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Feature article

Water-compatible molecularly imprinted polymers: Promising synthetic substitutes for biological receptors

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ABSTRACT

As a new class of synthetic receptors, molecularly imprinted polymers (MIPs) have shown great potential in many applications because of their good specific recognition ability, high stability, and easy preparation. The ultimate goal of molecular imprinting is to obtain MIPs that can be routinely used as alternatives to natural antibodies and receptors. However, the presently developed MIPs targeting small organic molecules mostly fail to show specific bindings in aqueous solutions, which is in sharp contrast to biological receptors and significantly limits their practical applications in such areas as biomimetic assays and sensors. Many efforts have been devoted to address this issue in the past two decades. In this feature article, I provide a detailed overview of the progress made in the development of water-compatible MIPs with an emphasis on our strategies to solve this challenging problem. Moreover, some still existing challenges and future prospects in this research area are also presented.

1. Introduction

In nature, molecular recognition events play an important role in virtually all life processes, such as the immuno response between the antibody and antigen, the ligand–receptor interaction, and enzyme catalysis [1]. The phenomenon of specific molecular recognition is also becoming increasingly important in both research and industry nowadays because it can lead to highly selective separations, catalytic processes, and sensitive chemical assays [2–4]. Although biological receptors can show high affinity and good selectivity towards their guest molecules over the close structural analogues and have been utilized in many practical applications including immunoassays, biosensors, and molecular devices, their low stability and high cost significantly limit their broad applications [5]. Therefore, the development of synthetic receptors with an affinity and specificity approaching those achieved in nature has become an area of intensive current interest. To this end, many synthetic low molecular weight organic receptors capable of encapsulating reagents have been designed by incorporating certain binding groups (e.g., hydrogen bonding, electrostatic, hydrophobic, etc.) into the cavity in a host that are complementary to the guest molecules [6]. However, their construction usually implies complicated multi-step synthesis, which severely limits their large-scale application. Therefore, other synthetically more accessible synthetic receptors are highly desirable.

As a new class of artificial receptors with tailor-made recognition sites, molecularly imprinted polymers (MIPs) have received considerable attention in recent years because of their easy preparation, mechanical, thermal and chemical stability, and highly selective recognition capabilities [7–22]. Such synthetic polymer receptors are prepared easily by the versatile and straightforward molecular imprinting technique and can have substrate affinity and specificity comparable to those of biological receptors. These highly appealing physical and chemical characteristics make MIPs very promising candidates for many applications, including chromatographic stationary-phase and solid-phase separation, antibody mimics (biomimetic assays and sensors), enzyme mimics, organic synthesis, capillary electrochromatography, drug development, drug delivery, and biomedicine.

The ultimate goal of molecular imprinting is to generate MIPs that can eventually replace biological receptors in practical applications. It is well known that biological receptors such as enzymes and antibodies can show outstanding molecular recognition ability in the aqueous media. However, the previously developed MIPs that target small organic molecules are normally only compatible with organic solvents, and they mostly fail to show specific template bindings in aqueous solutions (whereas peptide- or protein-imprinted polymers are intrinsically water-compatible [14,17,18]), which significantly limits their practical application in such areas as molecularly imprinted sorbent assays, biomimetic sensors, and

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biotechnology [4,23–28]. Note that although there have been many reports on the MIP-based solid-phase extraction of target analytes in real matrices [29–31], the selectivity of the MIPs in this case is controlled by the choice of solvents in the extraction procedure. The direct use of MIPs in real matrices is more difficult, as the conditions used are mainly fixed by the nature of the sample [25]. So far, many efforts have been devoted to the development of MIPs that can be directly utilized for the specific molecular recognition in aqueous solutions in the past years.

In the following part of this feature article, I will first briefly introduce the molecular imprinting technique and then provide a detailed overview of the progress made in the development of water-compatible MIPs in the past two decades. In particular, a series of facile, general, and highly efficient approaches for the preparation of fully water-compatible MIPs developed in our laboratory are highlighted. Finally, some still existing challenges and future prospects in this research area are also presented.

2. Molecular imprinting

The molecular imprinting technique can be defined as the formation of specific nano-sized cavities by means of template-directed synthesis (Fig. 1) [7–22]. It typically involves the copolymerization of a functional monomer (or a mixture of functional monomers) and a cross-linking monomer in the presence of a template molecule and a porogenic solvent. The functional monomers initially form a complex with the template. After polymerization, their functional groups are held in position by the cross-linked polymer structure. Subsequent removal of the template results in MIPs with binding sites complementary in size, shape, and chemical functionality to the template.

Depending on the interactions between the template and functional monomers involved in the imprinting and rebinding steps, molecular imprinting has been realized in three different ways through the covalent, non-covalent, and semi-covalent approaches. The covalent approach was pioneered by Wulff's group [7], where the functional monomers form complexes with template molecules via reversible covalent bonds (such as boronate ester, ketal and acetal, or Schiff base) prior to the polymerization, and the subsequent rebinding of the templates to the imprinted polymers also takes place through the formation of covalent bonds between them. The non-covalent approach was introduced by Mosbach and coworkers [8], which utilizes only non-covalent interactions (such as hydrogen bonds, ionic interactions, hydrophobic interactions, and metal-ion chelating interactions) for both the molecular imprinting and subsequent template rebinding processes. The semi-covalent approach (also called hybrid approach) was developed by Whitcombe and coworkers [11], where a covalently attached template was utilized in the imprinting process while the template rebinding step is non-covalent. Among them, the non-covalent approach has been most commonly used nowadays because it allows the easy preparation of MIPs in the absence of complicated synthetic chemistry and the broad selection of functional monomers and possible target molecules available. In addition, the imprinted polymers prepared by the non-covalent imprinting approach show much faster rebinding kinetics than those prepared by the covalent approach, which makes them particularly suitable for applications involving their use as stationary phases in HPLC system and as sensors. However, it is worth mentioning that the covalent approach usually produces a more homogeneous population of binding sites than the non-covalent approach does because of the greater stability of the covalent bonds, as confirmed by Shimizu and coworkers [32].

Since the success of the molecular imprinting process is very much dependent on the monomer–template interaction, the suitable choice of functional monomers is the most important characteristic in targeting a template molecule [33]. A large number of functional monomers have been successfully utilized in the molecular imprinting systems up to now, such as methacrylic acid (MAA), trifluoromethacrylic acid (TFMAA), 4-vinylpyridine (4-VP), and so forth. Among them, MAA has been the most widely used one, which can interact with amines via ionic interaction and with amides, carbamates, and carboxyls via hydrogen bonds. In addition, cross-linking monomers also play an important role in molecular imprinting and show significant influence on the final properties of the resulting MIPs because they constitute most part of the MIPs and are responsible for stabilizing the molecularly imprinted cavities. Ethylene glycol dimethacrylate (EGDMA or EDMA) has proven to be the most commonly used cross-linker. Furthermore, many other factors also have a significant effect on the molecular imprinting processes and thus on the properties of the resulting MIPs, such as the molar ratios of the reaction components, the amount of the solvents, and reaction temperature. Therefore, a better understanding of their influence on both the polymerization processes and the recognition properties of the MIPs is highly important for getting more fundamental knowledge to direct the effective preparation of MIPs. In this sense, the application of the combinatorial method together with the high-throughput technique [34–37], as well as of the computational approach [38,39], should be very useful for this purpose and will definitely accelerate the development of new and advanced MIP materials.

So far, significant progress has been made in the molecular imprinting field and a great number of MIPs with good memory for a variety of different templates ranging from small molecules (such as amino acids, steroids, carbohydrates, pesticides, drugs, dyes, metal ions, etc.) to large entities (polypeptides, proteins, whole cells, bacteria, and inorganic crystals) have been successfully developed for various applications [10]. Besides further exploring the fundamental knowledge of the MIPs and their application potentials, the researchers have been focussing on the rational design, synthesis, and characterization of advanced MIP materials with novel and improved properties for the purpose of solving the challenging problems in molecular imprinting field such as the water-compatibility of the MIPs.

3. Methodologies to obtaining water-compatible MIPs developed by others in the past two decades

In 1993, Mosbach and coworkers published their milestone work in Nature, which demonstrated for the first time that the MIPs

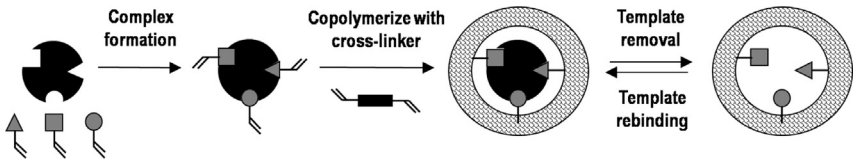

Fig. 1. Schematic representation of the molecular imprinting process.