New materials for analytical biomimetic assays based on affinity and catalytic receptors prepared by molecular imprinting

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Biological molecules (e.g., antibodies, enzymes and receptors) have been widely used as specific recognition elements in analytical assays, from homogeneous assays to biosensors, for applications in healthcare, environmental monitoring and industrial-process control. Limited stability, and difficulty and high cost of production are their main drawbacks. Artificial receptors and catalysts prepared by molecular imprinting technology are valuable in replacing biomolecules for molecular recognition in these kinds of assay.

In this review, we describe the most recent developments in non-covalent molecularly-imprinted polymers (MIPs) to replace natural receptors in ligand-binding assays and biosensors. A key factor underpinning the most significant advances in this field is obtaining materials that improve the specific recognition and, at the same time, favor transduction.

Composites of MIPs and carbon nanostructures or inorganic nanoparticles combine the recognition properties of MIPs with the electrical, optical or magnetic properties of the nanomaterials, resulting in new imprinted nanoreceptors with great potential as sensing materials. We summarize various methods to blend MIPs with different nanomaterials and highlight their application in biomimetic assays.

Electropolymerized MIPs (E-MIPs) offer an option for integrating the recognition elements as nanofilms on the surface of different transducers. We discuss recent advances in the use of E-MIPs for analytical applications.

MIPs mimicking natural enzymes are also among these new functional materials. We present the approaches to prepare catalytic non-covalent MIPs along with recent analytical applications and challenges for future developments.

Keywords: Affinity; Biomimetic assay; Catalytic receptor; Chemical detection; Electropolymerized molecularly-imprinted polymer (E-MIP); Imprinted nanoreceptor; Molecularly-imprinted polymer (MIP); Molecular imprinting; Nanoparticle; Sensing

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; ATRP, Atom transfer radical polymerization; Au, Gold; AuNP, Gold nanoparticle; CFME, Carbon-fiber microelectrode; CNT, Carbon nanotube; Co-PA-PPD, Polyaniline/Poly(*o*-phenylenediamine) copolymer; Co-PPD-PD, Poly(*o*-phenylenediamine)/Polydopamine copolymer; CPTMS, (3-Chloropropyl)trimethoxysilane; CV, Cyclic voltammetry; DLS, Dynamic light scattering; DPA, Dipicolinic acid; DPASV, Differential pulse anodic stripping voltammetry; DPV, Differential pulse voltammetry; EDC, 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; E-MIP, Electropolymerized molecularly-imprinted polymer; ESEM, Environmental scanning electron microscopy; GCE, Glassy carbon electrode; GE, Graphite electrode; GO, Graphene oxide; GPH, Graphene; HPLC, High-performance liquid chromatography; LOD, Limit of detection; MAC, Methacryloylamidocysteine; MIC, Catalytic molecularly imprinted polymer; MIP, Molecularly-imprinted polymer; MNP, Magnetic nanoparticle; MTMC, *m*-Tolyl methylcarbamate; MWCNT, Multi-walled carbon nanotube; n/a, Not available; NHS, N-hydroxysuccinimide; NIPAM, N-isopropylacrylamide; PA, Polyaniline; PD, Polydopamine; PEG, Polyethylene glycol; PGE, Pencil-graphite electrode; P*m*AP, Poly(*m*-aminophenol); PMB, Phenylmagnesium bromide; PMBI, Poly-2-mercaptobenzimidazole; P*o*AP, Poly(*o*-aminophenol); P*o*AT, Poly(*o*-aminothiophenol); PP, Polyphenol; P*p*AT, Poly(*p*-aminothiophenol); PPD, Poly(*o*-phenylenediamine); PPY, Polypyrrole; QD, Quantum dot; RAFT, Reversible addition-fragmentation chain transfer polymerization; SAM, Self-assembled monolayer; SPR, Surface-plasmon resonance; SWCNT, Single-walled carbon nanotube; SWV, Square-wave voltammetry; TEM, Transmission electron microscopy; TSA, Transition-state analogue

Symbols: C_0, Catalyst concentration; k_{cat}, Turnover; K_m, Michaelis constant; v_{max}, Maximum rate of the catalytic reaction

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1. Introduction

Molecular recognition plays a key role in biological systems. This process lies at the heart of not only many essential biological processes but also many analytical systems. However, efforts are being directed to the design of artificial biomimetic materials capable of displaying selectivity and efficiencies comparable to those of biological receptors for analytical purposes. Among the various strategies to produce biomimetic systems, molecular imprinting has emerged as one of the most efficient approaches [1]. Due to the inherent advantages of molecularly-imprinted polymers (MIPs) (e.g., mechanical and chemical stability, easy preparation, low cost and high selectivity), MIPs are suitable recognition elements for the development of analytical applications.

An overview of the literature reveals that the main applications of MIPs are in separation [2], although they are also used in catalysis [3] and sensors [4,5]. A major challenge in developing chemical sensors based on MIPs is to find an effective way of transducing the recognition process into an analytical signal. Just as conjugation of biomolecules and nanoparticles (NPs) is providing new forms of electronic or optical transduction for biological recognition, coupling of nanosized MIPs and inorganic NPs or carbon nanostructures into hybrid systems is yielding new materials that could expand the applications of MIPs in analysis. These nanocomposites are designed to enhance the properties or to impart new functionalities to MIPs, improving specific recognition as well as making detection possible, easier or more sensitive. However, *in situ* preparation of MIPs as thin films by electrochemical polymerization is another approach that could allow integration between polymer and transducer in a very simple way.

The aim of this review is to summarize the different approaches to synthesizing MIP nanocomposites and electropolymerized molecularly-imprinted materials, highlighting some of the fundamental properties that make them very promising for the development of new analytical biomimetic assays and sensors. In addition to selective recognition, catalysis is another of the desirable features of this type of functional material. The incorporation of appropriate reactive groups into the molecular receptors obtained by molecular imprinting can provide them with catalytic properties and thereby open new horizons for the design of analytical detection tools. We review the synthesis and the properties of catalytic non-covalent MIPs with a critical assessment of the few analytical applications described so far and an indication of future directions.

2. Nanocomposites for affinity receptors

Traditional imprinting techniques provide microporous monoliths that are subsequently crushed and sieved, giving way to irregularly shaped particles from a few nm to hundreds of μm with low binding capacity, poor site accessibility and slow binding kinetics to the target

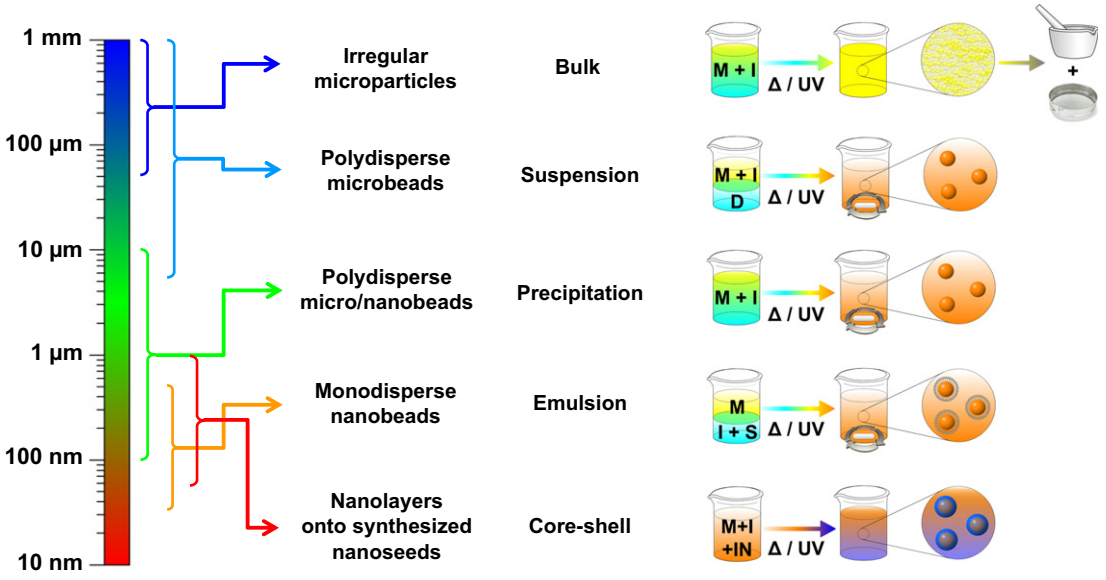

Figure 1. Polymerization methodologies. M, Monomers; I, Initiator; D, Dispersing phase; S, Surfactant, IN, Insoluble nanoseeds.