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REVIEW

A Review on Bio-macromolecular Imprinted Sensors and Their Applications

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Abstract: Molecular imprinted technology has been maturely applied to analyze and detect small molecular organic compounds, also increasingly applied in biological macromolecules assay. This review addresses the perspective of bio-macromolecular imprinted sensors and their applications, including optical molecular imprinted sensors, electrochemical molecular imprinted sensors and mass-sensitive molecular imprinted sensors. In addition, the opportunities, challenges, and further research orientations of molecular imprinted sensors for bio-macromolecules detection were prospected.

Key Words: Molecular imprinting sensors; Biomacromolecules; Application; Review

1 Introduction

1.1 Introduction of molecular imprinting technique

1.1.1 Development of molecular imprinting technique

Molecular imprinting technique (MIT) originated in 1930s. Polyakov[1] and Dicky[2] for the first time proposed the silica gel with specific adsorption capacity. Dicky's study focused on the development of silica with specific molecular recognition ability for methyl- and ethyl orange dyes. Since then, researchers have been confined to the concept of "Antigen-antibody". Until 1972, Wulff[3] proposed the concept of "molecular imprinting", and successfully prepared the molecular imprinted polymer (MIP) with the chiral recognition ability for *D*-glycerol acid, which was a breakthrough in MIT development. In 1993, Mosbach's group[4] published their study on MIP of theophylline, which promoted the rapid development of MIT in the next two decades. The specific recognition ability of MIPs was then first described systematically, which was vividly called "plastic antibody"[5]. Currently, MIT has been extensively applied in the fields of material science[6], analytical chemistry[7], biochemistry[8,9] and biological medicine[10]. However, it is still a challenging task in imprinting biological macromolecules. In 1985, the protein imprinted polymer was first prepared by Glad group[11] using organic silane as function monomers, which showed the affinity for glycoprotein in high performance liquid chromatography. Due to the vast size and complex conformation of biological macromolecules, the progress in application of MIT has been slow. Until the emergence of surface imprinting[12] and epitope imprinting[13] techniques, the macromolecular imprinting has gradually became a hot spot. The present review is supposed to give a "visual" of how far scientists go with the bio-macromolecule imprinted sensors.

1.1.2 Principle of MIT

A broader and more complete definition[14] of molecular imprinting can be stated as the process of template-induced formation of specific recognition sites in MIPs where the template directs the positioning and orientation of the structural components via cross-linking agent or electropoly-

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merization, followed by the elution of template to leave cavities which are complementary with the template molecules in the shape, size and steric configuration. The essentials of MIT include (1) Functional monomers binding to template molecules and providing recognition sites after elution; (2) Cross-linker fixing the template-monomer interactions by trapping them in a highly cross-linked polymeric matrix; (3) Initiator. In the process of forming a polymer, initiators (light, electricity, heat etc.) are usually required to initiate the polymerization process; and (4) Elution. The templates are removed from the polymer matrix by elution to leave the binding sites which specifically recognize template in shape and size, etc.

Based on the interaction between the functional monomer and the template molecule, researchers put forward three kinds of polymer binding modes. The first one is reversible covalent interaction mode proposed by Wulff[3]. The functional monomer and the template molecules are combined with reversible covalent bond. Due to the stable covalent bond, the formation of MIPs is more stable, which produces uniform imprinting cavities on the binding sites, and also leads to the difficulty of elution and recognition. The second mode is noncovalent interaction mode suggested by Mosbach[4]. Monomer and template molecules are combined through hydrogen bonds, van der Waals force and π bond, which thus reduces the difficulty in elution of template molecule and speeds up the response time. The last mode was semi-covalent interaction method. A new method of molecular imprinting for compounds with single (or spatially separated) hydroxyl groups was described by Whitcombe[15], which involved covalent attachment during the imprinting (polymerization) step, but gave rise to a noncovalent recognition (binding) site. It enhanced the stability of the molecularly imprinted polymer and speeded up the response time. Using this strategy, a MIP for cholesterol was successfully prepared.

1.1.3 Features and application of MIT

Molecular imprinting, as discussed above, is a method of creating synthetic polymers with bio-mimetic molecular recognition capability for the templates. In general, MIT has the following features. (1) Conformation reservation. The pre-polymerized complex is supposed to determine the formation of an imprinting of the template which is then achieved by "freezing" in the structures that result from molecular self-assembly and polymerization; (2) Recognition specificity. A rigid spatial structure of MIPs is formed by the interaction of monomers, cross-linking agents and template. After elution of template, the polymer cavity has the sites specifically binding to the template molecules, similar to antigen-antibody interaction; (3) Environmental tolerance. The rigid structure of the polymer has decided that it has excellent resistance to environmental factors, such as acidity, high temperature, etc.; (4) Reusability, low cost and high stability. All these features have laid a solid foundation for the application of MIT in the fields of biomimetic sensors[16,17], targeting drug deliver[18], mimic enzyme[19,20], solid phase extraction[21,22] and so on. However, organics[23–27], metal ion complexes[28,29] and other small molecular compounds were often used as templates in the application of MIT. But the application of MIT in the recognition of biological macromolecules such as proteins, DNA, viruses is in the primary research stage. Therefore, it is necessary to make a greater breakthrough based on existing application of molecular imprinting in biological macromolecules.

1.2 Introduction of biological macromolecular imprinted technology

Biological macromolecules[30] refer to the organic molecules that have biological activity in vivo and their molecular weights reach to tens of thousands Da or more. Most of the biological macromolecules are made of simple biological molecules. For example, the unit of the protein is amino acids, and the nucleotide is the basic unit of the nucleic acid. Proteins, nucleic acids and polysaccharides are three main categories of biological macromolecules, whose molecular structure and physiological functions vary greatly. However, they exhibit common in the following aspects. Inside living cells, the conversion between biological macromolecules and small molecules is completed commonly through dehydration condensation or hydrolysis reactions. Furthermore, protein chain (peptides), nucleic acid chain and sugar chain typically has directivity, although in different ways. Simultaneously, biological macromolecules have respective typical advanced steric structure. Proper steric structure is the premise for biological macromolecules to perform their function. With the rapid development of biomedicine and proteomics, the detection of proteins and other biological macromolecules has also been a great concern. To establish a fast, simple, specific and high throughput detection approach for biological macromolecules has become one of the research focuses of analytical science. In 1991, Arnold[31] firstly prepared the surface molecularly imprinted polymers which could achieve the molecular recognition of the imidazole compounds. Up to now, the application of MIT in detecting protein[16,32,33], DNA[34–37], cell[38,39] and virus[40,41] is one of the main research fields of MIT. The number of related literatures published each year rose rapidly. According to Web of Science statistics, the amount of relevant literatures published each year increased from 10 in 1996 to 100 in 2014.

Compared with the small molecular imprinting, the bio-macromolecular imprinting technique has more difficulties and challenges. First of all, the elution and recognition of template molecules is the primary issue in the bio-macromolecular imprinting technology. Currently, strong