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Luminescent molecularly-imprinted polymer nanocomposites for sensitive detection

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ABSTRACT

Molecularly-imprinted polymer nanocomposites (MIP-NCs) have been widely employed to produce stable, robust and cheap materials with specific binding sites for recognition of target molecules such as proteins, drugs, pesticides and explosives. MIP-NCs with luminescent properties possess intrinsic capability as signal transducers with excellent molecular recognition properties. The exploration of luminescent and magnetic MIP-NCs with high-specificity affinity toward analytes has great significance for clinical diagnosis, environmental analysis and homeland security. Here, we summarize the novel approaches to fabrication of luminescent MIP-NCs and their recent applications in sensing.

Contents

Abbreviations: AA, Acrylic acid; Ant, Anthracene; AM, Acrylamide; APTS, 3-aminopropyltrimethoxysilane; BHb, Bovine hemoglobin; Bis, *N,N′*-methylenebis(acrylamide); Cbz-L-Phe, *N*-carbobenzyloxy-L-phenylalanine; cGMP, Cyclic guanosine monophosphate; DNase I, Deoxyribonuclease I; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; EDMA, Ethylene glycol dimethacrylate; EGDMA, Ethylene glycol dimethacrylate; FRET, Fluorescence resonance-energy transfer; HEMA, 2-hydroxyethyl methacrylate; HRP, Horseradish peroxidase; MAA, Methacrylic acid; MIP, Molecularly-imprinted polymer; NC, Nanocomposite; NIPAm, *N*-isopropylacrylamide; PAH, Polycyclic aromatic hydrocarbon; Per, Perylene; Phe, Phenanthrene; Pyr, Pyrene; PPV, Poly(*p*-phenylenevinylene); RAFTPP, Reversible addition-fragmentation chain-transfer precipitation polymerization; St, Styrene; S/V ratio, Ratio of surface area to volume; TBAm, N-*tert* butyl acrylamide; TEOS, Tetraethyl orthosilicate; UCNP, Upconversion nanoparticle; VBIDA, N-(4-vinyl)-benzyl iminodiacetic acid; VP, 4-vinylpyridine; VPBA, 4-vinylphenylboronic acid.

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1. Introduction

Luminescent nanoparticles (NPs), including dye-doped silica [1], fluorescent quantum dots (QDs) [2], rare-earth-doped downconversion (DC) NPs and upconversion (UC) NPs [3–6], have been widely investigated for sensing and imaging in analytical chemistry, bioanalytical chemistry, biomedical engineering and environmental science. In order to endow the NPs with specific recognition ability for targeting imaging and selective detection, by mimicking the specific interactions occurred in nature, functional peptides, antibodies and DNA have been bioconjugated to the surface of luminescent NPs [7]. However, with respect to practical applications, those lacked high stability and cost effectiveness in manufacture. As an alternative to these recognition biomolecules, molecularly-imprinted polymers (MIPs) [8,9] are attractive, synthetic materials with specific recognition ability comparable to natural systems, which makes them promising candidates in construction of smart nanoplatforms by coating MIPs on luminescent NPs for applications [10], including recognition and separation of target molecules [11,12], biological and chemical sensors [13], catalysis and sorbent assays [14,15].

MIPs are similar to antibodies and biological receptors in their predetermined selectivity to detect particular analytes, while MIPs are more stable than their biological counterparts in harsh environments, such as mechanical stress, elevated temperatures and high pressures, due to their good mechanical, thermal and chemical stability [13]. Although traditional MIPs, usually with μm particles, are easy to prepare with low cost and are widely used, several disadvantages limit their applications, such as low binding capacity caused by the low ratio of surface area to volume (S/V ratio), difficulty in removing target molecules from binding sites after *in-situ* polymerization, and templates easily hindering each other [16].

With progress in nanotechnology, these problems can be solved by MIP nanocomposites (MIP-NCs), with particle sizes are down to 100 nm. Due to the smaller particle sizes, the S/V ratios are significantly increased and accordingly enable improved sensitivity, binding capacity and speed of response. MIP-NCs are therefore extensively utilized for constructing platforms for sensing and separation. Furthermore, MIP-NCs with luminescent properties possess intrinsic capability as signal transducers with excellent molecular recognition properties, and have the potential to enhance selectivity and sensitivity of sensor devices.

Generally, the conventional method for synthesis of MIPs is *in-situ* polymerization [Scheme 1 (i)]. Given that there is plenty of experience with this method and the handy components that could be used, luminescent MIP-NCs [17,18] could be achieved in the following ways:

1 using fluorescent monomers, basically following the synthesis route for preparing conventional MIPs, affording fluorescent MIPs;
2 copolymerization of luminescent nanomaterials, such as QDs, UCNPs, fluorescent dyes with functional monomers, cross linkers and template molecules [Scheme 1 (ii)]; and,
3 using pre-synthesized polymers together with templates to fabricate MIP-NCs, where the nanomaterials and templates are "fixed" by pre-synthesized polymers through chemical or physical methods, the so-called encapsulation method [19].

The first two methods involve using functional monomers and MIPs are obtained through polymerization. Such methods normally require excess amounts of templates during synthesis in order to ensure enough binding sites in the MIP-NCs. Also, the nature of the template, to a large degree, limits the choice of functional monomers, cross-linkers and initiators. For example, with a hydrophilic template, only those components with hydrophilic properties could be utilized.

The encapsulation method, is a rather novel way of fabricating MIP-NCs, and could avoid the drawbacks above.

Nevertheless, every method has its own pros and cons, and we discuss all the methods further in detail below. The progress of conventional MIPs in terms of preparation and applications was covered in several published reviews [10,13,20,21].

With respect to luminescent MIP-NCs, an emerging field, preparation and applications are rarely covered. In this review, we focus on recent advances in luminescent MIP-NCs in clinical diagnoses, environmental analysis and homeland security with representative examples (Table 1) and discuss the challenges for future research.

2. Synthesis of molecularly-imprinted polymer nanocomposites

2.1. *In-situ* polymerization

The conventional approach to synthesizing MIP-NCs is based on copolymerization of polymerizable mixtures, namely functional monomers, cross-linkers and templates, in the presence of an initiator (Scheme 1). The template molecule would form a complex with functional monomers bearing functional groups that are complementary to some structural moieties of the template. Then, the complex formed is polymerized, forming a porous polymer matrix. Besides covalent bonds, there are several weak interactions between templates and functional monomers, including hydrogen bonds, and dipole-dipole and electrostatic interactions, which help to hold template molecules in the polymer matrix. After removing the template by disrupting these covalent/non-covalent interactions, there remains a molecular memory of templates (target analytes) with the presence of cavities complementary to the template in size, shape and position of a certain group. Such cavities allow selective rebinding of analytes over other closely related molecules, so endowing the MIP-NCs with specific binding properties toward the analytes.

The luminescent MIP-NCs acquired through the *in-situ* polymerization method employed fluorescent monomers or incorporated luminescent NPs. The former approach requires use of fluorescent monomers, which limits the choice of monomers, since most of the monomers used are non-fluorescent. The latter effectively circumvents this problem by using luminescent nanomaterials, in some situations using nanomaterials with different functions. The second approach has been employed frequently in construction of luminescent MIP-NCs. However, as mentioned above, the drawbacks of *in-situ* polymerization are that excess amounts of template molecules are required in order to ensure enough binding sites in each nanocomposite. Also, the ratios of each component are tedious to optimize in order to obtain MIP-NCs with the desired properties.

2.2. *Encapsulation*

Multifunctional luminescent MIP-NCs can also be achieved through an easy encapsulation strategy (Scheme 2). The template, functional monomer, luminescent NPs and other NPs with different properties, such as magnetic NPs (MNPs), could be simultaneously incorporated into one nanocomposite through chemical methods or physical techniques. Following template removal, MIP-NCs are obtained and show potential as nanosensors for different applications. Unlike the conventional concept of preparing MIP-NCs through polymerization, this technique involves pre-synthesis of polymers, followed by fabrication of luminescent nanocomposites in the presence of templates. Such an encapsulation strategy has several merits. For example, it allows a wide range of templates. Previously, only hydrophilic templates could be used in preparing hydrophilic MIP-NCs, while hydrophilic MIP-NCs could be prepared with hydrophobic templates when using an amphiphilic polymer with an oil-in-water emulsion encapsulation strategy.