Int. J. Electrochem. Sci., 12 **(2017)** 8082 – 8094, doi: 10.20964/2017.09.67

International Journal of ELECTROCHEMICAL SCIENCE
www.electrochemsci.org

Mini Review

Sensors Based on Molecularly Imprinted Polymers

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Received: 2 June 2017 / *Accepted:* 23 July 2017 / *Published:* 13 August 2017

Molecularly Imprinted Polymer (MIP) is a polymer having imprinted a molecule on its surface and the surface is able to interact with the molecule chemically equivalent or at least resembling the template molecule. A matrix based on MIP has broad technical applicability in various disciplines like chemical separation, medical use or in analytical chemistry. This paper is devoted to the survey and discussion of MIP use in sensors construction. Materials and analytes are written in details and actual studies in this field are discussed.

Keywords: affinity; antibody; biosensor; biorecognition; interaction; membrane; molecularly imprinted polymer; piezoelectric

1. INTRODUCTION

Analytical devices arising by a connection between a physical sensor platform (or a physico-chemical transducer in some sources) and a material of biological origin (also biorecognition element or a biorecognition part in some sources) are called biosensors. The devices have broad use and they are suitable for the determination of a wide number of analytes. Several biosensors were prepared in the past. Glucose oxidase biosensors for the determination of glucose blood level, glycaemia, were the first type of biosensor invented in the early 1960s [1,2]. Since this time, a wide number of biosensors have been constructed and introduced into praxis. Enzymes, antibodies, organelles, whole cells and chromosomes can be exampled as the typical biorecognition parts suitable for biosensors construction [3-5].

Though several types of biosensors were successfully introduced into praxis and many others exert promising parameters, there remain some drawbacks relating to the biorecognition parts.

Production, storage and expiration of the biorecognition parts go up in price which may cause decrease in competition to the standard analytical techniques. In many cases, it is not easy to reproduce methods based on a biological systems or systems of biological origin. Because of the aforementioned reasons, there is an extensive research on materials providing specificity like the biorecognition elements but producible by a synthetic process which would be implemented into a mass production, allowing simple reproduction and not depending on an expensive technology.

The current review is focused on materials which can replace the biorecognition parts of biosensors: Molecularly Imprinted Polymers (MIPs). The MIPs appears as a suitable tool for production of various sensors with broad practical applicability [6-17]. The MIPs are close to antibodies in an analytical point of view because they can interact in target molecule by an affinity mechanism close to antibodies. When considered analytical use, the MIPs can easily replace many types of biorecognition parts in biosensors. In this review, MIP based analytical devices are introduced as tools for construction of biosensors like devices. Their construction, preparation, and use are given here and the facts are discussed.

2. MEMBRANES FOR A TEMPLATE IMPRINTING

MIPs are polymers having imprinted shape of a molecule in their surface. After removal of the template, the MIP is able to lock the template or template like molecule again when presented in a tested sample. Simplified scheme of the imprinting and repeated interaction with the modified polymer is depicted in figure 1.

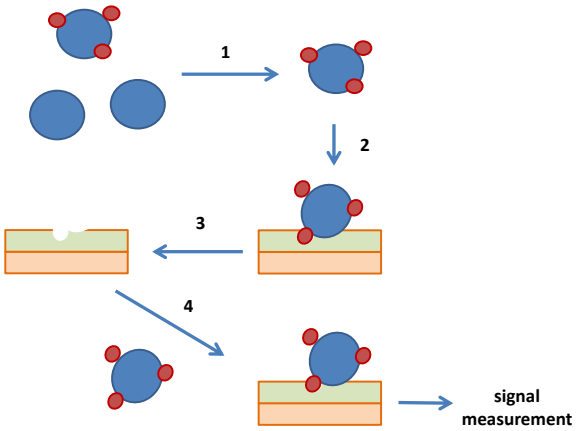

Figure 1. Description of imprinting procedure; 1 – isolation of target molecule; 2 – imprinting of fragments into polymer (light green) and anchoring of the polymer on a sensor surface (pink);3 – remove of template molecule; 4 – interaction of MIP based sensor with analyte molecule.

Heterogeneous group of polymers is used for the MIPs construction. There is a demand that the polymer should keep shape of the original object and not degrade it and not collapsing itself. Polarity and the other physical and chemical properties are important for choice of materials because

inappropriate polarity of the surface can cause no or only weak binding of the analyzed molecule. Size and shape of the cavity after template has to be, of course, complementary to the original molecule.

In a brief survey, wide number of materials like polymer composed from styrene methacrylic acid and ethylene glycol dimethacrylate [18]; acrylic acid, N-vinylpyrrolidone and N,N'-(1,2-dihydroxyethylene) bis-acrylamide [19], metal – organic copolymers [20], poly(2-hydroxyethyl methacrylate-methacryloylamidoaspartic acid) [21], sol-gel polymers [22] and methacryloylamidophenylboronic acid [23] can be mentioned as examples suitable for MIPs construction. In following paragraphs, the most important materials are described and discussed.

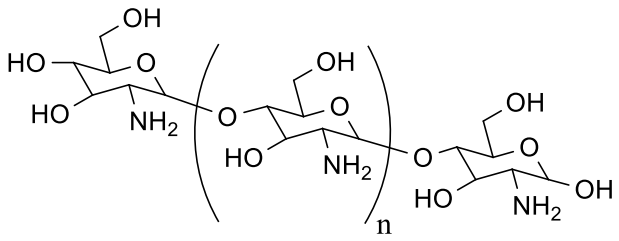

Figure 2. Chitosan.

Though there are a lot of materials available, many of them are based on the same chemical pattern. Chitosan (structure depicted in figure 2) can be introduced as the first molecule. It can be prepared from chitin by an alkaline deacetylation or any other form of chemical deacetylation [24-26] but some fungi like Aspergillus genus are able to produce chitosan by metabolic processes because of enzyme deacetylase [27,28]. Chitosan is a biocompatible molecule that has no or only minimal risk to human health and it also does not make persisting waste in the environment after use because of biodegradability. In a chemical speak, chitosan is an unbranched chain of β (1→4)-2-acetoamido-2-deoxy-D-glucose which exerts unique chemical properties like ability to make complexes with cations. Ionic forms of zinc, copper, nickel, rhenium, iron, cobalt can be introduced as metallic cations firmly binding to or onto chitosan matrix [29-36]. There is also significant affinity of some drugs to chitosan and interactions between chitosan as an carrier and methotrexate (amethopterin), dipeptidyl peptidase-IV inhibitor, ibuprofen ((αS)-α-methyl-4-(2-methylpropyl)-benzeneacetic acid), scutellarin (7-(β-D-glucopyranuronosyloxy)-5,6-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one), paclitatex (Taxol) are known [37-41]. The fact that chitosan has affinity to the aforementioned compounds can be easily exploited for construction of MIPs. An ideal sensor having imprinted target molecule on its surface is not only fully complementary but also chemically compatible with analyte. Chitosan can be used directly in a pure form but is not stable enough to be used repeatedly and the imprinted structure can be washed out. Instead of direct use, chitosan can be further modified resulting in more durable material. A copolymer composing from chitosan and methyl methacrylate can be introduced as an example [42]. The copolymer contained an imprint of 5-fluorouracil which is a drug for chemotherapy of cancer. The drug had affinity to the MIP and it was released from the matrix due to ambient conditions where pH played a crucial role. In a work by Rahangdale and coworkers, chitosan was

stabilized by crosslinking using epichlorohydrin [43]. Salicylic acid and cadmium were imprinted into the membrane and it exerted a binding capacity 38 respective 24 mg/g for cadmium respective salicylic acid. Chitosan in the form of cover over magnetic core formed nanoparticles in another study [44]. The chitosan contained imprinted cytosine.

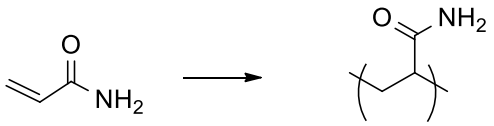

Figure 3. acrylamide and its polymerization to polyacrylamide.

MIPs derived from acrylamide are another available platform. The polymerized form, polyacrylamide, has broad application and polyacrylamide gel electrophoresis is based just on this compound. The polymerization principle is depicted in figure 3. Choice of polyacrylamide for the MIPs is not surprising when considered its availability, low price and experiences from electrophoretic experiments. Despite many parameters of acrylamide are promising, toxicity and carcinogenicity of acrylamide should be also emphasized as a risk factor [45,46]. Manipulation with acrylamide before polymerization should be made in specialized laboratories. There can be mentioned chloramphenicol extraction using acrylamide matrix with the molecule imprint on surface [47]. The matrix served for screening of chloraphenicol in milk and rapid extraction from it. In another application, flavonoid luteolin was selectively captured on a copolymer based on acrylamide and ethylene glycol dimethacrylate [48]. The matrix was used for molecularly imprinted solid-phase microextraction of the luteolin and it was further coupled with liquid chromatography-quadrupole time-of-flight tandem mass spectrometry. As mentioned in the aforementioned citation, acrylamide can be crosslinked to ethylene glycol dimethacrylate but the ethylene glycol dimethacrylate can serve alone as a matrix for MIPs. It was chosen by many researchers and found as a reliable platform for extractions or determination of various compounds. We can introduce some functional applications. Ponzio and coworkers produced nanoparticles composed from ethylene glycol dimethacrylate and poly(9,9-dioctylfluorene-alt-benzothiadiazole) and recommended to use them for a MIP [49]. Ethylene glycol dimethacrylate can be also crosslinked with 2-vinylpyridine and toluene as mentioned in work by Madikizela nad Chimuka [50]. Employing the polymer, the authors created a solid-phase extraction method for ibuprofen, naproxen and diclofenac in wastewater samples and the concentrated drugs were then eluted and determined by a chromatography with diode array detection.

Sol-gel materials as matrices for an imprinting procedure can be employed when a MIP constructed. Sol-gel is a material containing a precursor of ceramics (metal or semimetal oxides) in form of colloidal suspension (sol) converged to a gel form by various condensation and hydrolysis chemical reactions. Sol-gel applications can be demonstrated on work by Liu and coworker where tetraethyl orthosilicate or tetrabutoxytitanium were chosen as semimetal respective metal oxides [51]. The oxides were further treated with aminopropyltriethoxysilane; diethylaminopropyltrimethoxysilane and trimethoxy-phenylsilane (TMP) as functional monomers and then hexanoic acid, nonanoic acid

and benzoic acid were imprinted. The MIP was created on a quartz crystal microbalance sensor and presence of the imprinted aldehydes was determined by the piezoelectric principle.

Aptamers are single stranded DNA or RNA oligonucleotides which can be designed to have affinity toward a target structure. Some researchers denote artificial peptides with affinity to the target structures as aptamers. The aptamers resemble antibodies; however, the antibodies are prepared from viable organisms or cells by immunological protocols or protocols typical genetic engineering and they are typical protein structures [52,53]. Comparing to the antibodies, aptamers can be produced by chemical processes beside the biotechnology one giving good opportunity to establish a mass production with good reproducibility [54,55]. Since their discovery, aptamers have gained broad applicability potential and they appears to be promising for analytical purposes as a recognition elements [56]. A MIP with aptamers were constructed by Li and coworkers for assay of an antibiotic lincomycin [57]. They immobilized the aptamer via electropolymerization on carbon dots and the particles provided chemiluminescence when interacted with lincomycin on the gold-nanoparticle-functionalized graphene oxide. Similar scheme of assay was utilized also in study for assay of enrofloxacin [58]. In another example, MIPs was used for assay of adenosine [59]. The study was focused on immobilization of the aptamers and the second batch was fluorescently labelled and the whole assay worked on quenching principle. The authors reported dissociation constant for the adenosine equal to 27 μmol/l. The previous applications of aptamers appear to be promising. On the other hand, this material has its drawback as well. Firstly, it should be mentioned that fabrication of aptamers is a little more elaborative comparing to low price materials like chitosan or acrylamides. Fact that some enzymes presented in samples can degrade aptamers is another disadvantage. The stability can be improved chemical modification which prevents from nuclease binding and degradation by this enzyme [60].

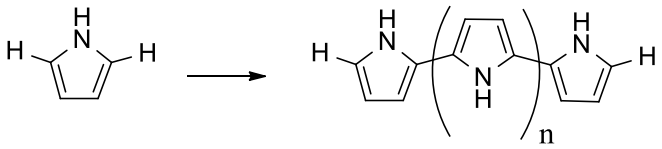

Figure 4. polymerization of pyrrole to polypyrrole.

Pyrrole derived molecules can be employed for surface modifications of sensors and have broad applicability for MIP manufacturing. The polypyrrole scaffold can be created from the pyrrole by chemical polymerization or by an electrochemically controlled process (see figure 4). Electrochemistry has advantage over simple chemical polymerization because the process is easily controllable by voltage magnitude and current density and it is suitable for creation of nanostructured rods on electrode surface. The pyrrole based MIP can be exampled on work of Tang and coworkers who prepared titanium dioxide nanotube covered with polypyrrole with imprint of formaldehyde [61]. The constructed sensor worked on a voltammetric principle and was able to detect formladehyde with limit of detection in the parts per million (ppm) range. Similar adaptation was made for 1,4-

dihydroxyanthraquinone [62], bisphenol A [63] and phenothiazine [64]. High toxicity of pyrrole can be mentioned as an important drawback of pyrrole. Neurotoxicity as well as hepatotoxicity in a combination with good penetration to organism make pyrrole dangerous precursor when wrongly manipulated. On the other hand, polypyrrole is quite stable polymer with low toxicity hence final products do not bring significant risk for marketing [65,66].

β-cyclodextrin is another compound creating polymer suitable for MIP creation and template imprinting [67]. Similarly to pyrrole, cyclodextrins can be polymerized by an electrochemical way giving the opportunity to control the process by adjusting of parameters like voltage range, rate of voltage change, number of cycles etc. Layer of cyclodextrins overs an electrode is easily producible in an electrochemical process [68-73]. Overview of the aforementioned materials is given in table 1.

Table 1. Materials suitable for MIP sensors

Material for MIP	Imprinted molecule	Purpose of imprinting	References
chitosan and methyl methacrylate copolymer	5-fluorouracil	controlled drug release	[42]
chitosan crosslinked by epichlorohydrin	cadmium, salicylic acid	model system	[43]
acrylamide	chloraphenicol	screening of chloraphenicol in milk and rapid extraction from it	[47]
copolymer based on acrylamide and ethylene glycol dimethacrylate	luteolin	microextraction of luteolin prior to mass spectrometry	[48]
Ethylene glycol dimethacrylate crosslinked with 2-vinylpyridine and toluene	ibuprofen, naproxen and diclofenac	solid-phase extraction for water samples prior to chromatography with diode array detection assay	[50]
orthosilicate or tetrabutoxytitanium	hexanoic acid, nonanoic acid and benzoic acid	piezoelectric assay of the imprinted molecules	[51]
chemiluminiscence caused by carbon dots covered with an aptamer when interacted with lincomycin containing gold nanoparticles	lincomycin	assay of lincomycin	[57]
titanium dioxide nanotube covered with polypyrrole as a electrochemical electrode	formaldehyde	assay of formaldehyde	[61]

3. IMPRINTING AND REMOVAL OF THE IMPRINTED TEMPLATE

Removal of the imprinted template is an important step in MIP fabrication and many protocols have been established for this purpose. A combination of physical combination and a suitable solvent are typically necessary for the removal and the choice of removing procedure should consider two

parameters. Efficacy of the template removing is the first parameters of course. Unfortunately, some organic solvents or conditions like high temperature cause degradation of MIP so keeping of the imprinted structure and the whole membrane should be ensured and generosity of the removal procedure should be considered as the second parameter. The process of template removal is not essentially elaborate and not based on expensive reagents, contrary template removal can be accomplished by a simple solvent like water when the procedure is wisely made. Batlokwa and coworkers described a method using pressurized hot water extractions [74]. They fabricated MIPs from a copolymer prepared from methacrylic acid and ethylene glycol methacrylate with imprinted chlorophyll, quercetin and/or phthalocyanine. The researchers were able to effectively remove the chlorophyll and phthalocyanine from MIP weighting 800 mg with water warmed at 220 °C under pressure 50 bars and applied with a flow rate 2 ml/min while quercetin needed temperature a little higher (235 °C) to be removed. Warmed organic solvents are another option. In cited study, methanol-acetic acid in a ratio 90:10 (v/v) warmed at 80 °C was used for remove of nicotine from methacrylic acid – ethylene glycol dimethacrylate membrane [75]. The authors claimed good resistance of the MIP to the extraction and affinity of nicotine to MIP after template removing.

Table 2. Extraction of templates from polymer matrix

Extraction reagent	conditions	type of MIP	references
Pressurized hot water extraction	220 °C (for phthalocyanine and chlorophyll) or 235 °C (for quercetin), 50 bars	methacrylic acid and ethylene glycol methacrylate copolymer with imprinted chlorophyll, quercetin and/or phthalocyanine	[74]
methanol-acetic acid in a ratio 90:10 (v/v)	extraction at 80 °C	methacrylic acid as the functional monomer, and ethylene glycol dimethacrylate as the cross-linker with imprinted nicotine	[75]
acetonitrile-trifluoroacetic acid 99:1 (v/v)	laboratory conditions	methacrylic acid based gel with imprinted fluoroquinolones and xanthines	[76]
ethanol	laboratory conditions	poly-o-phenylenediamine with imprinted benzophenone	[77]
phosphate buffered saline	electrochemical oxidation of the analyte by repeated cyclic voltammetry performance	b-cyclodextrins on graphene oxide with imprinted epigallocatechin-gallate	[67]

In a work by Qiao and Yan, methacrylic acid based polymer with imprinted fluoroquinolones ofloxacin, ciprofloxacin, enrofloxacin and xanthines caffeine and theophylline were prepared [76]. The templates removal was caused by application of acetonitrile-trifluoroacetic acid in a volume ratio 99:1. Ethanol can be chosen as another suitable solvent which is gentle enough for used polymer film but effective for the template washing out. Successful removing of template by ethanol was described in a work where poly-o-phenylenediamine was the matrix and benzophenone was imprinted into the matrix [77]. The benzophenone was removed by a simple immersing of the polymer into ethanol. Template can be degraded by physical way like electrochemical oxidation causing change in physico-chemical properties and a fast removal from matrix. This way was chosen Liu and coworkers for removing of epigallocatechin-gallate from matrix [67]. The researchers imprinted epigallocatechin-gallate into β-cyclodextrins matrix located on a graphene oxide/glassy carbon electrode. After the membrane solidification, epigallocatechin-gallate was electrochemically oxidized by repeated cyclic voltammetry (used potential range -0.1 – 0.9 V) until its peak disappeared. Overview of template removing techniques is given in table 2.

4. SENSOR PLATFORMS FOR CONNECTION WITH MIPs AND EXAMPLES OF ASSAYS

Sensors having MIP as a recognition part are not rare devices. Contrary, the MIPs seem to be effective enough to selectively interact with analytes and having minimal affinity to interfering compounds. Many promising applications have been accomplished though commercialization of them is not finished. When searching in the current databases, matrices having affinity to simple low molecular weight compounds as well as assay of macromolecular markers of diseases can be found in the current literature. Wide number of analytes can be determined by sensors having sensitivity given due to MIPs. Bovine serum albumin using electrochemistry [78], acid green 16 textile dye isolation in an solid phase extraction [79], dacarbazine by electrochemistry [80], timolol by voltammetry [81], mosapride citrate by voltammetry [82], diniconazole by colorimetry/fluorimetry [83], cocaine by potentiometry [84], cinchonine by electrochemiluminescence [85], malachite green by fluorimetry [86], clenbuterol by piezoelectric microbalance [87], histamine by voltammetry [88], bisphenol A by electrochemical techniques [89] can be mentioned. Detailed examples of MIPs are given in following examples and overview is written as table 3.

MIP can work in a similar way like an antibody in an immunochemical assay. This fact was utilized by e.g. Tang and coworker who constructed an assay for the measurement of clenbuterol level [90]. Clenbuterol is a sympathomimetic amine acting as a bronchodilator known from the current pharmacology and the molecule of clenobuterol was imprinted into a an UV polymerable 2-(tert-Butylamino)-1-(3,5-dichloro-4-methacrylamidophenyl) ethyl methacrylate. The authors adapted the developed MIP to be performed in microplates in a way like the standard Enzyme-Linked Immunosorbent Assay (ELISA). They reported good limit of detection equal to 10^{-7} μg/l.

An electrochemical principle of detection accomplished Yang and coworkers who developed an impedance sensor for the detection of cholesterol [91]. The researchers chose aminothiophenol and electropolymerized it on surface of a glassy carbon electrode and the surface was then modified via

electrodeposition of gold nanoparticles with polydopamine as a surface adherent material. The assay was found very sensitive to traces of cholesterol which is obvious from parameters of the assay exerting linear response range 10^{-18} – 10^{-13} mol/l and calculated limit of detection equal to 3.3×10^{-19} mol/l.

Microwave sensor working on Doppler effect principle is another option how to connect a sensor platform with MIPs. This approach was for instance successfully adopted for iprodione assay [92]. Iprodione is a low molecular weight fungicide and it is also used as a nematicide in the current agriculture. Because of wide use and need to control its level in the environment, there are demanded field tests to prove iprodione level. The authors of the quoted paper imprinted iprodione into a sol-gel polymer prepared by condensation of (3-aminopropyl)trimethoxysilane and tetraethoxysilane and were able to reveal as low as 10^{-9} mol/l of the compound.

T-fluvalinate, in a chemical word N-[2-Chloro-4-(trifluoromethyl)phenyl]-D-valine (RS)-cyano(3-phenoxyphenyl)methyl ester, is a synthetic pyrethroid used as an insecticide. Level of t-fluvalinate in the environment is regulated and residual content in the crop is also an object of control. In an adaptation, silicon oxide nanoparticles covered by fluorescent molecularly imprinted polymer composed from either trimethylolpropane trimethacrylate or 3-(methacryloyloxy)propyltrimethoxysilane and allyl fluorescein were fabricated with imprinting of t-fluvalinate [93]. The particles exerted high fluorescence when remained uncovered by t-fluvalinate but the fluorescence significantly dropped when t-fluvalinate was bound to surface of the particles.

Podophyllotoxin assay can be mentioned as the last example. Podophyllotoxin was analyzed by an electrochemical sensor having MIP prepared by electropolymerization of o-phenylenediamine on a glassy carbon electrode [94]. The sensor exerted quite long linear range $4x10^{-8}$ to $3.2x10^{-5}$ mol/l and limit of detection equal to $4.8x10^{-9}$ mol/l.

Table 3. Materials suitable for MIP sensors

Type of sensor and principle of assay	type of MIP	analyte	limit of detection	references
spectral assay	2-(tert-Butylamino)-1-(3,5-dichloro-4-methacrylamidophenyl) ethyl methacrylate	clenbuterol	10^{-7} µg/l	[90]
impedance assay	electropolymerized aminothiophenol modified via electrodeposition of gold nanoparticles with polydopamine	cholesterol	3.3×10^{-19} mol/l	[91]
microwave sensor working on Doppler effect	sol-gel	iprodione	10^{-9} moll	[92]
fluorescence	either trimethylolpropane trimethacrylate or 3-(methacryloyloxy)propyltrimethoxysilane and allyl fluorescein on silicon oxide particles	t-fluvalinate	12.1 nmol/l	[93]
electrochemistry	electropolymerization of o-phenylenediamine on a glassy carbon electrode	podophyllotoxin	$4.8x10^{-9}$ mol/l	[94]

5. CONCLUSIONS

MIPs are a promising technology expecting to be introduced into praxis in the future. Comparing to biosensors where biorecognition part is necessary and has to be isolated, MIPs can be prepared by a chemical process. It gets a promise of the both good reproducibility and easy mass production in a technology process. Though there predominate assays of low molecular weight analytes by MIP sensors, promising adaptations for the determination of macromolecular compounds like protein biochemical markers outlines the next research.

ACKNOWLEDGEMENTS
This work was supported by a Ministry of Defence of the Czech Republic - long-term organization development plan Medical Aspects of Weapons of Mass Destruction of the Faculty of Military Health Sciences, University of Defence.

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