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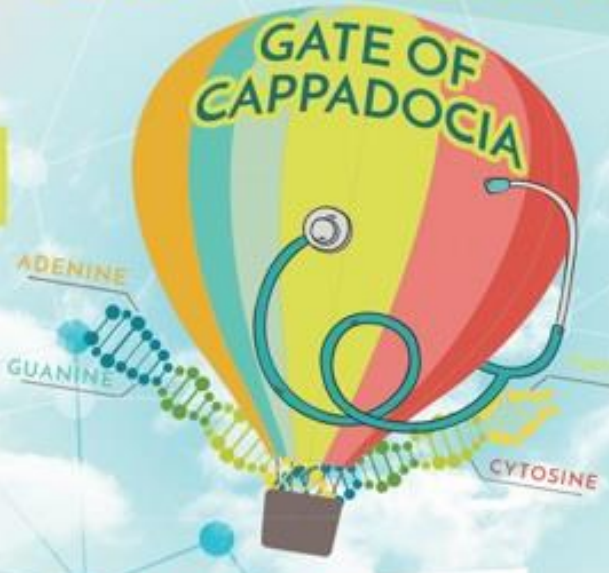

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ORAL PRESENTATION

Development of Molecular Imprinting Technology and The Effective Use of Molecular Imprinted Polymers

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Abstract

Highly selective molecules used for antibodies or enzymes have great importance in chemistry, diagnosis and biology. However, the production of these natural receptors is difficult and expensive. Their longevity and applicability are also limited. Molecular imprinting technique (MIT) has been developed to overcome these limitations. The functional groups of the polymerizable monomers are combined with the template molecule to enable the desired selectivity. After polymerization in the presence of cross-linkers, template molecules in the polymer are removed to obtain molecularly imprinted polymers (MIPs) recognizing the size, shape and surface chemistry of the template molecule. Polymers that are selective to template molecule are cheaper, simpler and more durable than their counterparts. Polymers with different properties can be produced using a wide variety of monomers. MIT development has been ongoing for over 30 years and it's an effective method for preparing synthetic molecular recognition systems with similar binding properties like natural antibodies. MIPs used as initial separation methods are polymers, synthetic enzymes, biological receptors and biosensors with catalytic activity under the influence of progressive studies and technological developments. MIT can be adapted to the Enzyme Linked Immunosorbent Assay (ELISA), an immunological assay based on antibody-antigen interaction. MIPs are used in drug development studies, drug delivery and medicine as biomimetic antibodies. In our study, we showed that MIP imprinted against template molecule, can bind its target molecule in *in vitro* cell culture assays and can also be used in an ELISA.

Keywords: Molecular Imprinted Polymer, Biomimetic Antibody.

1. Introduction

MIPs have gained importance due to their wide applications in chemical sensing, separation, drug delivery, and extraction [1]. In the presence of template molecule, MIPs can be synthesized by co-polymerization of functional monomers and cross-linkers. The cross-linkers have function of stabilizing the binding sites after removal of the template molecule and forming recognition cavities for MIPs to detect similar molecules [2]. MIPs have important properties, such as specific recognition and high stability at high temperatures, compared to other analysis techniques [3]. In antibody-antigen interactions, , the antibody recognizes an epitope of the antigen [4–6]. The use of commercially available antibodies for isolation and purification is quite expensive and difficult to store for long periods [7]. MIPs obtained by the polymerization process around the surface of template molecule with the cross-linker can perform an antibody-like function after template molecule has been removed and recognize the same molecule using specific binding sites [8]. MIPs can now be used in a wide range of applications, such as separation (e.g., chromatography, capillary electrophoresis, solid-phase extraction, and membrane separation, etc.), immunoassays, antibody mimics, artificial enzymes, (bio)sensors, catalysis, organic synthesis, drug delivery and drug development [1].

2. Materials and Methods

Materials

Template Molecules

The purpose of molecular imprinting is to produce MIPs with affinity and specificity that are comparable to those of biological receptors, and ultimately alter these biological entities in real applications. An ideal template molecule should contain functional groups that do not inhibit polymerization, exhibit excellent chemical stability during the polymerization reaction and contain functional groups capable of complexing with functional monomers [2]. MIPs have recently been successfully applied for the identification and detection of various small organic molecules. In addition, large structured species such as viruses and cells have also been reported for MIPs [9–12]. However, great challenges remain for imprinting of proteins and other bio-macromolecules [13, 14].

Functional Monomers

Functional monomers providing functional groups have a role in forming a pre-polymerization complex with the template molecule. Therefore, it is important to select suitable functional monomers which can interact strongly with template molecule and may form specific donor-receptor or antibody-antigen complexes prior to polymerization [1]. Among the functional monomers, methacrylic acid (MAA) has been used as a functional monomer because of its hydrogen bonding, receptor properties and its dimerization modestly increases its imprinting effect [15]. It was also shown that high molar fractions of MAA will result in large pore size of the polymeric materials and further enhance the binding capacity of the polymers [16].

Cross-linkers

In polymerization process, cross-linkers are used to fix the functional monomers around template molecules, so that even after removal of template molecules, a highly crosslinked solid polymer is formed. The amount and type of cross-linker has a significant effect on selectivity and binding capacity of MIPs [17].

Solvents

The fluorogenic solvents generally act as dispersing media and pore forming agents in the polymerization process therefore play an important role in polymerization. Generally, the solvents used for the MIP synthesis are 2-methoxyethanol, methanol, tetrahydrofuran (THF), acetonitrile, dichloroethane, chloroform, N, N-dimethylformamide (DMF) and toluene [18].

Initiators

Most MIPs are widely prepared by free radical polymerization (FRP), photo-polymerization and electro-polymerization. FRP can be thermally or photo-chemically initiated for various functional groups and templates. As well as peroxy compounds, azo compounds are also widely used as initiators. One of is the azo compound is azobisisobutyronitrile (AIBN), which is optimally used at decomposition temperatures around 50-70 °C. In order to achieve the polymerization reaction, it is very important to remove dissolved oxygen from polymerization solutions prior to proliferation. Cleaning the oxygen can be achieved by bubbling an inert gas such as nitrogen or argon [1].

Preparation of MIPs

Molecular imprinting is carried out by polymerization of functional monomer around the template molecule in the presence of cross-linker [17]. First, template molecule-monomer complex is obtained by using different molecular imprinting technologies between selected molecule and complementary functional monomers [19]. After the polymerization reaction around the complex, template molecule is extracted and as a result, the three-dimensional polymer with complementary binding sites is obtained with the geometry and position of template molecule functional groups. In the production of MIPs, two main methods are usually used based on covalent and non-covalent interactions between template molecule and functional monomers. Covalent imprinting provides the formation of functional monomer residues in the imprinted cavities. However, covalent imprinting is considered to be a less flexible method because of its limited reversible reactions. In addition, the strong covalent interactions result in slow binding and dissociation, making it difficult to reach the thermodynamic equilibrium [20]. Non-covalent imprinting may occur by ionic interactions, hydrogen bonding, van der Waals forces and π-π interactions. The most common non-covalent interaction is the hydrogen bonding between MAA groups and primary amines in non-polar solvents [21]. Recently, non-covalent imprinting has become the most popular synthesis strategy due to its ease and quickness of binding and extraction.

Characterization Methods

Morphologic properties of MIPs are widely studied by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). In addition, atomic force microscopy (AFM) and various fluorescence techniques are also used for the characterization of thin film MIPs. However, there has been a recent trend in spectroscopic studies of ligand-MIP interactions [1].

3. Results and Discussion

In this study, fundamentals of MIPs are summarized briefly and production processes are emphasized. Solid phase extraction (SPE) is widely used for MIPs called molecular printed SPEs. Molecularly imprinted SPE absorbers are available in a variety of forms such as cartridges, discs, SPE pipette tip, 96-well SPE microtiter plates [22]. Solid phase micro extraction (SPME) is widely used for sample preparation in analytical laboratories due to its simple, solvent-free and short-term results. Stir bar sorption extraction (SBSE) derived from SPME has a similar extraction mechanism

like SPME. SBSE has some advantages as high enrichment factor, reproducibility, high adsorption capacity and solvent-free and has been applied in environment, food and biological samples [23, 24]. In addition to their wide application areas in pre-treatment techniques, MIPs are also used as stationary phases in chromatography techniques such as HPLC [25], capillary electrochromatography (CEC) [26] and capillary LC (CLC) [27]. On the other hand, similar tests have been developed with enzyme-linked immunosorbent assay (ELISA) by coating microplate wells with MIPs [28]. MIP-based sensors are first proposed by Mosbach for specific binding of vitamin K_1 to the silicon surface by surface-imprinting method and using an optical surface ellipsometry [29]. In addition, MIP-based sensors can be developed by designing and preparing MIP particles or films. MIPs are widely applicable but their high volume production and large-scale applications are rarely reported. For these reasons, computational and combinatorial tools are required for synthetic MIPs.

5. Conclusion

This study shows that molecularly imprinted polymers can be used in chemical detection, separation, drug delivery and extraction applications. In addition, MIPs can be used in pseudo ELISA assays however further investigation is needed to produce high volume and large scale of MIPs.

Acknowledgements

This work was supported by the Scientific and Technological Research Council of Turkey (TUBITAK) (project no: 115S224)

Conflicts of Interest

There is no conflict of interest

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