified PbS NPs/ Fe_3O_4@Au–multi-walled carbon nanotubes–chitosan	DPV	$1.5\cdot10^{-9}$	injection solution	[88]
		Nanogoldencapsulated poly(*o*-phenylenediamine) shell/ Fe_3O_4 magnetic nanoparticles	SWV	$1.7\cdot10^{-11}$	milk, honey (spiked samples)	[89]
	Vancomicyn	Methacrylic acid/ethylene glycol dimethacrylate/trimethylolpropane trimethacrylate	CV	$8.3\cdot10^{-3}$	-	[65]
	Sulfamethoxazole	Methacrylic acid/pyrrole on Fe_3O_4 magnetic nanoparticles	EIS	10^{-12}	spiked seawater	[20]
	Tetracycline	AuNPs functionalized with *p*-aminothiophenol	LSV	$2.2\cdot10^{-16}$	honey	[36]
		methacrylic acid/ethyleneglycol dimethacrylate	potentiometric	$2.5\cdot10^{-5}$	spiked aquaeous solutions	[90]
	Doxycycline	Polypyrrole	DPV	$4.4\cdot10^{-5}$	pharmaceutical forms	[63]

	Tulathromycin	*p*-aminothiophenol/gold nanoparticles	DPV	10^{-12}	liver, muscle and sebum samples	[76]
	Chloramphenicol	methacrylic acid/ethyleneglycol dimethacrylate/carbon nanotubes composite/ CuNPs	CV	10^{-5}	milk	[64]
		3-hexadecyl-1-vinylimidazolium chloride (C16VimCl)/ multiwalled carbon nanotubes/ mesoporous carbon/3D porous graphene	DPV	10^{-10}	milk and honey spiked samples	[91]
Antibiotic and antiprotozoal	Metronidazole	*o*-phenylenediamine imprinted on a nanoporous gold leaf	CV	$1.8 \cdot 10^{-11}$	tablets fish samples	[59]
		3-aminoprophyltriethoxysilane/ tetraethyl orthosilicate/ Fe_3O_4@SiO_2 nanoparticles	DPASV	$1.6 \cdot 10^{-8}$	milk, honey spiked samples	[92]
Opiate (narcotic) analgesics	Tramadol	amino-imide monomer/ethylene glycol dimethacrylate/ Fe_3O_4@SiO_2 magnetic particles	SWV	$4 \cdot 10^{-6}$	human urine pharmaceutical forms	[93]
		tyrosine/cystine/cubic AgNPs/C@Fe_3O_4	SWSV	$1.2 \cdot 10^{-13}$	serum, plasma, urine spiked samples pharmaceutical forms	[94]
		tetraethoxysilane/phenyltriethoxysilane polypyrrole/functionalized multiwall carbon nanotubes	SWV	$3 \cdot 10^{-11}$	tablets	[95]
	Morphine	methyltrimethoxysilane/ tetraethylorthosilicate/ multiwall carbon nanotubes and AuNPs	SWV	$2.9 \cdot 10^{-9}$	human urine blood samples	[77]
		poly(3,4-ethylenedioxythiophene)	amperometric	$2 \cdot 10^{-4}$	-	[96]
Bronchodilator	Theophylline	methacrylic acid/ethyleneglycol dimethacrylate/SiO_2/TiO_2 coreshell nanoparticles	DPV	$1.2 \cdot 10^{-9}$	tea human serum urine	[97]
		4-amino-5-hydroxy-2,7-naphthalenedisulfonic acid	DPV	$3.2 \cdot 10^{-7}$	tablets	[62]
Antiplatelet drug	Dipyridamole	methacrylic acid/ethyleneglycol dimethacrylate/ Fe_3O_4@Au/amine-multi-walled carbon nanotubes	DPV	$3 \cdot 10^{-8}$	human serum	[98]
		ethacrylic acid/ethyleneglycol dimethacrylate	DPASV	$9.9 \cdot 10^{-11}$	tablet human serum	[99]
Beta 1 blockers	Metoprolol	pyrole/ multi-walled carbon nanotubes	DPV	$2.9 \cdot 10^{-9}$	serum tablets	[100]

		methacrylic acid/ethyleneglycol dimethacrylate	potentiometric	$1.3\cdot10^{-7}$	urine, plasma tablets	[101]
	Propranolol	dopamine/multi-walled carbon nanotubes	DPV	$2.5\cdot10^{-8}$	tablets	[102]
Nonsteroidal anti-inflammatory drug	Naproxen	methacrylic acid/ethyleneglycol dimethacrylate	potentiometric	$3\cdot10^{-10}$	capsules	[18]
Anticancer drugs	Gemcitabine	*p*-aminothiophenol/AuNPs	LSV	$3\cdot10^{-15}$	spiked serum drug formulations	[35]
	Mitoxantrone	*β*-cyclodextrins	DPV	$3\cdot10^{-8}$	spiked urine pharmaceutical formulations	[75]
H1 antihistaminic	Loratadine	methacrylic acid/ethyleneglycol dimethacrylate	DPV	$1.5\cdot10^{-7}$	human serum	[103]
Anabolic androgenic steroid	Testosterone	*o*-phenylenediamine/graphene-oxide	EIS	$4\cdot10^{-16}$	human serum	[104]
Antidepressant	Fluoxetine	methacrylic acid/vinyl benzene/ethylene glycol dimethacrylate embedded within a carbon paste electrode	DPV	$2.8\cdot10^{-9}$	spiked plasma samples/ pharmaceutical capsules	[17]
	Venlafaxine	silica coated magnetite nanoparticles	DPV	$6\cdot10^{-9}$	human urine blood serum	[105]
Antitussive	Dextromethorphan	methacrylic acid OR acrylonitrile/ ethylene glycol dimethacrylate	potentiometric	$1.9\cdot10^{-6}$ 10^{-6}	tablets and syrup samples	[19]
Antiviral (prodrug)	Famciclovir	methacrylic acid/Ethylene glycol dimethacrylate/ methylene chloride	CV	$7.5\cdot10^{-7}$	pahrmaceutical forms	[21]
Histamine H_2 receptor Antagonist	Ranitidine	methyl trimethoxysilane / tetraethylorthosilicate /multiwall carbon nanotubes with carboxylic functional group layer/AuNPs	SWV	$2\cdot10^{-5}$	spiked human urine	[106]

CV - cyclic voltammetry; LSV - linear sweep voltammetry; DPV - differential pulse voltammetry; SWV - square wave voltammetry; DPASV - differential pulse adsorptive stripping voltammetry; EIS - electrochemical impedance spectroscopy

Several sensors based on MIPs were developed for antibiotics detection using voltammetric and impedimetric methods. The functionalization of the electrode with various materials such as magnetic nanoparticles, AuNPs, carbon-based materials and other nanostructures, determined the improvement of the selectivity and sensitivity towards the target analytes (different antibiotics in this case). For example, the use of Fe_3O_4 based magnetic nanoparticles functionalized with pyrrole allowed

the impedimetric detection of sulfamethoxazole with a pM limit of detection [20]. This is probably due to the electronic and electrocatalytic properties of magnetic nanoparticles for this analyte. Moreover, magnetic nanoparticles are versatile and can be easily functionalized with different functionalities, thus providing synergistic effects in electrochemical sensors that can significantly improve their properties. Another successful approach was the use of AuNPs, both for the functionalization of the monomer (*p*-aminothiophenol) before the polymerization and for the generation of a metallic network in MIP film during the polymerization. The previously cleaned electrodes were immersed in an ethanolic solution of *p*-aminothiophenol for 24 h at 4 C in order to obtain a self-assembled monolayer. Afterwards, the electrochemical polymerization of poly-thioaniline and AuNPs film was performed by CV in a solution of ferri-ferrocyanide in PBS containing a mixture of AuNPs functionalized with *p*-aminothiophenol and tetracycline. The non-imprinted films were prepared in the same manner, without adding tetracycline to the polymerization mixture. This step was followed by the extraction of the template, leaving complementary rebinding sites available for the tetracycline molecules. This technique provides high sensitivity, as the effect of the charging current is minimized. This strategy allowed the detection of tetracycline in honey in fM range by using LSV in the presence of hexacyanoferrate/hexacyanoferrite as redox probe [36]. This very simple experimental protocol was further adapted for the detection of several molecules, including the detection in fM range of the anti-neoplastic drug gemcitabine in serum and pharmaceutical formulations [35]. The schematic representation of the protocol used for the elaboration of MIP-based sensor for tetracycline is provided in Figure 4 [13].

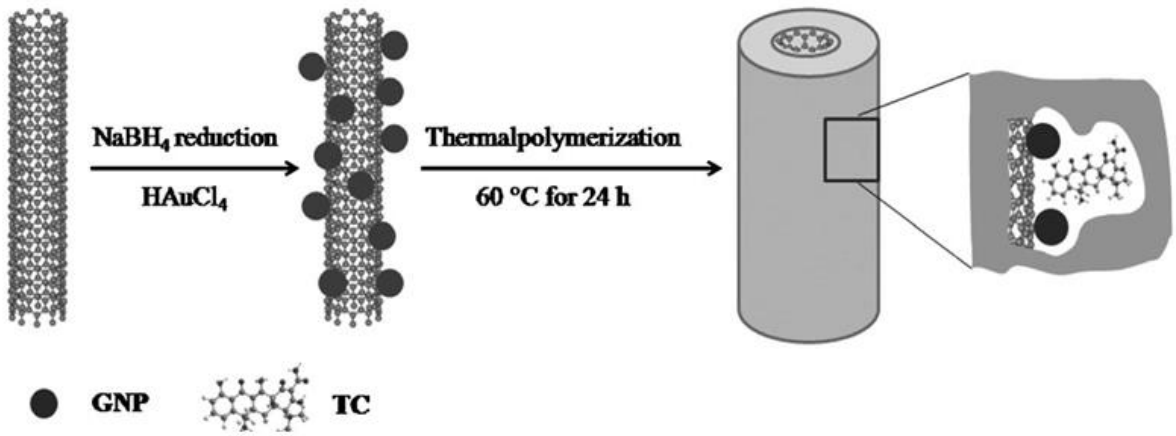


Figure 4. MIP based sensor for tetracycline elaboration protocol. "Reprinted with permission from [4]. Copyright (2018) John Wiley and Sons"

Moreover, the use of carbon based materials such as carbon nanotubes, graphene and graphene derivatives for the elaboration of MIP-based platforms used in electrochemical sensing devices, improved the results obtained compared to configurations for which these materials are not used. The presence of carbon based nanomaterials in MIP structure also improve the mass transport rate, increase

the surface area and allow a better control and stability of the polymeric layer. These characteristics are directly linked to a high selectivity and reproducibility of these sensors. As it can be observed in Table 3, the limits of detection for the configurations with carbon nanotubes were improved for the same analyte [77, 98, 100, 102]. The same observation can be also done in case of using graphene-based materials for the production of MIPs [87, 104].

Comparing the results obtained with all configurations based on carbon nanotubes and graphene, it can be noticed that the analytical performances of the MIP sensors obtained by using these materials are similar. In each case the further functionalization of the carbon nanomaterials with other modifiers, such as metal or magnetic nanoparticles, determined the enhancement of the selectivity towards the target. The electrocatalytic properties of both carbon nanotubes and graphene for the detection of drugs can be linked to their functionalization, that improves the electrode reactivity compared with the one registered in the absence of these materials. Thus, in the case of the opiate analgesic tramadol, the functionalization of magnetic nanoparticles with cubic silver nanoparticles and the use of this composite material for the elaboration of a MIP film based on tyrosine and cystine, allowed the highly selective detection of the target analyte in various matrices (serum, plasma, urine and drug formulations) with a limit of detection below the pM level [94].

3.3. Real samples analysis

The performances of almost all configurations based on MIPs were tested on real samples, such as commercial pharmaceuticals, biological samples (urine, blood, and serum) and food samples. In case of such complex matrices, the high selectivity of the MIP sensor for the detection of these analytes is a mandatory condition. The composition of the reaction mixture, the entire experimental protocol, the polymerization method and the mechanism, together with the electrochemical method used for sensor testing should be all optimized in order to allow the detection of the target analyte in real samples without previous separation.

3.3.1. Real samples preparation and electrochemical drugs detection

3.3.1.1. Biological samples

Several pretreatment steps are usually required before performing tests for the detection of drugs on real samples by using electrochemical methods. Depending on the sample type, the protocol could be more or less complicated. Hence, the simplest pretreatment cited in the literature is filtration or dilution, the protocol evolving to protein precipitation and separation or extraction of the analyte from tissue, environmental or food samples.

Regarding blood and serum samples the required pretreatment tests differ according to the type of platform used for MIP sensor elaboration. Therefore, for the detection of theophylline in blood, no pretreatment was performed except a simple filtration [97]. On the other hand, for the detection of other drugs, such as warfarin [58], morphine [77], venlafaxine [105], loratadine [103] or dipiridamole

[99], a chemical deproteinization was needed, followed by centrifugation and filtration for protein removal. At the same time with deproteinization, a dilution was obtained [58].

The detection of drugs from urine samples requires similar pretreatment steps as for those mentioned above for the blood ones. The major advantage of using electrochemical sensors for drugs detections applied to plasma and urine is that no prior extraction step is required.

3.3.1.2. Food and environment samples

The complexity of food and environmental samples leads to the necessity of an extraction procedure before any additional steps. In case of tissue or organs samples as well as honey and tea ones, different solvents were used for this particular step, such as methanol (for metronidazole extraction from organs) [59], water (for theophylline extraction from tea samples) [97], ethanol (in case of tetracycline extraction from honey) [36], or solvent mixtures: methanol with H_3PO_4 for tulatromicyn [76], or with water for streptomycin [87], ethyl acetate and acetonitrile, respectively for the extraction of chloramphenicol from milk [64]. When extraction step was not required, only protein precipitation was performed, like in case of metronidazole detection from milk and honey, where trichloroacetic acid was used [92]. Additionally, in case of sulfametoxazole detection in sea water, a mixture of methanol and acetic acid was used to minimize matrix complexity [20].

After performing the previously mentioned steps, the samples are processed in the same manner as the biological ones.

3.3.1.3. Pharmaceutical forms

Based on the type of pharmaceutical form, the pretreatment steps are different. Hence, solid oral dosage forms require grinding, dissolving or extraction of the active pharmaceutical ingredient, filtration and dilution, while for liquid pharmaceutical dosage forms (both oral or parenteral) only dilution is generally enough.

In case of tablets and capsules containing API such as: acetaminophen [60], fluoxetine [17], dextromethorphan [19], metronidazole [59], famcyclovir [21], doxycycline [63], dipyridamol [99] or loratadine [103], the preparation of the sample usually requires grinding, homogenization, dissolution, centrifugation and filtration, followed by a dilution, when needed.

The use of electrochemical methods for drug quantification in real samples allows the fast detection and also leads to good analytical parameters, such as limit of detection, recovery rates, and standard deviation. This certifies the feasibility and practicability of these methods in pharmaceutical industry and for biomedical applications.

4. CONCLUSIONS

In the last years, MIPs have been enjoying an increased attention within the scientific world. Their undoubtedly advantages, such as low costs, facile synthesis and high selectivity, have increased the research within this domain. New imprinting techniques and polymerization methods have been

studied along with testing new monomers mixed in different ratios with the template molecules and other reagents helping the elaboration processes. Moreover, the coupling of MIPs with other innovative nanomaterials, like graphene oxide, carbon nanotubes and/or metal or magnetic nanoparticles, enhanced the sensitivity of the analysis. In addition to that, using electrochemical methods for the detection of a large variety of target molecules brings up new improvements: need of smaller sample quantities, facilitation for automation and also the arisen prospects of developing miniaturized devices for monitoring drugs from a wide range of samples.

The promising results obtained with MIP-based electrochemical sensors for the detection of drugs in complex matrices, such as biological fluids, pharmaceutical formulations, food and environmental samples, revealed their useful prospective applications, including food safety, medical diagnostic and environmental monitoring. Furthermore, their advantages such as low cost, easy preparation, high sensitivity and higher selectivity and stability should be also considered.

Even if there is an increased number of MIPs dedicated to drug analysis, their applications are focused mainly in environmental and biomedical fields. The possibility of miniaturization along with the fast analysis, small number of pretreatment steps to no pretreatment at all, relatively low costs and robustness, are key advantages for further developing this methods within the pharmaceutical industry field for in process quality control of the active pharmaceutical ingredient in different formulations. However, the validation of MIP based sensors, necessary to their implementation in drug manufacturing, is still an unsolved issue that deserves special attention in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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