Metal–Ligand Interactions in Molecular Imprinting

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Abstract

Molecular imprinting enables the design of highly crosslinked polymeric materials that are able to mimic natural recognition processes. Molecularly imprinted polymers exhibit binding sites with tailored selectivity toward target structures ranging from inorganic ions to biomacromolecules and even viruses or living cells. The choice of the appropriate functional monomer, crosslinker, and the nature and specificity of template–monomer interactions are critical for a successful imprinting process. The use of a metal ion mediating the interaction between the monomer and template (acting as ligands) has proven to offer a higher fidelity of imprint, which modulates the molecularly imprinted polymers (MIPs) selectivity or to endow additional features to the polymer, such as stimuli-responsiveness, catalytic activity, etc. Furthermore, limitations in using nonpolar and aprotic solvents are overcome, allowing the use of more polar solvents and even aqueous solutions as imprinting media, opening new prospects toward the imprinting of biomacromolecules (proteins, DNA, RNA, antibodies, biological receptors, etc.). This chapter aims to outline the beneficial pairing of metal ions as coordination centers and various functional ligands in the molecular imprinting process, as well as to provide an up to date overview of the various applications in chemical sensing, separation processes (stationary phases and selective sorbents), drug delivery, and catalysis.

Keywords: molecular imprinting, metal pivot imprinting, ion imprinting, drug delivery systems, catalysis, metal-ligand interactions, sensors, surface imprinting, chiral analysis

1. Introduction

Molecular recognition is indispensable to most of natural occurring phenomena, such as antibody–antigen immune response, ligand-receptor interactions, and enzyme catalysis. The complexity and specificity of these phenomena is the refined product of millions of years of evolution inciting scientists to search ways of mimicking these natural processes. The most

promising and advanced field of biomimetics is molecular imprinting (MI), a technique that gained popularity after the 90s, even though the first reports of imprinting date back to 1931, related to the findings of the Soviet chemist M. V. Polyakov. Compared with their natural counterparts, molecularly imprinted polymers (MIPs) possess, besides a similar selectivity, good chemical and thermal stability, ease of preparation, and low-cost production. By far, their main applications have been reported in the analytical field, and especially in separation techniques, where they have been used as stationary phases for (electro)chromatography and chiral separations and as selective sorbents in solid phase extraction [1]. They have also been applied as promising recognition elements in the development of biosensors, particularly electrochemical [2] and optical [3] ones. In the last few years, MIPs have proven to be versatile engineered materials in the construction of drug delivery systems [4] and as catalysts [5].

The MI process is a relatively simple concept, enabling the synthesis of highly crosslinked polymeric materials of various formats with highly specific binding sites for target structures. The synthesis procedure is relatively easy, versatile, and straightforward, and in general, five components are required: template molecule, functional monomer(s), crosslinking monomer, solvent (porogen), and initiator. The polymers are prepared in the presence of the target molecule itself as template. The first step in MIP-preparation is the self-assembly of template-functional monomer into a complex to immobilize the template molecules throughout the polymerization process. After the addition of the remaining components, the polymerization is initiated and the functional monomer (linked with the template) is incorporated into the rigid 3D structure of the polymer with the functional groups locked toward the template. Upon the subsequent removal (extraction) of the template, cavities are unveiled in the structure of the rigid polymer, which are complementary in size, shape, and functionality to the template. Hence, a molecular memory is created into the polymeric matrix, which has now the ability to selectively and reversibly bind the analyte or its structural analogs. The strength of the interactions between template and monomer determines the efficiency of the imprinting process [6].

Traditionally, MI is classified according to the chemical nature of the interactions that occur during the functional monomer–template complex formation and template rebinding, into two main approaches: the noncovalent and the covalent approach [7, 8]. By far, the most frequently employed approach is the noncovalent one, based on weak, noncovalent interactions in the template-functional monomer complex formation and also in the subsequent recognition step. These interactions, such as hydrogen bonding, electrostatic interactions and van der Waals forces, are similar with those occurring in biological recognition systems. Because of the weak nature of these bonds, the formed complexes are unstable and a large excess of functional monomer, as compared to the template, is required during the polymerization step in order to favor the formation of the template-monomer assemblies. However, this excess generates a high number of heterogeneous binding sites as a result of random incorporation of the monomer's functional groups outside the imprinted cavities. Moreover, because the complex formation is governed by an equilibrium, a special attention must be paid to the employed porogenic solvent. Usually, nonpolar, aprotic solvents, such as chloroform and toluene promote the template-functional monomer association, whereas polar solvents like methanol and water tend to disrupt the noncovalent interactions in the prepolymerization

complex. The covalent approach or the preorganized approach employs reversible covalent bonds between the functional monomer and template, such as reversible esterification or condensation reactions (boronate ester, ketal/acetal, and Schiff's base formation) both prior to the polymerization, and also in the subsequent rebinding step of the template. This strategy leads to the generation of a higher yield of specific and more homogeneous binding sites along with reduced nonspecific adsorption. However, the applicability of the covalent imprinting approach is limited because of the small number of compounds bearing required functionalities (alcohols (diols), aldehydes, ketones, amines, and carboxylic acids). Removal of the template is generally more difficult, and the chemical cleavage must be achieved under mild conditions. A third, semi-covalent approach, (also called hybrid approach) [9], developed by Whitcombe et al. [10] combines the advantages of the previous two methods. While reversible covalent bonds are employed during the polymerization step, the re-binding is entirely non-covalent in nature.

Unfortunately, most authors neglect in their classification a different strategy, metal ion coordination, even though its first report dates back to 1985 [11]. It has been employed as an alternative to enhance template and functional monomer association in water by introducing a metal ion as mediator [12]. The use of metal ions allows the formation of a ternary complex between the functional monomer, metal ion, and template. The heteroatoms of monomer and template bind to the metal ion (generally first row transition metals) by donating electrons to the unfilled orbitals of the outer coordination sphere of the latter [13]. Coordination of metal ions to natural (e.g. structural elements of DNA, peptides, alkaloids, etc.) or synthetic ligands bearing a large variety of donor atoms has proven to be well suited for the preparation of polymers with outstanding molecular recognition properties, put into good use in a wide variety of applications fields.

Initially, the design and development of MIPs, regardless of the employed imprinting approach, aimed for the rebinding of the template with the highest selectivity. Nevertheless, instead of using the metal ion as mere mediator in the formation of the imprinted polymer, the selective rebinding of a target metal ion is often of interest. Thus, based on the principle of MI, the concept of ion imprinting has also been introduced, in which case the metal ion assumes the role of template.

2. Metal pivot imprinting (metal ion as mediator)

In this approach, metal ions act as a bridge between the functional monomer and the template. Compared to noncovalent interactions, coordinative bonds are stronger, leading to a better stability in aqueous media. The stronger the interactions within the ternary complex, the more specific the recognition sites. Thus, the functional monomer and the template are maintained in close and fixed positions throughout the polymerization step [14]. Monomers are regularly positioned around the template via coordinate bonds, the relative motion of species is restrained, thus leading to improved imprinting factors and lower number of nonspecific binding sites. A key role in the imprinting process is represented by the nature of the

metal ion, which needs to simultaneously meet several requirements, that is, no inhibition of the polymerization process, well-defined coordination sphere, and optimal affinity toward the template and monomer.

2.1. Metal ion

Generally, only a small number of transitional metal ions are employed as pivots in MI, such as: Co(II), Co(III), Cu(II), Ni(II), Zn(II), Cd(II), Fe(II), and Fe(III). Due to their high ability in forming coordination compounds with the majority of ligands of interest cobalt [15–26] and copper [27–33] ions are most often chosen by default. Nevertheless, in the absence of rational guidelines for matching the optimal metal pivot ion with the ligand of interest, a systematic pairing process would be required for each individual set of components.

Wu and Li [27] reported Cu(II) being complexed in the pre-polymerization step by 2 molecules of monomer (4-vinylpyridine (4-VPy)), one of template (picolinamide) and two acetates. They also have shown that the anion in the copper salt participates in the recognition process and in the complex formation [27]. Even though Cu(II) forms the most stable coordination compounds with ligands bearing N-donor atoms, the best imprinting efficiency is achieved in the case of Co(II), as evidenced in multiple studies that compared the imprinting performances of multiple metal ions [15, 18, 21]. In an attempt to separate the enantiomers of mandelic acid, the R(+) enantiomer and 4-VPy were used as template and functional monomer, respectively, alongside different metal ions as pivot (Co(II), Ni(II), Cu(II), and Zn(II)) to create imprinted monoliths [15]. The best resolutions were obtained using Co(II) and Ni(II) as mediators (R_S = 1.87 and R_S = 1.41, respectively), while in the case of Cu(II) and Zn(II) no separation was observed. The smallest template retention recorded in the case of Zn(II) monolith implies that no ternary complex (template:metal ion:monomer) is formed due to zinc's weak coordination capacity. In the case of Cu(II), even though it produces the most stable hexa-coordinated complexes, because of Jahn–Teller distortion, these coordination compounds are known to be susceptible to tetragonal distortion (elongation/ compression) [34]. In another study, the Co(II) mediated imprinted monolith showed the best retention (k = 2.75) and imprinting factors (I.F. = 3.1) for the gallic acid (template), in comparison with Ni(II) mediated polymer (k = 2.49) or different other ion-mediated MIP monoliths that were tested [18]. The Co(II)-mediated MIPs emerge also in other two studies [21, 22] in which ketoprofen and ketoprofen with naproxen, respectively were used as templates. In the first study, [21] the ability of molecular recognition of the ion-mediated imprinted polymers decreases in the order: Co(II) > Ni(II) > Zn(II). The binding affinity of Ni(II) to the N containing ligands (especially aminoacids containing compounds) was employed in creating imprinted polyacrylamides as artificial receptors for different peptides (cholecystokinin C-terminal pentapeptide (CCK-5) [35] and His-Alac [36]). The functional monomer (nitrilotriacetic acid) occupies four positions in the octahedral coordination sphere of Ni(II), leaving the remaining two for selective interactions with the template. Both Fe(II) and Fe(III) were successfully used in developing MIP adsorbents for tetracyclines enriching [37, 38]. It was found that Fe(II) could form a ternary complex with tetracycline (template) and methacrylic acid (MAA) (functional monomer), made of one molecule of template, one Fe(II) and four MAAs. The same mole ratio 2:1:2, methacryloyl-l-cysteine methyl ester (functional

monomer):Fe(III):template (uric acid) was found in the coordination compound used for the surface plasmon resonance (SPR) detection of uric acid [39]. Fe(III)-MIP was developed as a drug carrier that showed larger drug loading capacity and a higher amount of drug release at its equilibrium state compared with the Fe-free MIP. Moreover, the Fe-MIP drug release rate was more controlled than that of the MIP and the non-imprinted polymer (NIP), especially at the early stages of release [40].

2.2. Template as ligand

Metal–template binding should be stable under polymerization conditions yet labile enough to allow removal of substrates-templates. With few exceptions, [41] the design of MIPs for the selective recognition of amino acids and peptides has been limited to the traditional imprinting strategy, which employs polyacrylates with MAA as the functional monomer in organic solvents. Bulkier templates, such as macromolecules (especially proteins) are not compatible with the organic media because of their low solubility and tendency toward denaturation, thus using water as solvent is essential. However, polar solvents will interfere in template-monomer hydrogen bonding, therefore metal-coordination interactions represent an effective alternative in imprinting biological-relevant compounds. The affinity of N-terminal histidine for Ni(II) allowed the creation of MIP receptors for peptides with exposed histidine residues [36]. It was shown that the metal ion works not just as a link between the monomer and template, it also influences the steric environment around the metal ion during polymerization step. The superior performance of metal-ion mediated imprinting compared with the metal-free approach, was demonstrated for CCK-5 [35]. MIPs produced in the presence Ni(II) showed a more than double average rebinding value and an I.F. of 1.9 with respect to the traditionally imprinted polymer. A Co(II)-mediated imprinted polymer for the bovine serum albumin (BSA) recognition (I.F. = 14.9), was synthesized and compared with the BSA ion-free MIP [17]. The Co(II)-mediated MIP presented an 8-fold increase in the I.F. and a reduced cross-selectivity by a factor of 2.5 compared with the BSA-MIP. Using Cu(II) chelation strategy, the cytochrome c was successfully imprinted into a supermacroporous cryogel, which was employed for template separation from a mixture of proteins (cytochrome c, lysozyme, and BSA).

Protein imprinting is still a challenging task mainly because of their huge molecular size and conformational flexibility and complexity, which makes template removal and the subsequent protein rebinding onto imprinted sites very difficult. One alternative to the protein bulk imprinting is the metal-ion mediated surface imprinting in which the specific recognition sites are located at the surface of MIP. Porcine serum albumin was imprinted on the surface of silica microparticles via a metal chelating strategy in phosphate buffer [32]. The thickness of the imprinted polymer layer was about 20 nm, allowing fast binding kinetics (~1 min), the binding of protein template reaching more than 90% of the maximum capacity. Satisfactory selectivity was obtained using three competitive proteins: cytochrome c, ribonuclease B and myoglobin. Another metal-ion imprinted thin polymeric film was synthesized on the surface of cellulose nanofibers for the selective recognition and purification of hemoglobin from hemolysate [33]. The obtained MIP was able to rebind 8 times more template protein

compared to the corresponding NIP. z-Histidine was also imprinted in polar organic solvent (methanol) via the mediation of Co(II) ions [20]. However, it was found a small difference in the rebinding capacities between the polymers prepared in the presence of z-His/Co(II) and Co(II) when they were exposed to the Co($C_2H_3O_2$)$_2$(z-Histidine)] coordination compound.

Metal chelating approach was employed for the chiral discrimination of different amino acids, like phenylalanine, tyrosine, alanine, valine, leucine, isoleucine [29], and Boc-L-Phe-OH [25] and other compounds (mandelic acid [15]). The amino acid's side group's size plays a crucial role in obtaining a good enantioselectivity. The MIPs prepared with aliphatic amino acids showed no or little enantioselectivity. Amino acids containing aromatic or heterocyclic groups yielded MIPs with good chiral discriminative properties. According to the three-point interaction model, these bulky groups are responsible for the third necessary interaction with the polymer matrix, sterically hindering the opposite enantiomer.

Regarding the smaller and simpler (no multiple functional groups) molecules, non-covalent imprinting is more difficult because of the smaller number of possible interactions between the template and functional monomer, especially in aqueous media. It is the case of formate, acetate and propionate anions, which showed no imprinting effect using 4-VPy as functional monomer. However, if these anions are part of a ternary complex with picolinamide as ligand and Cu(II) ion as mediator (during the polymerization process as well as during the rebinding step), their indirect analysis is possible [28].

Metal ion mediated approach may be an alternative for compounds with strong intramolecular hydrogen bonds that can interfere in the formation of template-monomer intermolecular hydrogen bonds, thus inhibiting the MI effect. For example, picolinamide cannot be imprinted through the noncovalent approach, but if it is included in a ternary Cu(II) complex with 4-VPy (both as ligand and monomer), the imprinted polymer showed a high molecular recognition ability [27]. Metal ion-mediated imprinting was also used to prepare different MIPs for the specific recognition of multiple drugs with high metal chelating capability: tetracyclines [37, 38], quinolones [37], ketoprofen [21], furosemide [40], and naproxen [26]. Two pharmaceutical compounds, naproxen, and ketoprofen were simultaneously imprinted using metal chelating strategy without loss of selectivity and it was found to give better results versus traditional MIPs [22]. A SPR sensor for a biological-relevant molecule (uric acid) was developed and applied for the metabolite's detection in urine [39].

Because of the stronger coordination binding compared with noncovalent imprinting, metal ion mediated imprinted polymers can be successfully used as selective sorbents for the concentration and the clean-up of different pollutants and toxic compounds (methylmercury from human hair and soil [42], organohalide pesticide 4-(2,4-dichlorophenoxy)butyric acid (2,4-DB) [16], thiabendazole fungicide in citrus and soil samples [31]).

MIPs were also used as extraction media of active compounds from complicated natural products, using metal coordination interactions. Quercetin was shown to form coordination compounds with Zn(II) through 3-hydroxyl-4-ketone electron donor functionality from its structure [43]. Epigallocatechin gallate was separated from natural plant extracts employing gallic acid as a dummy template in order to reduce the MIPs manufacturing costs [18].

The combination of using ionic liquid ([Bmim]BF$_4$) and metal pivoting was employed in imprinting a polar compound, methyl gallate, exhibiting superior recognition abilities than the ion-free polymer [24]. It is assumed that the ionic liquid improves the imprinting process by limiting the polymer swelling and shrinkage [44].

2.3. Functional monomer

A successful metal ion-imprinting process is achieved if the formation of the template-metal ion-functional monomer ternary complex involves strong coordination interactions. Therefore, the choice of the functional monomer is very important. It must interact with the metal ion and template in a particular geometry offering the anchor point for the coordination compound on the polymer backbone.

One approach is to synthesize the metal ion-functional monomer complex before the addition of template, complex that will be incorporated into the polymer matrix and will be preserved after template removal [16, 17, 29, 35, 36]. Thus, in the rebinding step, the MIP should be exposed only to the free-form of the template. Examples of such coordination compounds: nitrilotriacetic acid–nickel (Ni–NTA) complex [35, 36], Co-porphyrin (Co(III)tetrakis(o-aminophenyl) porphyrin [16], Co(II)-(E)-2-((2 hydrazide-(4-vinylbenzyl) hydrazono)methyl)phenol, Fe(III) chloroprotopor-phyrin, vinylferrocene, Zn(II) protoporphyrin [17], and Cu(II)–N-(4-vinylbenzyl)iminodiacetic acid [29].

However, in the metal-mediated imprinting, the most widely used functional monomer is by far 4-VPy, because of its ability to form strong coordination bonds with a large spectrum of divalent metals. Different metal ion-4-VPy molar ratios have been used, ranging from 1:1 [43], 1:2 [19, 20, 27, 28], 1:4 [22] up to 1:6 [15, 18, 23]. It appears that with the increasing molar ratio of functional monomer, the IFs are also increasing up to a ratio of 1:6. An excess of functional monomer is needed in order to stabilize the ternary complex and to achieve good fidelity of the binding sites.

Surprisingly, when 4-VPy was investigated as functional monomer versus acrylamide, and MAA, the best performances were exhibited by acrylamide-imprinted polymer, even though among the three monomers, acrylamide generates the lowest binding energy.

However, acidic acrylates (itaconic acid [37], MAA [25, 32, 38], and acrylic acid (AA) [40]) were successfully employed in metal-ion imprinting using Fe(II) and Fe(III) as central ion.

3. Ion imprinting (metal ion as template)

Commonly used monomers in MI often possess the ability to universally bond a multitude of metal ions, with variable selectivity. Thus, the use of monomers and/or ligands with structural features that enable metal ion chelation has opened new perspectives in the management and analysis of metal ions. First introduced by Nishide et al. [45], the concept of metal ion imprinting has been increasingly developed during the last two decades on the principle of MI.

The series of reviews published throughout the years offer general guidelines and concepts on the development of ion imprinted polymers (IIPs) (synthesis, characterization, types of imprinting, and assessment of analytical performance) and various applications (selective detection, sample enrichment, recovery, and decontamination of metal ions) in the biomedical and environmental fields [46–50]. Herein, several aspects on different materials, natural and synthetic, used in the design of IIPs and the particular features that allow these materials to selectively bind distinct metal ions will be pointed out.

The choice of the chelating agent, the complexation mode, the particular geometry of the coordination compound, the charge, and the size of the imprinted metal ions are key factors in determining the selectivity of the resultant imprinted polymer [34, 51, 52].

The inclusion of the metal binding entity in the polymerization matrix can be achieved through four distinct approaches: (a) crosslinking of linear chain polymers carrying metal-binding groups, (b) chemical immobilization, (c) surface imprinting, and (d) trapping of ligand in the polymeric matrix [47].

3.1. Crosslinking of linear chain polymers carrying metal-binding groups

This approach is currently used mainly with natural linear polymers, such as chitosan (CTS) and cellulose. CTS units, copolymers of glucosamine and N-glucosamine are widely used as functional monomers due to the material's abundance, lack of toxicity, biocompatibility, and biodegradability that add to its particular structure with numerous amino and hydroxyl functional groups which enable structural modifications and crosslinking [53].

The uptake of metal occurs mainly by chelation and is most likely to occur inter- or intra-CTS chains via one to four amino groups, with the nitrogen atoms in the amino and N-acetyl amino groups acting as electron donors. Upon deprotonation, hydroxyl groups may also be involved in metal ion coordination [54]. The poor selectivity, low stability in acidic solutions, and weak mechanical strength of nonimprinted raw CTS renders it inappropriate as selective metal ion sequestrant; these drawbacks, however, may be addressed by crosslinking and functionalization [53–55].

Nevertheless, crosslinking may decrease the metal uptake efficiency as, often, the functional groups of CTS involved in metal binding are also involved in the crosslinking reaction. The reactive amine and hydroxyl groups most likely to be involved in metal chelation are protected by ion imprinting prior to crosslinking [56, 57]. The commonly used crosslinkers include, but are not limited to, aldehydes (formaldehyde, glutaraldehyde, and glyoxal), heterocyclic compounds [epichlorohydrin(ECH)], and ethers [crown ethers, ethylene glycol diglycidyl ether (EGDE)]. Various modes of functionalization intended to modulate selectivity of CTS toward different metal ions have been reported: carbomethylation and thiourea/glutaraldehyde grafting for Ag(I) [58], carboxylation via ketoglutaric acid for Cu(II) [59], derivatization with aminobenzaldehyde for Ni(II), Cu(II) and Pd(II), [60, 61] dithiocarbamate for Sr(II), [62] tetraethylenpentamine for Pb(II) [63].

A different approach was employed by Hande et al. [64] for the design of a Pb(II) imprinted interpenetrating polymer by simultaneous polymerization of MAA and CTS in the presence of Pb(II) ions as template.

3.2. Surface imprinting

Chemical immobilization, trapping, and crosslinking of linear chain polymers, prepared mainly by traditional polymerization methods (bulk, precipitation, and suspension), present several drawbacks (i.e. relatively low rebinding capacity, slow mass transfer, and incomplete removal of template) that arise mostly from the restricted accessibility of the binding site, enclosed in the rigid polymeric mixture [48, 65]. Surface imprinting addresses these issues by generating binding cavities at the surface of the imprinted polymer. A thin imprinted layer is immobilized on the surface of fibers or small sized particles of organic or inorganic nature [48].

Selective sorption of Cu(II) was achieved by copolymerization of ethylene glycol dimethacrylate (EDMA) and $Cu(MAA)_2$ on the surface of a polystyrene core [66]. Li et al. grafted glycidyl methacrylate on polypropylene fibers [67]. A polypropylene membrane was used as support for a Pb(II) imprinted composite material in a process that implied grafting polymerization of AA on the polypropylene membrane and subsequent covalent immobilization of CTS [68].

Surface-imprinting modification of magnetic particles such as TiO_2 and Fe_2O_3 is particularly appealing since the post processing of solid-phase extraction is reduced to a simple magnetic separation. Chen et al. [57] developed thiourea-modified magnetic ion imprinted CTS/TiO_2 for highly effective Cd(II) adsorption and simultaneous 2,4-dichlorophenol degradation via TiO_2 photocatalysis. Fe_2O_3 magnetic particles were immobilized on carbon disulfide modified CTS-Fe(III), for the effective and simultaneous removal of Cd(II) and tetracycline from water samples. The synergistic effect of tetracycline and Cd(II) adsorption was found to be due to the formation, at pH = 8, of a tetracycline-Cd(II) complex bridging the adsorbent and adsorbate [56].

Modified silica gel particles are extensively used as support for the imprinted layer because of their mechanical and chemical stability, low cost, and ease of preparation and functionalization through the silanol groups. A facile approach with good results in terms of selectivity (selectivity coefficients above 50) was reported by Zhang et al. [69] and involved the use of two commonly employed functional monomers, 4-VPy and MAA to obtain ternary Pb(II) complexes, immobilized by polymerization with EDMA and subsequently grafted on hollow mesoporous silica by co-condensation between Si-OH and EDMA. Pb(II) imprinted silica sorbents were designed using a tetradentate chelating silylating agent derived from 3-[2-(2-aminoethylamino)ethylamino]propyltrimethoxysilane and 2-pyridinecarboxaldehyde [70] or a N,N-bidentate group in the structure of the functional monomer 4-(di(1H–pyrazol-1-yl)methyl) phenol [71]. Iminodiacetic functionalized silane ((3-glycidyloxypropyl)trimethoxysilane) [72] and the bifunctional ligand monomer [3-(γ-aminoethylamino)-propyltrimethoxysilane] [72, 73] were used for the imprinting with Ni(II) and Cd(II) ions and the imprinted sites were embedded in mesoporous silica.

3.3. Chemical immobilization

The chemical immobilization technique employs bifunctional ligands that possess both polymerizable functional group (i.e. a vinyl group for free radical polymerization or a silane

coupling agent for sol–gel processes), and electron donor groups for the chelation of metal ions [48, 74].

Currently, the technique is a one-step process that implies mixing together the metal ion, the bifunctional monomer and the crosslinker prior to co-polymerization. Isolation of the binary complex prior to polymerization is a more complicated approach but it offers the advantage of the control of the amount and of the structure of the coordination compound embedded into the polymer's structure [34, 48].

Common monomers such as 4-VPy, 1-vinylimidazole, AA or acrylamide may serve for chemical immobilization, but they show low binding capacities and low selectivity. MAA was used simultaneously with 1-vinylimidazole [75] or 4-VPy [76, 77] to prepare Cd(II), Cu(II), and Zn(II) imprinted polymer particles, respectively. Considering however that the use of simple, commercially available monomers results in materials with generally low binding capacity and selectivity, new tailored bifunctional ligands, bearing both chelating functionalities and polymerizable groups, have been proposed.

Particular features that differ from those of their open-chain analogs such as controlled size and the "macrocyclic effect" that translates into high selectivity and stability, make crown ethers interesting candidates as ligands in ion-imprinting. Benzo-15-crown-5-acrylamide, 4-vinylbenzo-18-crown-6, and 2-(allyoxy)methyl-12-crown-4 have been successfully employed for the imprinting of K(I), [78] Pb(II) [79] and Li(I) ions [80, 81].

Calix[4]resorcinorene, a resorcinol-based macrocyclic compound with a bowl-shape molecular cavity formed by four resorcinol units, was used by Yusof et al. [82] to synthesize diallyl-aminomethyl-calix[4]-resorcinarene, as host for imprinting Pb(II) ions.

Amino acids or amino acid derivatives bearing vinylated groups, (e.g. N-methacryloyl-(L)-histidine), [83, 84] vinylated SALEN, [85] [N-(4-vinybenzyl)imino]diacetic acid, [34] are other examples of bifunctional ligands that have been reported for the chelation of various metal ions and subsequent copolymerization with a suitable crosslinking agent.

Based on the ability of Hg(II) to form stable coordination compounds with thymine (T), T-Hg(II)-T interactions, Xu et al. [74] synthesized 3-isocyanatopropyltriethoxysilane, bearing thymine (T) bases as recognition elements for the imprinting of Hg(II).

Using 5-(bisulfate N,N-diallyl-N-methyl ammonium)methyl salicylaldoxime, Zhang et al. [86] anchored chelating salicylaldoxime units onto the polymer networks through quaternary ammonium cations serving as spacers.

Chemical immobilization shows the advantage of ligands not being leached out during the elution of the template. The magnitude of the imprinting effect is however rather low; this adds up to the difficulty of the vinylation procedure [47].

3.4. Trapping of the ligand in the polymeric matrix

In case of trapping, ligands do not require the insertion of polymerizable functions, but instead they are used as such and are entrapped inside the network during the polymer's formation,

without being chemically bound to the polymeric network. The stability of the binding sites depends upon the correct immobilization of the ligand in the polymeric matrix and the presence and the integrity of the ligand during and after the template removal [47, 48].

The first trapping procedure was reported by Rao et al. in 2003. The imprinted polymer was synthesized by co-polymerization of a coordination compound between Dy(III), 5,7-dichloroquinoline-8-ol and 4-VPy, in the presence of divinylbenzene (DVB) as crosslinker [87].

The entrapped species may be a metal ion:ligand binary complex, as in the case of Zn(II):8-hydroxyquinoline (1,2) and Al:8-hydroxyquinoline (1,3) coordination compounds embedded in the polymeric matrix formed by MAA and DVB [88]. In most cases, however, a ternary metal complex is formed, the metal ion being coordinated by both the ligand ensuring selectivity and the functional monomer (e.g. 4-VPy, MAA) bearing, it too, electron donating heteroatoms, and therefore coordination ability. The ternary complex can be prepared in situ, just before the polymerization step or synthesized, isolated and characterized before being introduced in the polymerization. Comparative studies on the efficiency of polymers prepared with such ternary complexes vs. binary species where the coordination environment is ensured by the presence of the ligands alone, revealed the importance of the presence of bifunctional species acting as complementary complexing agents. Alizadeh used 4-VPy as functional monomer and quinaldic acid as complexing agent to imprint Cd(II) and employed experimental design to study various binary and ternary mixtures [89]. IPs prepared from binary complexes were found to be less efficient than those prepared with ternary complexes.

Crown ethers and derivatives with cavities of appropriate size were trapped in the polymer network by using suitable functional monomers and crosslinking agents and the polymer imprinted with alkali metals ions. Dicyclohexyl-18-crown-6, [90] dibenzo-21-crown-7, [91] dibenzo-24-crown-8 ether [92] and the aza-thioether crown containing a 1,10-phennathroline subunit (5-azamethyl-2,8-dithia [9],(2,9)-1,10-phenanthrolinophane), [93] were used by Shamsipur and coll. to imprint K(I), Rb(I), Cs(I) and Ag(I) ions, respectively, in the presence of MAA as functional monomer and EDMA as crosslinker.

Other ligands used for ion-imprinting via trapping include isatine for Cu(II), [94] diphenyl-carbazide (for Cd(II)), [95] 1,10-phenanthroline for Ag(I) [93] or neocuproine for Cd(II), [96] 8-hydroxyquinoline for Ni(II), [97] etc.

As compared to chemical immobilization, the trapping approach is easier to implement. The stability of the binding sites created via the trapping approach, however, depends upon the correct immobilization of the ligand in the polymeric matrix and the presence and the integrity of the ligand during and after the removal of template [48].

4. MIPs in drug delivery

Polymers have played an integral role in the advancement of drug delivery systems (DDS) through the last three decades, improving safety, efficacy, and patient compliance during

long-term medication therapy by providing sustained release of both hydrophilic and hydrophobic therapeutic agents [98]. MIPs used as excipients of solid pharmaceutical dosage forms have been tested for tuning drug release profiles and eventually protect their load from enzymatic degradation while being freight through the body, nevertheless the inherent feature of these polymers, their selectivity, has not been put to a proper use. Therefore, efforts have been made to integrate MIPs in therapeutic systems for intelligent drug release or as targeting drug vectors [99].

These tailor-made IPs would be therapeutically advantageous for several reasons as they can act as molecular trap (sequestrant) systems, [100] as reservoir for prolonged release of a particular drug, they can enable an increased loading capacity of the therapeutic formulation, facilitate environmentally or physiologically responsive intelligent release of the therapeutic agent [101] and if required, they can confer an enantioselective load or release [102, 103]. Using conventional drug formulations, repeated administration would help in building up the required therapeutic levels of the drug in various biological compartments (blood, tissues, urine, etc.); however, in case of bioactive molecules with a narrow therapeutic index (i.e. digoxin, cyclosporine, sirolimus, theophylline, warfarin, lithium, phenytoin, and flecainide) or with very short plasmatic half-life (i.e. 5-fluorouracil (5-FU), acetylcholine, GABA, catecholamines, adenosine, and NO) repeated administration could lead to elevated risks or severity of toxic side effects.

Several comprehensive reviews have been published concerning the use of MIPs in general as DDS for controlled/sustained drug release or as intelligent drug delivery (DD) platforms (responsive release systems) either for oral, ocular, transdermal, or implant-associated local delivery routes of the therapeutic agent [99–101, 104–108].

Targeted DD relies on the MIP's ability to specifically recognize certain bioreceptors, such as a cell surface epitopes, which could further convey to cellular internalization of the drug loaded carrier and subsequent release of the active pharmaceutical compound. In the initial and most simple approaches the payload of biologically active molecule was non-covalently bound (hydrogen bonding, hydrophobic interactions, charge transfer, or van der Waals forces) to the imprinted polymer network [109]. Nevertheless, the overall controllability and reliability of DDS based on noncovalent binding might not be ideal in a living organism. Therefore, as an alternative, metal ion-mediated coordinate bonds between the functional monomer and the targeted drug molecule (template) has been investigated offering higher specificity and strength, as well as spatial directionality in comparison with noncovalent bonding. Additionally, metal coordination bonds are more compatible with the polar environment of living tissues and they can be easily manipulated through changes of the local hydrogen ion concentration, a feature extremely helpful in the development of pH-responsive delivery systems. Furthermore, MIPs prepared by noncovalent imprinting methods usually require using organic solvents, which eventually leave toxic traces, incompatible with biomedical applications.

Some of the imprinted polymers employed nowadays in intelligent DD [i.e. poly(2-hydroxyethyl methacrylate, (PHEMA)] were initially employed in the early forms of the non-imprinted DDS [98]. Various aspects about the encountered recognition and drug release mechanisms, optimization of the drug loading capacity, latest trends in various routes of DD, as well as

limitations and future prospects of such molecularly imprinted DDS may be found in different reviews [99, 104, 105, 110].

A wide range of biocompatible semi-synthetic and synthetic polymers have been tested as suitable imprinted frameworks for DD. PHEMA and its derivatives or nanocomposites continues to be one of the most widely used biomaterials due to their low toxicity, excellent and long-term biocompatibility (including hemocompatibility) and high resistance to degradation [111, 112].

Such molecularly imprinted biomaterials served for the fabrication of various drug-delivery systems, such as transdermal membranes, [113] ocular inserts [114, 115], and implants (subcutaneous, intra-peritoneal, etc.) [116].

Polymer biodegradability plays also an important role in the biomedical exploitation, patient compliance and safe use of such DD systems. Because PHEMA is not biodegradable, upon the release of the pharmacologically active load the implants must be removed from the body through minor surgery to avoid the formation of pseudocyst. However, in many cases, such as the localized treatment of spinal cord injuries, the use of hydrolytically degradable hydrogel implants is far more convenient. *In vivo* experiments showed that macroporous 2-ethoxyethyl methacrylate/ N-(2-hydroxypropyl) methacrylamide based hydrolysable hydrogels (adjustable degradation between 2 and 40 days) are promising candidates for implantation into tissue defects of the central nervous system [117].

Although metal ion coordination-based imprinting has shown promise in the creation of advanced recognition and DD systems up until now, literature is rather scarce in such studies. Nevertheless, there are some noteworthy publications in this field, such as the one reporting the sustained release (5 days) of copper salicylate, a metal-based nonsteroidal anti-inflammatory drug, successfully embedded in a metal chelate imprinted polymer using 4-VPy and 2-hydroxyethyl methacrylate (HEMA) as functional monomers and EDMA as crosslinker [118]. Another interesting study is the synthesis of Co(II) mediated imprinted hydrogels containing pendent chain linked template (drug) [119]. A pH responsive drug release could be achieved in the range of pH 3–6.8 due to the presence of an imidazole group within the proximity of the polymer-drug (ester or amide) bond responsible of the catalytic hydrolysis of the hydrogel.

Design of dedicated macromolecular architectures through MI able to recognize certain target molecules as well as capable of intelligent DD and release leads to the introduction of feedback-controlled drug release systems employing stimuli-responsive gel systems. As a result of oscillatory swelling, they are able to modulate release in response to pH, temperature, ionic strength, electric fields, or specific analyte concentration differences [101, 104]. The solvation of the hydrogel's macromolecular network is rather well adjustable by the local environment, this leading to a controlled swelling and release of the payload.

The inherent advantages offered by metal pivot-based MI have been successfully exploited in the imprinting process of hydrogels intended for stimuli-responsive DDS. The formation and cleavage of coordination bonds between different metal ions and various drugs of interest are pH-dependent, so by a rational design they could be specifically engineered for an intended use. As such, metal-mediated imprinting of HEMA-based hydrogel backbone crosslinked with N, N-methylenebisacrylamide (MBA) has been described for the pH-responsive and

controlled release of doxorubicine (within 7 days 60% of the drug released at pH 5.0 vs. 10% at pH 7.2). The anticancer drug was loaded onto the hydrogel as a preassembled Cu(II) ion bridged complex of doxorubicin (1,2 molar ratio) as template and 4-VPy as functional monomer [120]. Although by a slightly different approach, Liang et al. reported the encapsulation in self-assembled biodegradable zein/carboxymethyl chitosan (CMCS) nanoparticles of the same anticancer drug by electrostatic interactions [121]. The nanoparticles were additionally coated by a thin layer of metal-tannic acid layer, where the metal ions (Cu(II), Ca(II)) act as stimuli-responsive crosslinking agents, controlling the release of the guest molecule.

The intracellular conversion rate of a key anticancer agent, 5-FU, to its biologically active metabolites is very fast in the human body, however more than 80% of the administered pro-drug is inactivated by the liver (6 min plasmatic half-life) [122]. As a solution, various controlled localized DD approaches have been investigated [123, 124]. Nevertheless, the prospects of metal ion-mediated MI technology for the controlled delivery 5-FU has also been exploited by the formation of a metal-chelate complex of N-methacryloyl-L-histidine (MAH) functional comonomer and 5-FU via Cu(II) ion coordination in the prepolymerization step [125]. A free radical polymerization, crosslinking and a cryogenic processing lead to the formation of 5-FU imprinted PHEMA-N-methacryloyl-(L)-histidine methyl ester) cryogel discs, an interesting class of implantable biomaterials, particularly suitable for the controlled delivery of an antineoplastic agent directly to the site of tumor. *In vitro* studies have shown that drug release may be simply controlled by the amount of used crosslinker, whereas the delivery rate of 5-FU is further tuneable (faster at pH 4 vs. 7.4), through the influence of the coordination compound's stability, rendering the metal ion-mediated imprinted polymer pH-responsive [125].

Due to the inherent large surface area of porous metal–organic frameworks (MOFs) and to the excellent gas adsorption capacity of the active metal atoms, such structures have been described for the delivery of bioactive gas molecules, such as NO as an antithrombosis and vasodilation agent [126]. The gas can be stably stored by the covalently unsaturated metal atoms (Co or Ni) from their structure, each able to coordinate to one NO molecule (accumulating up to 7 mmol NO/g of MOF), whereas the bioactive gas is delivered through a water-triggered release. Although other porous MOFs were also described as promising DD systems, where the pharmaco-active payload is stored in a 3D network of nanoscaled cages by guest-host interactions, in the respective case the metal ion is not actively involved in the drug's (i.e. 6-FU) binding or release [127].

5. MIPs in catalysis

The use of MIPs in catalysis has been gaining in interest in recent years thanks to their low cost of manufacturing, good biocompatibility, and recognition properties and excellent stability compared to their bio-analogues such as enzymes. The main objective in this field is to produce MIPs capable of showing enzyme-like activities for reactions for which no enzyme exists, or to improve the performance of the existing catalytic systems [128]. Many natural enzymes contain metal ions capable of specifically coordinate different molecules.

A salicylaldiminato Co(III)-based catalyst was used for the preparation of Cibacron-reactive-red-dye-imprinted MIP with tert-butyl acrylate as a functional monomer and DVB as a crosslinker. Methyl aluminoxane activated the transition-metal coordination compound, which catalyzed the polymerization of tert-butyl acrylate, and high-molar-mass polymers with very low molecular weight distributions were generated, even in the presence of the polar dye. The obtained MIP was used for the selective rebinding and preconcentration of the red dye from tap water and textiles [129]. Co(II)- and Ni(II)-imprinted hydrogel catalyst were able to significantly improve the hydrolysis kinetics of $NaBH_4$ and NH_3BH_3 in H_2 production (total hydrolysis in 50 s at 60°C) [130]. Rare earth metal ions (Y(III), Ce(III), Nd(III), and La(III)) as doping ions were immobilized by ion-imprinting in photocatalysts on TiO_2 Halloysite. Using two aniline derivatives as monomers (o-phenylenediamine, m-phenylenediamine), the photocatalytic activity was demonstrated on tetracycline degradation (up to 78.80%) in simulated wastewaters under visible light irradiation [131]. Last but not least, as a more stable alternative to the natural enzyme phosphotriesterase (hydrolysis of organophosphotriester pesticides), a MIP was synthesized using a paraoxon analog as template and Co(II)–imidazole coordination compound mimicking the catalytic center of the enzyme. Polymers containing the Co(II)–imidazole coordination compound showed a 20-fold higher hydrolytic activity in comparison with polymers containing only imidazole or a solution containing only Co(II) ions. Additionally, the MIP synthesized using the paraoxon analog as template showed higher paraoxon hydrolysis activity than the control NIP [132].

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