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MATERIALS SCIENCE

Molecularly imprinted polymers: a new approach to the preparation of functional materials

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Abstract. Molecular imprinting is a method for creating specific cavities in synthetic polymer matrices with memory for the template molecules. To date molecularly imprinted polymers (MIPs) have obtained a strong position in materials science and technology, expanding significantly the list of functional materials. This article provides a short review of the molecular imprinting technique with special attention paid to electrosynthesized electrically conducting polymers (ECPs), polypyrrole and polyethylenedioxythiophene, as matrix materials for molecular imprinting. We describe two different ECP-based MIP systems: enantioselective thin films of overoxidized polypyrrole imprinted with L-aspartic acid and surface imprinted polyethylene-dioxythiophene for selective protein adsorption.

Key words: polymer materials, electrically conducting polymers, molecular imprinting, enantioselective recognition, surface imprinting, proteins.

INTRODUCTION

Functional materials are usually defined as materials with properties designed to serve a specific purpose in a controlled way. The physical and chemical properties of functional materials are either stable or sensitive to changes in the environment in a controlled way. Such changes include changes in temperature, pressure, electrical and magnetic fields, wavelengths of visible light, absorbed molecules, or acidity. One example of functional materials is the group of materials based on molecularly imprinted polymers (MIPs). Over the past two decades, a bulk of research has focused on the development of various formats of MIP materials, which has allowed the method of imprinting to expand into new scientific areas, namely chemo/biosensors [1,2], nanotechnology [3,4], biotechnology [5], chemical synthesis and catalysis [6], etc.

The history of molecular imprinting is traced back to the work by Polyakov on imprinted silica gel in the early 1930s [7]. In the 1950s a very similar methodology was used in the experiments of Dickey [8], who was inspired to create affinity for dye molecules in silica gel by Linus Pauling's theory how antibodies are formed [9]. Imprinting in organic polymers first appeared in the 1970s when covalent imprinting in vinyl polymers was reported [10]. Non-covalent imprinting in the form we know today was introduced about a decade later [11].

Today's concept of molecular imprinting has been widely recognized as the most promising methodology for the preparation of different tailor-made materials with selective adsorption. Investigation and development of artificial receptors [12] appears to be of particular interest. In comparison to their biological analogues, major advantages of the MIPs, other than possessing antibody-like molecular selectivity, include physical robustness, resistance to elevated temperatures and pressures, inertness to acids, bases, and organic solvents, as well as low production cost and ease of preparation.

The preparation of polymers with selective binding sites is generally performed in situ by co-polymerization of functional monomers and cross-linkers in the presence of a specific target (template) molecule (Fig. 1). This procedure usually produces macroporous polymers with a permanent pore structure and high inner surface area. Polymerizable functional groups are usually bound by covalent or non-covalent interaction to the template molecule. Under special conditions template molecules

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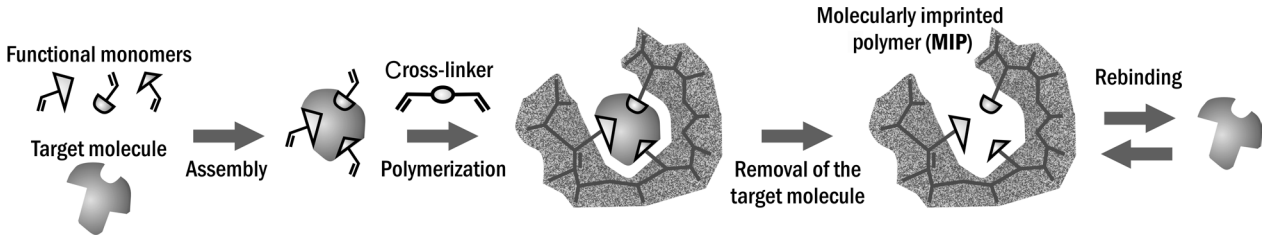

Fig. 1. Schematic representation of the molecular imprinting process.

can be removed from the structure in high percentage, leaving cavities in the polymer matrix, ready for selective binding of the target molecules. The selectivity depends on both the orientation of the functional groups inside the cavities and the shape of the cavities.

Covalent imprinting is performed by the use of templates, which will be covalently bound to polymerizable groups. In this case there is a stoichiometric relation between the template and the imprinted binding site. The covalent approach should provide more homogeneous binding sites, but the rebinding is slow because covalent bonds between the template and the MIP have to be formed. Unfortunately, only a limited number of compounds (alcohols, ketones, amines, and carboxylic acids) can be imprinted by this approach [13].

The groups of Mosbach and Sellergren initiated investigations also with the non-covalent imprinting method [11,14]. Today the non-covalent approach is the most widely used strategy because of easier production, faster rebinding of the template, and greater variety of available functional monomers than with the covalent approach. The limitation of this technique is that the template and target must form a sufficient number of noncovalent intermolecular interactions (i.e., hydrogen bonds, ion pair interactions, hydrophobic interactions, and Van der Waals forces) to generate the binding cavity during polymerization. Therefore, noncovalent imprinting is not particularly successful for template or target molecules that do not possess appropriate functional groups.

A better solution would be to combine these two methods, whereby in imprinting the covalent interactions and in rebinding the non-covalent interactions are used and the so-called 'semi-covalent method' is obtained [15]. Semi-covalent imprinting attempts to take advantage of both of the methods.

Generally, MIPs have been prepared via bulk polymerization in the form of a monolithic block. The process of grinding this block into a particulate product of controlled size is both time consuming and wasteful [16]. Moreover, most MIPs are hydrophobic in nature, which results in their poor recognition in aqueous systems. The low aqueous compatibility of MIPs is the greatest problem in their application for biological recognition like bioassays. Therefore, an increasing number of polymer formats and methods of polymerization have been developed, such as imprinting of beads [17], suspension polymerization [18], production of thin films or membranes [19,20], phase inversion [21], and surface imprinting, especially for imprinting large molecules [22]. Another very promising approach is the preparation of molecularly imprinted electrosynthesized polymers [23]. The electropolymerization process provides a superior control of the thickness, morphology, and spatial localization of polymeric films. This feature enables creating a direct communication between the coating and the surface of the transducer in a very simple way. Thus, the electrosynthetic approach could be very helpful in improving the molecular imprinting polymerization procedure itself as well as in extending applications of MIPs as sensing elements for chemical sensors with various transduction mechanisms. In the same direction, miniaturization, one of the major goals of chemical sensor technology, could also be easily realized.

From the numerous publications dealing with the preparation of molecular imprinting technology it can be concluded that the structure of the polymer to be used as a matrix for imprinting needs optimization. The polymer structure must be rigid to preserve the structure of the cavities after the removal of the template. On the other hand, high flexibility of the polymer should facilitate the processes of template release and reuptake. Also, high thermal and mechanical stability of the polymer structure is important and finally, the technology of the MIP structure preparation should be simple enough and reproducible. Most of these requirements can be satisfied by using electrically conductive polymers for the polymer matrix.

ELECTRICALLY CONDUCTING POLYMERS AS GOOD CANDIDATES FOR MIP SYSTEMS

Electrically conducting polymers (ECPs) can be easily prepared by electropolymerization from both organic and aqueous solutions in the presence of different counter ions (doping ions), which allows simple modification of the properties of the resulting films. Therefore, it is not surprising that ECPs were proposed

as candidates for a recognition matrix [24,25]. As this is a very promising approach to the MIP technology, we will dwell upon it at a greater length.

The ECPs are organic materials that have both electrical and optical properties similar to those of metals and inorganic semiconductors, but which also exhibit the attractive properties associated with conventional polymers, such as ease of synthesis and flexibility in processing [26,27]. The great potentiality of ECPs for a number of applications, such as charge storage devices [28,29], actuators [30], bio- and gas sensors [31], and ion-selective electrodes [32], has attracted much attention. Due to their biocompatibility and compatibility with aqueous solutions ECPs are prospective materials for bioanalytical and biosensor technology [33,34]. Among ECP materials, polypyrrole (PPy) has been studied in more detail as it can easily be synthesized by chemical and electrochemical polymerization, and has many attractive features, such as excellent conductivity and stability on various substrate materials, even in a neutral pH region [35]. As it has been demonstrated, PPy is also a good candidate as a matrix for molecular imprinting [25]. One advantage of electropolymerized PPy over conventionally prepared MIPs is that complementary cavities can be created with simultaneous expulsion of anionic template molecules through an overoxidation/dedoping process [24,25]. It was reported that, during overoxidation, PPy loses its electroactivity due to the ejection of the dopant (dedoping), and oxygen-containing groups such as carbonyl and carboxyl are introduced to the pyrrole unit [36]. According to Spurlock et al. [24], after imprinting the molecular sites are expected to remain in overoxidized PPy (oPPy) since overoxidation of PPy does not significantly alter polymer morphology, disrupting conjugation but maintaining the integrity of the polymer network. Moreover, Shiigi et al. [37] suggest that concomitantly with dedoping, curing of the polymer texture occurs to retain the complementarity of the cavity. The carbonyl oxygen facing the cavity surface can be a driving force for the uptake of cationic template molecules. Molecularly imprinted ECP applications as recognition matrices for different biological molecules are reported in [37–41].

This paper describes two different MIP systems based on the electrosynthesized ECPs, namely enantioselective thin films of oPPy imprinted with L-aspartic (L-Asp) acid and surface imprinted polyethylenedioxythiophene microrods for selective protein adsorption.

Polypyrrole thin films for enantioselective recognition of amino acids

The enantiomeric purity of various compounds is important in stereo-specific synthesis, production of pharmaceuticals, pesticides, and some food additives, where only one enantiomer may interact satisfactorily. The molecular imprinting technology offers a unique possibility of obtaining MIPs with predetermined enantioselective binding properties for given chiral targets [42,43]. Such chirally imprinted MIPs have several advantages over conventional chiral selector systems, for example, ease of preparation, low material costs, and flexibility to design various self-supporting formats. Various electrodeposited conducting polymers have been utilized to modify working electrodes in amperometry and voltammetry in order to use them in enantioselective uptake studies. Deore et al. reported on the enantioselectivity of oPPy films and colloids towards amino acids (L- and D-glutamic acid) [44].

Recently we reported on molecularly imprinted oPPy thin films discriminating between L- and D-aspartic (D-Asp) acid [45]. The L-Asp/D-Asp acid system was chosen motivated by the importance of L-Asp acid in human metabolism, such as removing toxins from the bloodstream and the use of L-Asp racemization ratios in human serum for age estimation [46]. The films were formed on gold-coated quartz crystals and the mass changes of the polymeric films during electropolymerization and overoxidation were determined by the electrochemical quartz crystal microbalance (EQCM). The EQCM technique is especially suitable for MIP system studies as the mass changes can be monitored in situ during the electrochemical modulation of the film [47,48]. The general scheme of the electrochemical setup used for EQCM studies of MIP systems is presented in Fig. 2. The individual selectivity for the

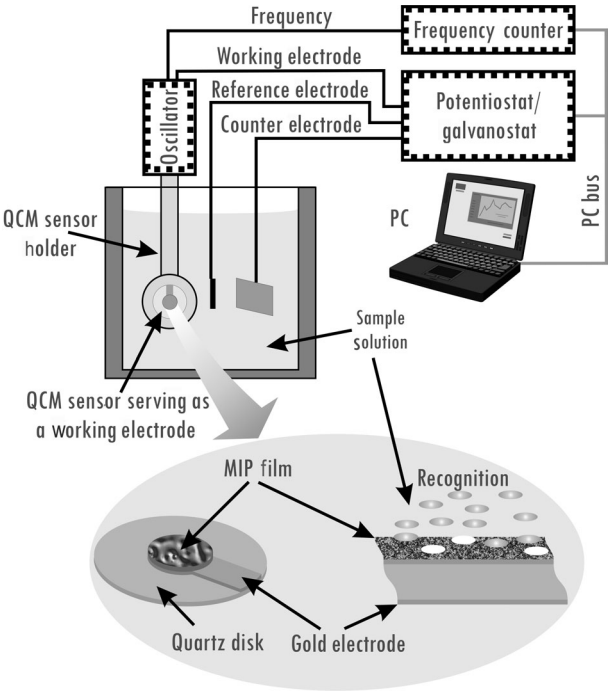

Fig. 2. Schematic of the electrochemical setup used for EQCM investigations of MIP systems.

L- and D-Asp of the imprinted oPPy/L-Asp films was determined under the conditions of no electrical perturbation applied and potentiodynamic polarization. For optimal selectivity the thickness of the imprinted oPPy film, pH, and ionic strength of the monomer–sample solutions were considered at the film synthesis and detection.

It was found that synthesis parameters, such as electrolyte composition and pH value, have a strong influence on the enantioselectivity of the resulting oPPy/L-Asp films. Thus, the electrodeposition from a weakly acidic solution containing pyrrole and L-Asp salt (pH 6) leads to films that do not exhibit enantioselectivity for L-Asp. This may be attributed either to the difficulty of doping PPy with L-Asp in the weakly acidic media or to the destruction of the recognition sites during overoxidation. The electropolymerization of pyrrole in the presence of L-Asp in alkaline media (pH 11), on the contrary, results in adherent smooth and homogeneous PPy/L-Asp films that after following overoxidation–dedoping (oPPy/L-Asp$_B$) exhibit rather good enantioselectivity at pH 1.6. Figure 3 shows frequency changes of an EQCM electrode modified with oPPy/L-Asp$_B$ during the negative potential (−0.4 V vs Ag/AgCl) applied in the buffered solution at pH 1.6. A frequency decrease of 56.6 Hz was observed as a result of L-Asp addition to the carrier solution, while the response of the same film for D-Asp was only 2.83 Hz. This means that the oPPy/L-Asp$_B$ films have approximately 20-fold selectivity for the enantiomer used as a template, which compares very favourably with the enantioselectivity of previously reported PPy based MIPs: maximal uptake ratio for tyrosine L/D = 9.4 ± 4.7 [49] and for glutamic acid L/D approximately 10 [44]. In the cases the oPPy film was synthesized in the presence of L-Asp salt and polystyrene sulphonate (oPPy/PSS/L-Asp), the frequency change obtained was markedly smaller. Obviously, this indicates that during the synthesis the PSS anions are predominantly incorporated into the PPy film, resulting in a lower concentration of L-Asp ions in the film and consequently, a lower density of the recognition sites is formed during overoxidation. The experiments show also that a higher doping level of the template molecule in the film enhances the selectivity of the reuptake. It was demonstrated that the uptake of L-Asp on oPPy/L-Asp films occurs only in the cases of potential-induced uptake/release of targeted molecules.

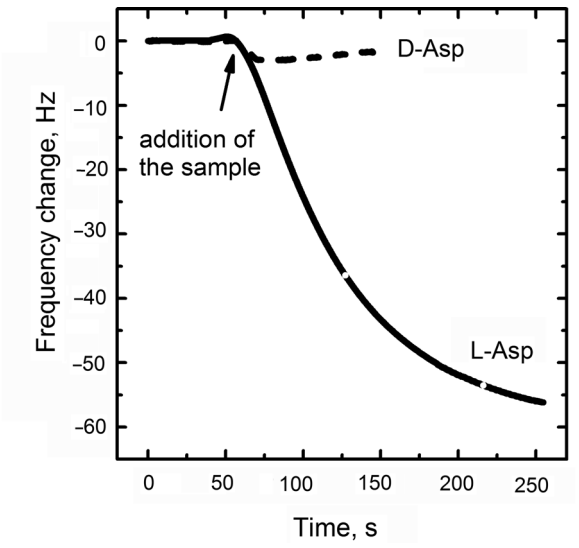

Fig. 3. Frequency changes of the oPPy–L-Asp$_B$ coated EQCM electrode held at a constant potential of −0.4 V (vs Ag–AgCl) after injection of L-Asp or D-Asp sample solution into the buffer (pH 1.6).

These results suggest that preparation of molecularly imprinted films by electropolymerization for the enantioselective recognition of amino acids is feasible and the EQCM is suitable for both monitoring the selective recognition and electrochemical modulation of the binding process.

Surface imprinted polyethylenedioxythiophene microrods for selective adsorption of proteins

As described above, MIPs have proved to be prospective materials for selective recognition of small biomolecules. At the same time, interest and demand for macromolecular recognitions are growing continually in medical diagnostics, clinical and environmental analysis, and especially in drug delivery systems [50]. MIP systems also have theoretically promising properties for selective recognition of macromolecular compounds, such as proteins and others, but the practical realization of these systems is still a challenge. The main problem lies in the limited mobility of these molecules in the bulk of polymer networks and hence the poor efficiency in binding kinetics [51]. Moreover, the structural complexity and large size of macromolecules lead to non-specific and heterogeneous binding sites, which in turn leads to a poor recognition ability [52]. Generally, there are three approaches to macromolecular imprinting: bulk imprinting, surface imprinting, and epitope imprinting. In this paper we will describe the application of the surface imprinting method for the creation of ECP-based micro- and nanorods. In general, the concept of surface imprinting can be explained as the creation of complementary cavities on the surface of MIP structures [53]. The surface imprinted polymers (SIPs) have many advantages: the sites are more accessible, mass transfer is faster, and hence the binding capacity is stronger. Mosbach and coworkers proposed a clever protocol based on the oriented immobilization of the template molecule on a solid support, such as porous silica beads [54]. Later,

this protocol was used for the imprinting of amino acids and peptides [55,56]. Li et al. reported a protocol for creating SIP nanowires by the immobilizing of target protein molecules within the pores of the nanoporous alumina membrane [57]. They used the template synthesis method where the polyacrylamide nanowires are prepared by the chemical polymerization of acrylamide and cross-linking monomer within the nanopores of alumina membranes preliminarily modified by proteins. However, the main disadvantage of this method is the weak adsorption of proteins on the alumina membrane requiring a multistep treatment of the alumina before attaching the proteins. Also, the control of the polymerization is complicated.

Recently we proposed, in collaboration with Gyurcsányi's group in Budapest, a novel approach and materials for producing surface imprinted micro- or nanorods with selective protein binding sites located on their surface [58]. This method is based on the template synthesis of SIP microrods, where we use poly(3,4-ethylenedioxythiophene) (PEDOT) as the molecular recognition matrix, which is formed within the pores of a track-etched polycarbonate membrane (PCM), modified with a target protein – fluorescently labelled avidin (Av-FITC). Figure 4 shows schematically the proposed surface imprinting protocol.

Compared to alumina membranes, PCMs adsorb readily protein molecules due to their hydrophobic nature, and therefore the target protein Av-FITC can be fixed onto the pore walls by simple physical adsorption. The PCM modified with target protein molecules was positioned on the surface of a gold electrode, and conducting polymer rods of PEDOT doped with PSS were synthesized electrochemically within the pores of the membrane. The membrane was subsequently removed by dissolving in dichloromethane or chloroform, leaving behind PEDOT–PSS microrods possessing complementary cavities for the target protein Av-FITC on their surface. Scanning electron micrographs (Fig. 5) obtained after the removal of the PCM indicate that the growth of the polymer rods was confined in the pores.

The specific adsorption of the target protein on the prepared SIP microrods was tested by binding assays. Surface imprinted PEDOT microrods were incubated in a buffer solution containing Av-FITC at various concentrations and then examined by epifluorescent microscopy. Non-imprinted PEDOT microrods (NIP) synthesized in the absence of the template protein were used as control samples. Fluorescent images of SIP PEDOT microrods presented in Fig. 6 (inset) show fluorescent rings around the microrods, indicating the adsorption of Av-FITC on the binding sites situated on the surface of microrods. The intensity of the fluorescent rings resulting from the binding of Av-FITC was measured and related to the concentration of Av-FITC in the test solution. A significant increase of the fluorescence signal with an increase in the concentration of Av-FITC was observed for SIP PEDOT microrods, while the binding of Av-FITC to the NIP microrods was insignificant (Fig. 6).

The selectivity of the prepared SIP PEDOT microrods was tested by competitive binding assays, where different

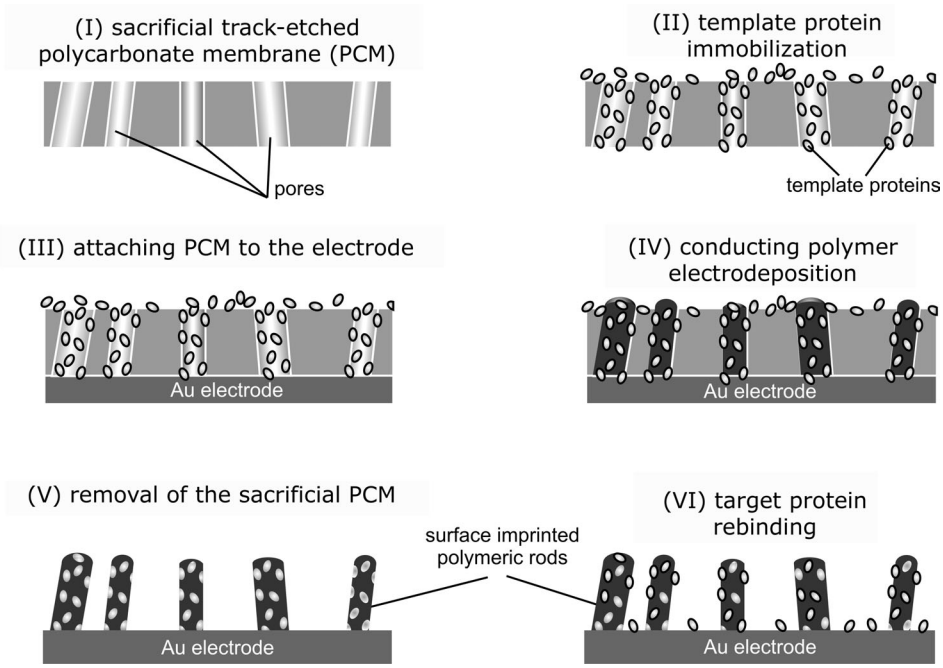

Fig. 4. Schematic representation of the surface imprinting protocol.

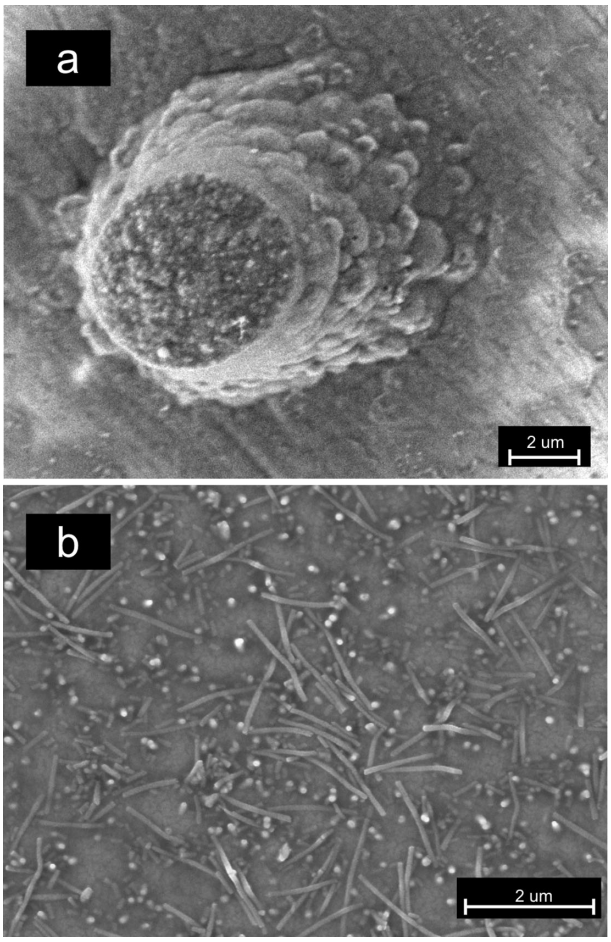

Fig. 5. SEM images of the micro- (a) and nanorods (b) prepared by the template electrochemical polymerization of PEDOT–PSS.

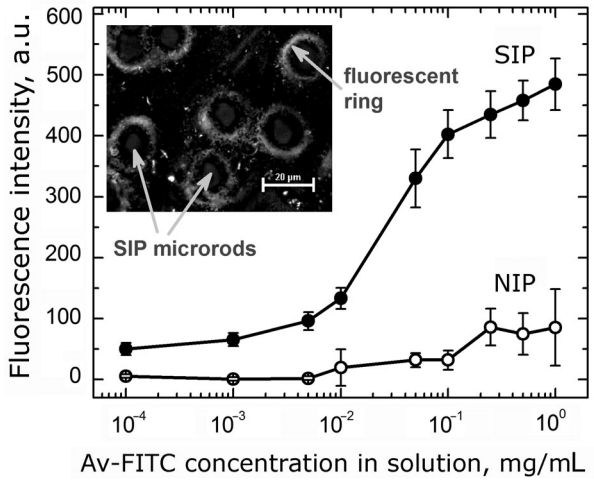

Fig. 6. The intensity of the fluorescent rings resulting from Av-FITC rebinding on the imprinted PEDOT–PSS microstructures as a function of Av-FITC concentration in the buffer solution (pH 7).

concentrations of either avidin or bovine serum albumin were allowed to compete with a constant amount of Av-FITC for the binding sites. The experiments demonstrated an increased binding of target protein (Av-FITC) on SIP PEDOT microrods compared with competitive proteins, confirming that the microrods prepared are selective towards the imprinted protein molecules [58].

On the basis of the experimental results, it can be concluded that the proposed method for the preparation of SIP microrods is promising for selective recognition of macromolecules because of its simplicity, excellent control of the polymerization and localization of the microstructures, and low non-specific protein adsorption of PEDOT–PSS.

CONCLUSIONS

Over a period of many years, the molecular imprinting method has obtained a strong position in materials science and technology, extending significantly the list of functional materials. The preparation of synthetic materials with selective recognition sites opens up many new interesting challenges for engineers and scientists in a very broad field of applications from artificial receptors in biochemistry to specific catalysts in classical chemical technology and industry. The application of electrically conductive polymers as a recognition matrix for MIP materials also allows for linking such materials with semiconducting technology that assist the use of MIPs in electronic devices. In addition, the proposed method for SIP microrods fabrication is expected to allow also the formation of nanosized MIPs opening up new options in biomedicine and biotechnology.

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Anna Menaker received her MSc degree in Analytical Chemistry from Tallinn University of Technology, Estonia, in 2004. She is presently a PhD student at the same university. Her current fields of interest include electrosynthesized polymers for molecular imprinting and synthetic receptors based on molecularly imprinted polymers.

Jekaterina Reut received her PhD from Tallinn University of Technology in 2004. Currently she is a research scientist at the Department of Materials Science of the same university. In 2004 she received the first prize in Natural Sciences and Engineering in the Estonian National Contest for Young Scientists at university level. Her research interests include electrically conducting polymers, their electrochemical properties, and use in molecular imprinting for the fabrication of artificial receptors.

Vitali Syritski studied chemistry at Tallinn University of Technology, Estonia, and received his PhD in 2004 in the field of inherently conducting polymers. Presently he is a senior researcher at the Department of Materials Science of Tallinn University of Technology. Since 2005 he has focused his activity on the developing of molecularly imprinted conducting polymers for biosensing.

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Molekulaarselt jäljendatud polümeerid – uus väljund funktsionaalsete materjalide valmistamiseks

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Tänaseks on molekulaarse jäljendamise meetod (MIP) leidnud kindla koha materjaliteaduses ja tehnoloogias, laiendades märkimisväärselt eri materjalide funktsionaalseid omadusi. Molekulaarse jäljendamise meetodi põhimõte seisneb sünteetiliste polümeeride maatriksis spetsiifiliste “mälupesade” tekitamises, mis on hiljem võimelised nn jäljendatud molekule uuesti siduma. Artiklis on antud ülevaade molekulaarse jäljendamise meetodi kasutamisest ja valmistamise võimalustest, pöörates põhitähelepanu elektrit juhtivate polümeermaterjalide – polüpürrooli ning polüetüleendioksütiofeeni – kasutamisele molekulaarselt jäljendatud süsteemides (MIP) maatriksmaterjalidena. On kirjeldatud üleoksüdeeritud polüpürrooli baasil valmistatud MIP-süsteemide enantioselektiivsust L-aspartaamhappe suhtes ja pindmiste mälupesadega polüetüleendioksütiofeeni baasil valmistatud molekulaarselt jäljendatud mikrovarraste (SIP) selektiivset adsorptsiooni proteiini molekulide suhtes.