Application of Magnetic Molecular Imprinted Technology in Fluoroquinolone Antibiotics

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Abstract. Fluoroquinolone antibiotics (FQs) have a good bactericidal effect on a variety of bacteria, and are widely used in the treatment of various diseases. Due to the low residue and high stability in foods and water environment, it is difficult to detect FQs. Magnetic molecular imprinted technology (MIT) is specifically used for detection and identification, and magnetic molecular imprinted polymers (MIPs) are obtained by combining modified magnetic materials with polymers with specific molecular recognition cavities, which not only improves the ability to select and recognize specific template analogs, but also enables rapid separation. This review summarizes the research progress of MIPs with natural magnetic materials, magnetic nanomaterials and magnetic molecular sieve materials as carriers according to the cost, points out the advantages and current problems of each magnetic material, and describes the current status and development prospects of magnetic MIPs.

1. Introduction

Fluoroquinolone antibiotics (FQs) are a class of broad-spectrum antibiotics, whose working principle is to inhibit bacterial DNA replication, and commonly used for treating and preventing bacterial infections in clinical and veterinary applications. Since most FQs are stable in various light, temperature, and pH conditions, and such structures determine the strong interaction with natural organic matter, as well as the adsorption on soil, their long-term accumulation poses risks to the environment[1].

Various measures have been studied to solve this problem, such as photo-degradation[2], and membrane separation[3]. Because of their low residual quantities in foods and water environment, FQs are difficult to detect. Molecular imprinted technology (MIT) for specifically identifying has become a particularly suitable detection method. Molecularly imprinted polymers (MIPs) have strong stability, specific adsorption capacity, high sensitivity, and lower preparation cost, as well as the ability for reusing multiple times, so they have attracted more and more attention.

Since MIPs have no fixed shapes and strong dispersibility, they are not conducive to recycling. They can be easily used after being fixed on the carrier. Ordinary carrier can only play a supporting role, but in practical applications, MIPs are usually used as adsorbents for magnetic solid phase extraction (MSPE) to enrich, purify and separate actual samples. This usually requires suction filtration or centrifugal separation steps, and the operation is relatively time-consuming and complicated. Therefore, it is impossible to achieve rapid separation and continuous production when common carriers are connected to MIPs. Due to unique properties, magnetic materials can be easily and quickly separated from the system under the external magnetic field, which makes them ideal carriers for MIPs[4]. This review...
briefly introduces the principle and research progress of magnetic MIPs, compares the advantages and disadvantages of different magnetic materials, and prospects the development trend.

2. Basic principles of magnetic MIT

Figure 1 shows the preparation and application processes of magnetic MIPs. The main preparation process is to use template as the central substance to connect functional monomers to build the polymer, and then add cross-linking agents to enhance the rigidity and stability of the polymer. The obtained polymer is mixed with magnetic material whose surface is modified with active groups. Finally, the template is repeatedly eluted through the solvent, leaving active cavities with specific sizes and shapes, and the specific magnetic MIPs used to form an electrochemical sensor are separated under the external magnetic field. Magnetic MIPs possess both rapid magnetic separation and molecular recognition properties. The interaction between the functional monomer and the template is divided into three types: covalent, non-covalent and coordination. The difference between covalent and non-covalent effects is mainly whether a covalent bond or a non-covalent bond is formed. The common main non-covalent interactions are usually hydrogen bonds, ion pairs, van der Waals forces, electrostatic and π-π interactions. Coordination is a special kind of covalent bond, and the shared electron pair is provided by one of the atoms alone[5].

![Figure 1](image-url)  
Figure 1 (a) preparation process of magnetic MIPs, (b) application of magnetic MIPs.

3. Application of magnetic MIPs in FQs

At present, there are many examples of using magnetic materials as imprinted molecular carriers, mainly because of the large surface areas and magnetic effects, which greatly enhances the specific adsorption and resolution of MIPs[6]. According to the cost, it is generally classified as natural magnetic materials, such as Fe₃O₄, natural carbon materials, and synthetic materials, such as nanomaterials, molecular sieves.

3.1. MIPs with Fe₃O₄ as carriers

In order to reduce costs, the most ideal magnetic carrier is the natural magnetic material. Fe₃O₄ particles become the first choice, due to the paramagnetic characteristics. When Fe₃O₄ particles are encapsulated inside the MIPs, the resulting polymers can have magnetic sensitivity characteristic and be easily separated from other substances under the external magnetic field[4]. Huang et al.[7] used the fluorinated compound (nonylfluorohexyl acrylate) and the boron-containing compound (1-vinyl-3-octylimidazolium tetrafluoroborate) as the functional monomers to modify the surface of Fe₃O₄ to synthesize a novel magnetic adsorbent for extracting FQs by means of fluorophilic and B-N coordination interactions in water environment and milk samples. In order to enhance the stability of the carrier, they introduced phenyl groups that could produce π-π interaction with FQs, and selected cross-linking agents. The detection results indicated good linearity within the studied concentration range and low limits of detection (LOD) was 0.0049-0.016 μg/L for water samples and 0.010-0.046 μg/kg for milk samples, respectively. The recoveries of different fortified concentrations were in the ranges of 80.1-
120% and 78.9-119% for water and milk samples, respectively, and the relative standard deviations (RSD) for reproducibility were all below 11%, which reflected the high sensitivity and satisfactory precision. Because Fe₃O₄ particles are hydrophilic substances, and MIPs are lipophilic substances, their binding ability is not strong, and there are few sites for MIPs, which limits their practical application.

3.2. MIPs with natural materials/Fe₃O₄ as carriers

Pomelo peel (PP), which can be used as the efficient natural adsorbent, belongs to a kind of biochar, mainly composed of cellulose, hemicellulose and lignin[8]. Making PP into MIPs can increase adsorption and separation ability. Huang et al.[9] used PP to obtain MSPE adsorbent by one-pot synthesis method. Parabens and FQs were used as templates to study the extraction performance of magnetic adsorbent under different conditions in environmental waters. They combined PP and Fe₃O₄ to produce a strong magnetic carrier, and used ethylenediamine to modify it to fix MIP, which could reduce its encapsulation rate. The results indicated that under the optimal extraction conditions, adsorbent showed satisfactory extraction performance for the two templates, and LOD for parabens and FQs were in the ranges of 0.011-0.053 μg/L and 0.012-0.46 μg/L, respectively. The spiked recoveries were in the range of 76.6-116% for parabens and 80.2-114% for FQs with RSD less than 10%, which showed good repeatability. Kaolinite is an inorganic layered silicate mineral composed of silicon-oxygen tetrahedron and aluminum-oxygen tetrahedron with the performance of low cost, non-toxic and high adsorption[10]. Mao et al.[11] synthesized the special magnetic MIP with FQ as the template and amino-modified kaolinite as the carrier. They found that it had strong stability and paramagnetic properties, and a larger adsorption capacity (89.36 mg/g) and better recognition ability. In order to improve the stability of MIPs whose carriers are made of natural magnetic materials, cross-linking agents and salt substances (such as NaCl) are usually added or they are stored and used under optimal conditions (such as pH and temperature). In order to graft more MIPs to the natural magnetic carrier, it is usually modified with SiO₂ and ethylenediamine, etc., so that the surface of carrier has more binding sites. Although these methods can improve the performance and reduce costs, the modified surface of carrier still has a few active sites for more MIPs.

3.3. MIPs with nanomaterials/Fe₃O₄ as carriers

Nanomaterial refers to the size of its structural unit ranging from 1 nanometer to 100 nanometers. Due to its particularity of self-organization and scale, it has many peculiar characteristics, such as magnetic, electrical conductivity and large specific surface area. Graphitic carbon nitride (g-C₃N₄) nanosheets, typical layered materials, have found application in many fields because of the distinctive electronic structure and excellent properties[12], which is helpful for improving performance for FQs. Wu et al.[13] proposed g-C₃N₄/Fe₃O₄/MoS₂ by hydrothermal method used as the adsorbent for MSPE for six FQs in chicken and eggs. Studies showed good linearity in the range of 2-300 μg/L, the correlation coefficient of determination ranging from 0.9993 to 0.9997 and good spiked recoveries over the range of 89.3–99.6%. The LOD was 0.5 to 2.0 μg/L, the limit of quantification (LOQ) was 1.7 to 6.7 μg/L, and RSD was less than 4.5%, which showed that the adsorbent had high analytical potential of preconcentration and determination of FQs. Cellulose nanocrystals (CNCs) are made from pulp fine cellulose fibers through an acid hydrolysis process, which are low cost, renewable and degradable. Different acid treatment methods can confer different active functional groups on the surface of CNCs, making CNCs ideal molecular carriers[14]. Ouyang et al.[15] synthesized magnetic carboxylated CNCs (M-CCNs) as carriers and combined them with MIP comprising amine moieties for extracting FQs. Adsorption experiments showed that the maximum adsorption capacity of M-CCNs@MIP after 2 minutes and 20 minutes was 34.09 and 40.65 mg/g, respectively, which was much higher with rapid equilibration time than the unimprinted polymer. In addition, the selective adsorption experiment showed that the spiked recoveries of seven FQs were between 81.2 and 93.7%, RSD was in the range of 0.6–7.5%, and LOD was between 5.4 and 12.0 ng/mL, which indicated that the selective adsorption had enhanced. After multiple uses, M-CCN@MIP could still maintain good selection performance. Compared with natural magnetic carriers, in terms of encapsulation of MIPs, the structure of the nanomaterial itself determines
that it can generate more active sites, so that MIP can be more widely dispersed on the carrier, and it is possible to avoid large-scale aggregation of MIPs. This will promote the exposure of effective active sites on MIPs, thereby improving adsorption performance. In terms of stability, due to the strong conductivity and stability of nanomaterials, when combined with MIPs, the electronic distribution of the entire system will be evenly dispersed, and the system itself will become more stable.

3.4. MIPs with molecular sieve/Fe₃O₄ as carriers
Molecular sieve is a system of pores and cavities with molecular sizes (usually 0.3~2 nm) formed by silicon oxygen tetrahedron or aluminum oxygen tetrahedron connected by oxygen bridge bond, which is a good choice for selective adsorbent. Chen and Chan et al. [16] combined solvothermal and self-assembly methods to produce magnetic molecular sieve material (Fe₃O₄@MCM-48), which was used as the adsorbent for eight FQs in food and drinking water samples. They found that the FQs detection system had good linearity (R² > 0.99) for concentrations of 5 to 1000 ng/L. LOD was ranging from 0.7 to 6.0 ng/L, LOQ was in the ranges of 2.5-20.0 ng/L and the repeatability of water samples was satisfactory (RSD <10%, n = 6), which showed sensitivity, precision, and accuracy of the adsorbent.

Since MCM-48 is a unique mesoporous molecular sieve material with highly interwoven and branched structure, its regular pore network should provide more favorable mass transfer kinetics. When it is used as a carrier, this unique mesoporous feature can effectively control the sizes of the connected MIPs, fundamentally avoid the possibility of MIPs aggregation, and at the same time completely expose the cavities of MIPs, thereby enhancing the adsorption performance of MIPs. We can also use this special function of molecular sieves to screen out substances that may interfere with the binding of MIPs to templates, thereby improving the accuracy of MIPs. However, due to the high cost of synthetic molecular sieve, it is still limited in some applications.

4. Conclusions and perspectives
Magnetic carriers can not only support MIPs, but also integrate dispersed MIPs for easy collection and reuse, and also improve the separation ability of MIPs, especially under external magnetic fields. Magnetic MIPs have good magnetic, electronic and selective adsorption properties. In general, the active sites on MIPs are increased by modifying the surface of magnetic carrier, thereby decreasing the encapsulation rate of MIPs. This is because the unfixed MIPs usually gather together, and it is easy to block the cavity positions on the MIPs. Once the MIPs are fixed, the possibility of aggregation can be reduced. In this regard, the mesoporous materials perform best because it can control the sizes of the connected MIPs. Nanomaterials perform well because there are many active sites on the surface that can connect with MIPs. The performance of natural magnetic materials is the worst, because there are a few grafting sites for connecting MIPs, which increases the possibility of self-aggregation of MIPs. The stability of magnetic MIPs is usually achieved by adding cross-linking agents and salt substances or controlling external storage and use conditions. These advantages can make magnetic MIPs have application prospects in many fields, but due to the cost and performance problems of magnetic materials, they are still in the experimental state. In order to put it into use as soon as possible, we should consider how to modify natural magnetic materials at low cost to increase the active sites of MIPs, improve stability and exposure, and then increase the adsorption capacity, and how to modify the surface of magnetic materials to increase the function of magnetic MIPs and broaden applications.

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