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Research review paper

Molecularly imprinted polymers for separating and sensing of macromolecular compounds and microorganisms

Zofia Iskierko [a], Piyush Sindhu Sharma [a,*], Katarzyna Bartold [a], Agnieszka Pietrzyk-Le [a,*], Krzysztof Noworyta [a,*], Wlodzimierz Kutner [a,b,**]

[a] Department of Physical Chemistry of Supramolecular Complexes, Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
[b] Faculty of Mathematics and Natural Sciences, School of Science, Cardinal Stefan Wyszynski University in Warsaw, Wóycickiego 1/3, 01-815 Warsaw, Poland

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ABSTRACT

The present review article focuses on gathering, summarizing, and critically evaluating the results of the last decade on separating and sensing macromolecular compounds and microorganisms with the use of molecularly imprinted polymer (MIP) synthetic receptors. Macromolecules play an important role in biology and are termed that way to contrast them from micromolecules. The former are large and complex molecules with relatively high molecular weights. The article mainly considers chemical sensing of deoxyribonucleic acids (DNAs), proteins and protein fragments as well as sugars and oligosaccharides. Moreover, it briefly discusses fabrication of chemosensors for determination of bacteria and viruses that can ultimately be considered as extremely large macromolecules.

Contents

Abbreviations: APDS, aminoethylpyridyldisulfide; APS, ammonium persulfate; ASP, apple stem pitting virus; AuNR, gold nanorod; BIS, *N,N*-methylenebisacrylamide; BSA, bovine serum albumin; BHb, bovine hemoglobin; CD, cyclodextrin; CNT, carbon nanotube; CV, cyclic voltammetry; CP, conducting polymer; Cyt *c*, cytochrome *c*; DMAPMA, *N*-[3-(dimethylamino)propyl]methacrylamide; DNA, deoxyribonucleic acid; dsDNA, double-stranded deoxyribonucleic acid; ssDNA, single-stranded deoxyribonucleic acid; DPV, differential pulse voltammetry; EIS, electrochemical impedance spectroscopy; ELISA, enzyme-linked immunosorbent assay; FET, field-effect transistor; FITC, fluorescein isothiocynate; GLaDiS, gel laser diffraction sensor; His, histidine; HIV-1, human immunodeficiency virus type 1; HPLC, high-performance liquid chromatography; HSA, human serum albumin; ISFET, ion-selective field effect transistor; LOD, limit of detection; LSPR, localized surface plasmon resonance; MBAA, *N,N′*-methylenebisacrylamide; MCMH, metal chelating methacryloylamide histidine; MDTA, ({[2-(2-methacrylamido)ethyldithio]ethylcarbamoyl}-methoxy)acetic acid; MIP, molecularly imprinted polymer; MIPPy, molecularly imprinted polypyrrole; MPC, 2-methacryloyloxyethyl phosphorylcholine; MWCNT, multi-wall carbon nanotube; NAD^+, β-nicotinamide adenine dinucleotide; $NADP^+$, β-nicotinamide adenine dinucleotide phosphate; NGAL, neutrophil gelatinase-associated lipocalin; NIPA, *N*-isopropylacrylamide; NMR, nuclear magnetic resonance; NP, nanoparticle; NT-proBNP, *N*-terminal of the prohormone brain natriuretic peptide; PM, piezoelectric microgravimetry; PSA, porcine serum albumin; QCM, quartz crystal microbalance; QCR, quartz crystal resonator; QD, quantum dot; OVA, ovalbumin; PEDOT, poly(3,4-ethylenedioxythiophene); PGE, pencil graphite electrode; Phe, phenylalanine; PPy, polypyrrole; PSS, poly(styrenesulfonate); PVC, poly(vinyl chloride); RGDS, arginine–glycine–aspartic acid–serine epitope; RNA, ribonucleic acid; SAM, self-assembled monolayer; SDS, sodium dodecyl sulfate; SERS, surface-enhanced Raman spectroscopy; SG, sol–gel (process); SPE, solid-phase extraction; SPR, surface plasmon resonance; TnT, human cardiac troponin; Trp, tryptophan; Tyr, tyrosine.

* Corresponding authors.
** Correspondence to: W. Kutner, Department of Physical Chemistry of Supramolecular Complexes, Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland and Faculty of Mathematics and Natural Sciences, School of Science, Cardinal Stefan Wyszynski University in Warsaw, Wóycickiego 1/3, 01-815 Warsaw, Poland.
E-mail addresses: psharma@ichf.edu.pl (P.S. Sharma), apietrzyk@ichf.edu.pl (A. Pietrzyk-Le), knoworyta@ichf.edu.pl (K. Noworyta), wkutner@ichf.edu.pl (W. Kutner).

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1. Introduction

Chemical and biochemical sensor devising and fabricating involves an interdisciplinary research. As the number of applications of these sensors is growing, their market demand increases (Turner, 2013). Now-a-days, this demand is not only limited to sensing systems for small-molecule analytes but that of the macromolecular compound sensing is enormously growing as well. Detection and quantification of the latter analytes in clinical analysis, e.g., in routine blood testing (Turner, 2013) involves huge money spendings. Moreover, the importance of these sensors is also appreciated in several other fields including biological and chemical security (Smith et al., 2008), environmental protection (Dorst et al., 2010; Wanekaya et al., 2008), and food safety (Alocilja and Radke, 2003). For the last few decades, chemical and biological sensors have attracted considerable attention because of their perceived ability to constitute sensing systems selective for determination of target analytes.

Generally, chemo- (Hulanicki et al., 1991) and biosensors (Thevenot et al., 1999) are composed of the recognition and transduction units. The former affords the so much desired selectivity via chemical interactions with analytes whereas the latter transduces these chemical recognition events into corresponding analytical signals also contributing to the sensor detectability. Therefore, both the recognition and transduction units are equally important elements of these sensors.

Synthetic receptors based on the concept of molecular imprinting are still more and more frequently being used as selective recognition units of chemosensors (Malitesta et al., 2012; Sharma et al., 2012a, b; Wackerlig and Lieberzeit, 2015; Whitcombe et al., 2014). Importantly, proper choice of the transduction platform is crucial for devising a highly reliable chemosensor (Huynh et al., 2013). Molecularly imprinted polymers (MIPs), most often prepared in the form of thin films, can be successfully integrated with different transducers for fabrication of selective sensing systems determining different analytes (Malitesta et al., 2012; Sharma et al., 2012b; Suriyanarayanan et al., 2012). Many reviews and an avalanche of original research articles describe preparation and application of selective MIP based chemosensors (Alexander et al., 2006; Malitesta et al., 2012; Sharma et al., 2012b; Wackerlig and Lieberzeit, 2015; Whitcombe et al., 2014). Most commonly, these chemosensors use voltammetry and amperometry, as well as electrochemical impedance spectroscopy (EIS), piezoelectric microgravimetry (PM), and surface plasmon resonance (SPR) spectroscopy for signal transduction. Several recent reports describe the possibility of integrating the same MIP film recognition units with different transducers to fabricate chemosensors of superior performance (Huynh et al., 2013). Other than the above mentioned transductions, field-effect transistor (FET) chemosensors are being prepared because of their ease of miniaturization and high detectability (Casalini et al., 2013; Ito et al., 2009). So far, however, reports describing application of FET transduction for the development of MIP chemosensing are scarce (Iskierko et al., 2015; Kugimiya and Babe, 2011; Kugimiya and Kohara, 2009).

Sensing is more complicated if macromolecule templates instead of small-molecule templates are used for imprinting. Recently, several reviews described imprinting of proteins and other macromolecular compounds (Blanco-López et al., 2004; Holthoff and Bright, 2007; Hvastkovs and Buttry, 2010; Li et al., 2014b). These reports conclude that progress in macromolecular imprinting is slow compared to that of small-molecule template imprinting. This difficulty arises from voluminous size and conformational instability of macromolecular compounds. However, these reports do not pay sufficient attention to the discussion on the effective ways of transduction of the recognition of macromolecular compounds by the MIP-based chemosensors. Therefore, we herein address more carefully the transduction techniques used, including SPR spectroscopy, surface-enhanced Raman spectroscopy (SERS), and FET aided transduction. Other techniques, such as PM at a quartz crystal microbalance (QCM) or electroanalytical techniques, such as voltammetry or EIS, are concisely discussed below as well.

But before discussing these techniques, we will briefly describe the idea of preparation of MIPs. Then, we will focus on chemosensor devising and fabricating along with imprinting of macromolecular compounds. Our review is divided into three main sections including determination of (i) oligonucleotides and DNAs, (ii) proteins as well as (iii) oligosaccharides and sugars. Moreover, determination of bacteria and viruses is briefly addressed separately.

2. Molecularly imprinted polymers as recognition units of chemosensors

The most important criteria that should be considered when devising a chemo- or biosensor include selectivity and sensitivity. Biosensors contain antibodies, enzymes or histones, nucleic acids or aptamers, and even whole animal tissues as recognition units. These bioelements provide the desired specific recognition (Turner, 2013). However, biosensors suffer from several drawbacks. First, their bioreceptors sometimes degrade during biosensor operation, particularly if they are immobilized under conditions different from those of their natural environment. Another deficiency consists in their limited stability because of low tolerance to extreme solution acidity or basicity, elevated or lowered temperature, the presence of organic solvents, and exposure to external electromagnetic, ultrasonic, or ionizing radiation fields. Moreover, availability of bioreceptors is in most cases low; therefore, their cost is high.

To overcome the above mentioned disadvantages, artificial recognition units capable of binding the target analytes with the affinity similar to that of the bioreceptors are being devised and fabricated (Sharma et al., 2015; Suriyanarayanan et al., 2012). MIPs are still more and more frequently used for that purpose. For preparation of these MIPs, functional and cross-linking monomers are co-polymerized in solution in the presence of a template (Sharma et al., 2012a). Before this polymerization, however, a template is allowed to self-organize with functional monomers in solution to form a pre-polymerization complex. Then, polymerization immobilizes this complex in the polymer matrix. Subsequent template removal, e.g., by extraction, from the resulted MIP vacates the imprinted molecular cavities. Importantly, the cavity shape, size, and orientation of its generated recognition sites correspond to the shape, size, and orientation of binding sites of the template molecule (Scheme 1). Noteworthy, the pre-polymerization complex is formed either by non-covalent self assembly or by covalent bonds.

Successful preparation of an MIP film directly contacting the transducer surface is the most important criterion for devising a successfully operating chemosensor. Different procedures have already been developed for this deposition. Toward that, conducting polymers (CPs) (Malitesta et al., 2012; Sharma et al., 2012b) using thiols (Balamurugan and Spivak, 2011) as functional monomers have frequently been used. Alternately, MIP films are drop-cast or spin-coated on a transducer surface (Holthoff and Bright, 2007). On average, all the above mentioned procedures are successful in the preparation of recognition units of chemosensors for the determination of compounds