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The Preparation of Molecularly Imprinted Polymers and the Application in Pharmaceutical Analysis

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Abstract. Molecular imprinting technology (MIT) is an artificial method for preparing polymers with specific recognition of target molecules. Molecularly imprinted polymers (MIPs) have been widely used in electrochemical sensors due to their simple preparation, good stability, and molecular recognition function. Especially in drug analysis, MIPs-based electrochemical sensors have become a research hotspot. Therefore, this work focuses on MIPs-based electrochemical sensors. The performance of MIPs is closely related to their preparation methods. In this work, the preparation methods of MIPs are discussed in detail. This work also discussed MIP-based electrochemical sensors. MIP-based electrochemical sensors have achieved accurate detection in flavonoid and antibiotic drugs. Meanwhile, as a polymer, MIPs can also have an impact on the conductivity of working electrode. Therefore, it is necessary to choose some nanomaterials with excellent conductivity for its modification. In the future, molecular imprinting technology will have more applications in electrochemical sensors. In drug analysis, more imprinting targets should be explored for detection by using this technology.

Keywords: Molecularly Imprinted Polymers; Detection; Pharmaceutical Analysis.

1. Introduction

Antibodies are produced against various foreign bodies. There is specific recognition between antibodies and antigens. However, such antibodies have several problems, including the requirement of good storage conditions, high cost of production, and low sensitivity [1]. To overcome these problem, molecularly imprinted polymers (MIPs) are explored as substitutes. MIPs are artificial polymers which have human-made binding sites on polymer matrices that is complementary to the size, shape, spatial arrangement and functional groups of the template [2]. Various ways have been invented to produce MIPs. These methods involve different raw materials and procedures. According to different situations, a suitable method would be chosen to produce MIPs.

The main mechanism of MIPs is lock and key. They are said to be sorbents that can selectively extract target molecules by this mechanism, which is similar to the natural biorecognition [3]. This makes MIPs selective and specific to target substance. MIPs also have many advantages. Apart from providing specificity and selectivity, the cost of the production of MIPs is relatively low. In addition, they can be stored for an unlimited period. Moreover, they can keep their function over a wide temperature range [1]. Apart from the above-mentioned advantages, there are some issues in MIPs. The properties of the binding sites can be affected by the structure of the binding sites. Moreover, the adsorption capacity is influenced by the ratio between the total mass and the number of the polymer. In addition, the availability of binding sites has a significant impact on adsorption capacity. Besides, if the pores on the solid are not kept open and continuous, the monolithic MIPs cannot be maintained, resulting in the aggregation of MIPs. There are also other limitations. The size of the pores which are not constrained may limit the target molecule enter the MIPs, leading to low adsorption capacity [4].

Considering some special properties MIPs have, they can be used with sensing technology. While applying electrochemical sensors to analyze complex organics, MIPs can be used as MIP-electrode to capture free drug from the microenvironment in the presence of electrochemically active drugs [4]. This is due to the specific binding sites MIPs have, which could enable them to selectively bind with

target molecules. In addition, compared with metastable protein affinity molecules, MIPs are more reusable, which is a great significance for electrochemical sensors.

This study will introduce some methods for producing MIPs. Meanwhile, MIPs combined with sensors and their applications in pharmaceutical analysis are also outlined.

2. Preparation

There are numerous cavities in MIPs that can be specifically identified by the target object. Therefore, the key to preparing MIPs is to form such cavities. The preparation process requires templates, monomers, and cross-linking agents [5]. The size, formats, properties and the thermal stability of a desired MIP should be wisely considered. Based on these factors, an appropriate preparation method can be selected [3]. Until now, there are many polymerization methods for producing MIPs. These methods are used in different situations, and they have some drawbacks at the same time.

2.1. Bulk Polymerization

Conventional MIPs are synthesized by bulk polymerization [6]. Bulk polymerization is simple and effective, and the desired sizes of MIPs can be achieved by sieving. At the beginning of the production, a pre-polymerization complex is produced by forming non-covalent interactions between the template and the functional monomer. After this, the cross-linker and the initiator are added in an appropriate solvent. To ensure that the final polymer has specific properties, the ratio of the cross-linker and the initiator needs to be explored. If the cross-linkers are insufficient, the stability of MIPs will be decreased. Meanwhile, the functional monomers will fall off. If the cross-linkers are in excess, there would be a reduction in the number of recognition sites of MIPs, decreasing the binding efficiency. Then, the polymer is synthesized after deoxygenating, degassing and photoinitiation or applying heat. To apply MIPs with suitable size, they need to be grained and sieved at the end of the whole procedure. However, this method has some disadvantages. A major problem is that the polymers produced have irregular shapes, leading to lower recognition capacity [3]. Another one is that the amounts of templates needed is extremely high [7]. This would cause economically inefficient if expensive template is used. Also, it is time-consuming for completing the whole procedure, and the yield of useful products is moderate [8].

2.2. Precipitation Polymerization

Another method for forming micro- or sub-micrometer MIP beads is precipitation polymerization [3]. It is a one-step way of production, so it is relatively simple. Compared to bulk polymerization, this method requires a greater volume of polymerization solvent. Due to the low solubility of polymeric beads in the dilute homogeneous monomer solution, these beads can settle out from the solution. It is worth noting that precipitation polymerization is mainly used to prepare polymeric beads with high-quality and does not require stabilizers or surfactant [9]. This method can improve the problem shown by bulk polymerization to some extent, which is the irregular shape of the final polymer. But it still has some disadvantages. The excessive use of pore forming agents is a primary problem, as well as the high consumption of template.

MIP beads with uniform size can be produced by suspension polymerization [3]. This is achieved by using insoluble or partially soluble monomers. The MIPs prepared by the previous two methods exhibit high recognition properties. For the as-prepared MIPs, the proportion of cavities in the body is high. The target molecule needs to diffuse into the interior of MIPs to bind with the cavity. This greatly limits the adsorption capacity of MIPs. Therefore, achieving uniform size during preparation is necessary. By using suspension polymerization, the problem can get improved by grafting the MIP layers onto the surface of the synthesized beads, which can be a major benefit of this method. Simultaneously, this method has some drawbacks. For example, the final products will have fewer binding sites, because of the aqueous dispersing agent and water [10]. As a result, the reaction kinetics between the functional monomer and the template might be delayed.

2.3. Surface Imprinting

Surface imprinting is also an effective method for preparing MIPs. At the beginning of the procedure, pre-polymerization complexes are produced by template and functional monomers [3]. Afterwards, with the help of initiators and the cross-linking agents, a imprinted layer formed on the surface of the solid substrate. By using physical or chemical methods, templates would be tapped out from the polymeric layer, and the three-dimensional cavities can be formed on the solid substrate [9]. This method is often conducted on support beads and used for depositing imprinted polymers. The final imprinted polymers would be imparted with the shell. This can be simply explained as the polymerization between the template and the monomer on the support beads, leading to an MIP shell on the core support material. Some examples of the support materials are polystyrene and chitosan.

Surface imprinting has many attractive advantages. Firstly, this method can be easily operated, and the size and the shape of the product can be controlled while using this method [11]. In addition, the product produced by this method would have large surface area with significantly selective binding sites [11]. Besides, the product is more reproductive and sensitive if this method is used [12]. There are some limitations of this method. One main problem is that after being repeatedly used, the MIPs thin-film may peel off [3]. Also, it is hard to control the thickness of the film. Surface imprinting can be applied in many cases. It can be used to imprint macromolecules, such as proteins, cells and viruses.

2.4. Selection of Methods

While choosing suitable methods for producing MIPs, several factors are needed to be considered. When MIPs are used as electrode modification materials, the formation of a thin film on the electrode surface by MIPs is beneficial for achieving efficient detection. Besides, the cost, the requirement for solution stability, and the unique manufacturing process should be taken into account. Therefore, the method for the production of MIPs should be chosen wisely [13].

3. MIP-Based Electrochemical Sensor

MIPs can be applied with sensors to detect specific molecules. These MIP-based sensors can analyze the contents of drugs, which is due to their selectivity provided by the unique binding sites. There are many types of MIP-based electrochemical sensors for analyzing small drugs.

MIPs can be used to modify potentiometric sensor. The working principle of the sensor is that the interaction of the target object and the modified ion-membrane. This interaction leads to the potentiometric response. In classical designs, it is preferred to conduct reversible monitoring through an internal reference electrodes or solutions. The chemical selectivity can be given by ion exchange agent. These agents will be incorporated to set up binding equilibrium [4]. The incorporation of MIP offers a distribution ability which is similar to that of ion exchange agent. At the interface of the membrane, the charge will separate which is caused by differential ion or counter ion partitioning. To avoid background drift, a highly stable reference electrode is required. It is worth noting that at low levels of concentration, a high concentration resolution can still be achieved, which is concluded from the log linear nature of the output values. This might be appealing for drug analysis at low concentration. However, in the case of non-specific ion binding and exchange, a wrong electromotive force can still be drawn. Besides, there are many possible structures of MIPs. In potentiometric sensors, the structures other than molecularly imprinted membranes are also worth exploring. Exploring other preparation methods of MIPs may help improve the performance of potentiometric sensors.

Electrochemical sensors are a simple and convenient analytical tool with high sensitivity, good selectivity, and the ability to achieve real-time detection. Constructing an electrochemical sensor using molecularly imprinted membranes as sensitive recognition elements can significantly improve the selectivity of the electrochemical sensor. There have been reports of applying this technology to the determination of flavonoid compounds in drugs. Natural flavonols are the main active ingredients in drugs for treating cardiovascular and cerebrovascular diseases. Most plants contain these

compounds in their roots, stems, and leaves. Due to the high structural similarity of natural flavonol compounds, traditional separation methods are complex and time-consuming. According to previous reports, using MIT in electrochemical sensor to detect flavonoid drugs can overcome these difficulties.

The abuse of antibiotics can cause drug residues and accumulate through the food chain, affecting human health. Therefore, developing fast and specific antibiotic sensors has important practical significance. The molecularly imprinted polymers which are obtained through molecular imprinting technology have good recognition function and specific recognition effect on the analyte. Therefore, MIP-based electrochemical sensors have attracted much attention in antibiotic detection. There are reports of using MIP combined with graphene to modify glassy carbon electrodes (GCE). By using this new type of working electrode, indomethacin (IDMC) can be detected accurately. In addition, electrochemical aptamer sensors based on molecular imprinting technology have also been reported for the detection of Amoxicillin (AMOX). By using gold nanoparticles and graphene to modify the working electrode, the effect of MIPs on electrode conductivity could be improved effectively.

4. Conclusion

MIP is a type of polymer with specific recognition ability. Its structure is closely related to the preparation method. Therefore, this work provides a detailed discussion on the preparation method of this material. MIPs materials can be used in electrochemical sensors to form MIP-based electrochemical sensors, thus improving the recognition ability of target molecules. This method is very useful for the detection of drug components, especially for trace drugs. Meanwhile, MIP itself would have an impact on the conductivity of the working electrode. Therefore, it is necessary to select some nanomaterials with excellent conductivity for modification. In the future, in-depth research on this topic is highly valuable. This work will contribute to the application of MIP-based electrochemical sensors in promoting drug analysis.

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