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Design and development of molecularly imprinted biodegradable polymers for nanomedicine

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ABSTRACT

Polymer-based drug delivery systems have been extensively studied for decades. These systems must be degradable, capable of controlling drug release kinetics, and of reaching a precise target organ. While degradability is an intrinsic property of the material, controlled and targeted drug delivery is achieved with proper system design. The Molecular Imprinting technique can be used successfully to control the drug release kinetics and to achieve drug targeting. To date, the literature reports a very limited number of studies related to molecularly imprinted polymers for nanomedicine. The lack of applications is mainly due to the difficulties of obtain degradable materials with this technique. The present review reports a summary of the applications and characteristics of molecularly imprinted polymers, with a focus on their potential in nanomedicine. The advantages of their use and any limitations will be highlighted. Finally, the applications of the molecular imprinting technique, developed so far, to the preparation of degradable materials will be reported.

1. Introduction

Drug-releasing systems are designed to delivery one or more active principles with a controlled delivery kinetics [1]. Degradable matrices embedding the drug are used in implantable scaffolds [2], coatings [3], hydrogels [4] and in nanoparticle preparation [5]. After implantation or administration, drug-releasing devices in contact with the physiological environment release their payload. The polymer matrix is then degraded and eliminated by the body, avoiding bioaccumulation. The main advantages of such systems are the prolonged and sustained drug delivery provided after a single administration [6–8], and the controlled delivery enabling side effects and toxicity limitation [9].

Among all the proposed systems, nanoparticles are very promising, allowing a minimally invasive administration and high customizability, in terms of surface properties, functionalization and size [10]. The literature reports a large number of studies on degradable nanoparticles, in which different combinations of polymeric matrices, drugs and applications are investigated [11–14]. Past works underline the good ability of nanoparticles to protect the active molecules from physiological metabolic and enzymatic actions, and the better biodistribution compared to the free drug [15–17]. Nanoparticles can also govern the release kinetics and timing, providing a programmed and modulated drug administration, also exploiting specific signals that occur in the host body [18].

Furthermore, the *perfect* drug carrier should selectively reach the disease site and avoid drug delivery to healthy tissues. The ability to selectively target the pathological site is called *drug targeting* and represents a modern challenge in nanomedicine. A controlled and targeted drug administration allows more efficient therapies, a significant reduction of side effects and a better drug distribution. A convenient way to achieve a *perfect* drug vector is the Molecular Imprinting (MI) [19].

MI is a synthetic technique that allows polymeric materials to be equipped with recognition sites toward a target molecule. These recognition sites enable major interactions with the target molecule and therefore can be used in nanomedicine for two main purposes. The first potential application of MI in nanomedicine is replacing the target ligands with the recognition sites. The targeting ligands commonly investigated for such purpose are generally molecules of biological origin (e.g., peptides, viruses or fragments thereof), which have high costs, limited stability, are complex to manage during the conjugation to the vector and to store. A replacement of biologically derived targeting units, such as the

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recognition sites offered by MI, could overcome all the cited limitations. This application of MI will be discussed in more detail in Section 3. The second potential application of molecularly imprinted particles is the control of the drug release kinetics by modulating the interactions between the recognition site and the drug molecule. Among the main advantages in the use of a polymeric nanocarrier for the drug release there is the possibility to maintain the plasma concentrations, systemic or local, within the therapeutic range of the drug itself. Often, however, the task of controlling the release kinetics is completely entrusted to the chemical and morphological characteristics of the polymeric matrix. The presence of recognition cavities generated by MI, has a much wider potential in controlling release kinetics. This aspect will be discussed in more detail in Section 4.

Despite the great advantages offered by MI in the production of nanocarriers for controlled and targeted drug delivery, this technology still finds little application. This is mainly due to the difficulty of obtaining imprinted degradable polymers. The difficulty of translating the MI technique to degradable polymers lies mainly in the intrinsic characteristics of these materials. In fact, degradable polymers are by definition not chemically stable over time. The lack of chemical stability of these materials is due to the degradation reactions that take place within their molecules. These degradative processes lead to a progressive decrease in the average molecular weight of the macromolecules and to the loss of the smallest oligomeric fragments. This can lead to the loss of the topochemical characteristics of the recognition cavities, with a significant decrease in performance related to MI.

Furthermore, most of degradable polymers have mechanical properties not suited to molecularly imprinted polymers (MIPs). Mechanical properties are also critical for a MIP. This feature mainly affects the morphological stability of the polymer. In MIPs, morphological stability is a fundamental characteristic for obtaining efficient recognition sites, consequently materials with low morphological stability are not suitable for this application.

Another important limitation which hinders the diffusion of the MI technique in the class of degradable polymers is the impossibility of applying this technique in a simple and efficient way to all types of synthetic processes. For example, polyhydroxyalkanoates are produced by bacterial cultures and, consequently, the MI during their synthesis cannot be applied. Another example is the synthesis of degradable aliphatic polyesters, which are conventionally obtained in bulk, without solvent, and at very high temperatures. Such procedure makes the MI complex to apply.

Despite all the limitations mentioned, some efforts have been made to translate the MI technique also to degradable polymers. To date, the literature reports a very limited number of works concerning the preparation and characterization of degradable molecularly imprinted nanoparticles. Although the limited number of works, the potential of MI nanoparticles as drug carriers and as diagnostic agents emerges. This potential lies both in the possibility of exploiting the recognition cavities to control the drug release kinetics, and in the possibility of having functionalized vectors capable of recognizing a precise targeting. This review aims to summarize the related literature with a potential outlook. Aspects related to biodegradable molecularly imprinted particles will be discussed in Section 6.

This review aims to give an overview of the MI technique in the preparation of nanocarriers for drug delivery, with a particular focus on the translation of this technique to degradable materials. Section 2 will report the state of the art on aspects related to the chemistry and synthesis procedures of molecularly imprinted materials, indicating the various classes of materials that can be obtained using this technique. Section 3 will summarize the aspects related to the active drug targeting with MIPs. Section 4 will report the recent literature related to drug delivery from MIPs and the different delivery mechanisms and kinetics obtained. In Section 5 more additional opportunities given by MIPs are summarized, with a focus onto their responsivity to external stimuli to modulate their properties. Section 6 will report the literature related to degradable and biodegradable MIPs and particles developed.

2. The molecular imprinting technique

The MI technique serves to add molecular recognition properties to a material [20]. MI is a processing or synthesis that can be combined to other chemical strategies [21–23] to strictly control the properties of the final product.

The MI process is the formation of the polymer or the polymeric structure around a *template* molecule. The arrangement of macromolecules, preformed or polymerized, around the template generates in the material some functional cavities complementary, in shape, dimension and chemical characteristics, to the template itself [24]. The template is then extracted after preparation. If the polymer matrix is enough stiff to preserve the macromolecular arrangement after the template extraction, functional cavities enable a lock-and-key mechanism toward the same molecule [25]. Recognition properties of obtained functional cavities could be useful in a variety of *in vivo* applications [26,27].

Small-sized templates give better recognition properties [28] but strategies to imprint large macromolecules have been also developed [29,30]. As an example, the epitope approach [31,32] is a good workaround to obtain recognition properties towards large macromolecules by using a fragment thereof as template [33].

MI performances are measured via batch rebinding experiments [34]. In batch rebinding experiments, extracted MIPs are put in contact with a solution of the template with known concentration, and the residual template concentration in the rebinding solution is monitored over time to calculate the amount of template sequestered from the MIPs. Specific recognition properties are quantified via the *imprinting factor*, calculated as the ratio between the binding capacity of the MI material on the non-MI reference polymer [35], prepared without the template molecule. Higher imprinting factors are related to larger amounts of retained molecules and to a more specific recognition.

The MI technique offers a variety of possibilities (Fig. 1). As previously mentioned, the MI technique is suitable both for processing preformed polymers and for synthesizing new macromolecules starting from monomers. Thus different procedures can be followed to obtain MI functionalities. In both cases, the recognition cavities can be obtained within the structure of the material (bulk imprinting) or mainly on the surface (surface imprinting). The positioning of the recognition cavities is a feature that greatly influences the final performance of the MIP.

In MIPs synthesized from monomers, the interaction between functional monomers and template molecule is a fundamental parameter governing the final performances. Two types of monomer/template interactions can be exploited to synthesize MIPs, the non-covalent and the covalent interactions. The nature of the interactions is related to the chemical properties of the monomers as well as those of the template. Hence, one can have one or the other type of interaction based on the choice of starting reactants. This choice mainly depends on the final application.

Basing on different production procedures, MIPs are classified as described in the following sections.

The present Section is not exhaustive but only summarizes some basic concepts that will be useful for understanding the Sections thereafter. For more details, please refer to the literature [36–42].

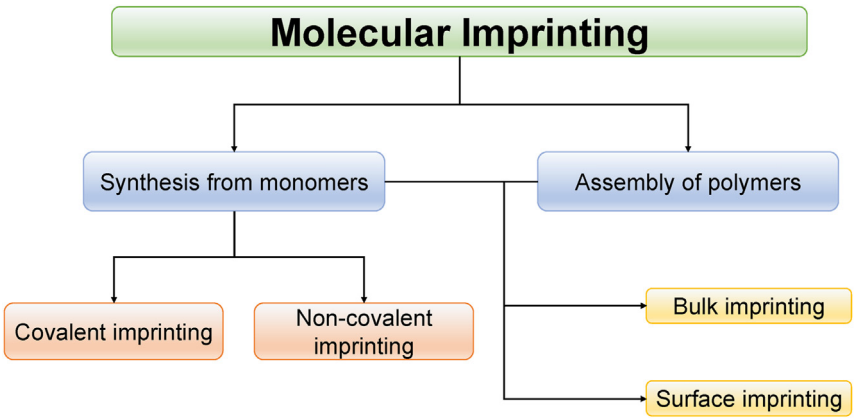

Fig. 1. Schematization of the different possibilities that Molecular Imprinting offers in the preparation of MIPs.

2.1. MIPs from functional monomers vs. preformed polymers

MIPs are prepared both from functional monomers and preformed polymers.

The synthesis of MIPs from functional monomers is the most common procedure. In this case, monomers and template are dissolved in a common solvent (*in solution* step, Fig. 2a) in which they interact and form stable complexes (*complexation*, Fig. 2b). Low-molecular-weight monomers have high mobility in solution and it favors the self-assembly around the template. A good self-assembly provides more stable complexes and more powerful molecular recognition properties. Polymerization takes place in the presence of a crosslinker which provides rigid and stable structures (*crosslinking*, Fig. 2c) and involves the functional groups present on monomers. Upon polymerization, the polymers are washed to extract the template and free the recognition cavities (*extraction*, Fig. 2d).

The synthesis of MIPs from monomers allows selecting some important parameters, like the optimal crosslinker [43] or the solvent [44], to maximize the recognition performances. This approach was already used to prepare drug-releasing MI nanoparticles for cancer treatment [45,46].

Preformed polymers can be also molecularly imprinted. In this case, imprinted cavities are obtained from the organization of the macromolecules around the template, or upon post-functionalization of reactive side-groups over the polymer chain. In the first case, MIPs are generally less effective, and template extraction should be mild to avoid structural changes in the macromolecular arrangement. The second way is most effective, but needs a chemical reaction that can be induced via chemical route or photoinitiation [47].

The preparation of MIPs by crosslinking of preformed polymers was described for the first time by Takagishi and Klotz [48]. Their work reported the preparation of a microgel from the crosslinking

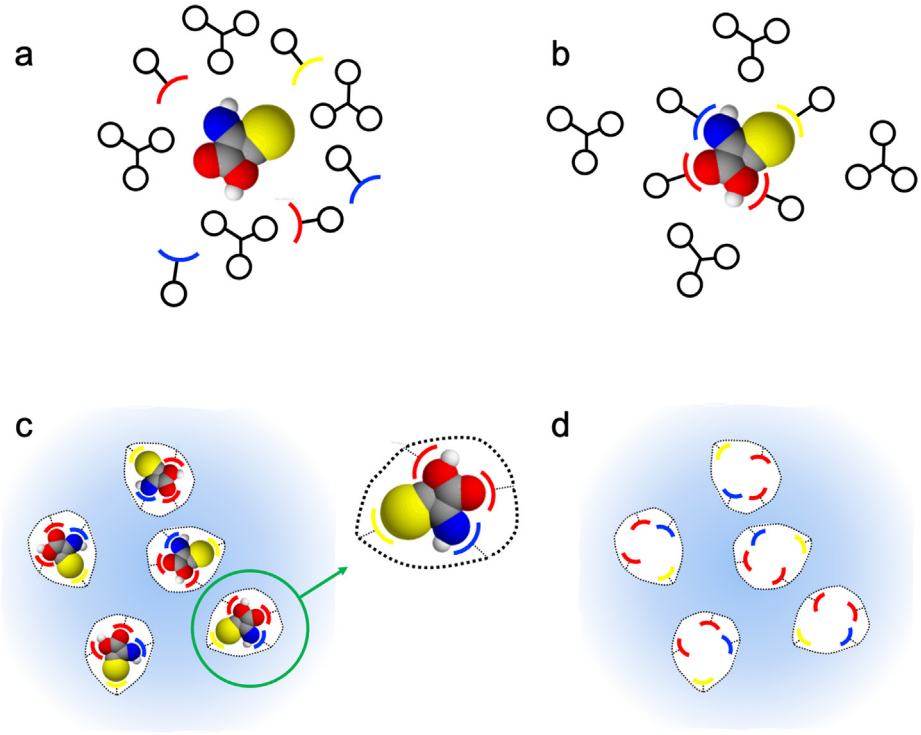

Fig. 2. Steps in the synthesis of MIPs from functional monomers: **a** *in solution*, template, functional monomers and crosslinker are dissolved in a common solvent; **b** *complexation*, the template chemical functionalities interact with functional groups on the monomers to form stable complexes; **c** *crosslinking*, monomers are crosslinked to form a solid and stable structure; **d** *extraction*, template molecules are extracted, leaving free functional cavities.

of linear polyethyleneimine with methyl orange as template. While the strategy to obtain MIPs from preformed macromolecules was proven, the applications of such materials are limited, mainly for the difficult to prepare crosslinkable precursors able to also interact with the template. More recently, MIPs were prepared via phase inversion of the polymer in a non-solvent [49]. In the cited paper, the polymer polyether sulfone was dissolved with the template Bisphenol A and added dropwise to the coagulation solvent. Formed particles were not crosslinked, thus the setup of polymeric precursor was simpler but particle dimension was poorly controlled. The same technique was refined by Lee and co-workers, obtaining composite nanoparticles imprinted against salivary proteins [50].

The formation of MIPs from polymeric precursors has a strong limitation related to the poor motility of the macromolecular reactant, thus the complexes formed with the template are commonly less stable than those obtained with small monomers.

2.2. Non-covalent vs. covalent MIPs

The difference between non-covalent and covalent MI relies on the chemical interactions between the monomers or the imprinted material and the template.

In non-covalent imprinting, the template interacts only through physical weak bonds, such as hydrogen bonds, hydrophobic interactions or π-π stacking. Such interactions depend on the chemical properties of template, monomers and polymers, and on the environment where the MIP is formed. To maximize the non-covalent interactions, the accurate selection of the starting materials is fundamental. Solvents and functional monomers are selected on template properties [51,52]. Theoretical studies have exploited numerical techniques, like the density functional theory (DFT), to optimize the selection of functional monomers and solvents, and molar ratios for specific templates [53–55].

While the system setup can be complex for non-covalent MI, the extraction of the template from the matrix is commonly simple, and consists in a washing with proper solvent.

In covalent imprinting the matrix/template interaction relies on strong covalent bonds. For the synthesis of covalent MIPs, the template is not added to the reaction but it is part of the functional monomers, like a functional side-group. The synthesis results simpler than that of non-covalent MIPs, because the maximization of monomer/template interactions is not needed. While the synthesis is simpler in respect to that of non-covalent MI, the template extraction needs of further reactions to selectively break only chemical bonds between template and functional cavities [56].

The non-covalent imprinting is preferable for poorly stable, degradable or sensitive polymers. In such cases, a mild extraction of the template can preserve the polymer structure. On the other hand, a covalent imprinting leads to better recognition properties [57,58]. In drug-releasing MIPs the active molecule generally acts as a template, and it is not extracted upon the preparation but it should be released with a controlled kinetics. Drug molecules should be motile and free to be delivered, and imprinted cavities are necessary only to tune the release profiles. For this reason, non-covalent imprinting is the most common choice for imprinted drug-releasing polymers. A stimuli-controlled release kinetics is provided by linking the drug molecules with moieties that are cleavable only in specific conditions.

2.3. Bulk vs. surface MIPs

The classification bulk *vs*. surface MIPs refers to the position of functional imprinted cavities. In bulk MIPs, the template is homogeneously embedded in the polymer matrix and functional cavities are present in the whole structure. In surface imprinting, the functional part is the surface [59]. Bulk MIPs are obtained by hydrogel monolith crushing or by precipitation polymerization [60], while surface MIPs are prepared on a preformed structures, mainly a nanoparticle acting as core, and the imprinted shell is obtained by polymerization [61,62].

Bulk MIPs have a higher number of rebinding sites than surface MIPs but the availability of imprinted cavities differs. Small molecules, which can easily diffuse across the polymer matrix, can access the bulky cavities while large molecules, like proteins, have smaller motility and a surface imprinting is preferable to rebind such molecules.

3. Active drug targeting and molecularly imprinted particles

Targeted drug delivery allows selectively increase the drug concentration in a specific site by using a nanovector. Drug targeting can be passive or active. Passive drug targeting takes advantages from pathological tissue anomalies. A well-known mechanism for passive drug targeting exploits the enhanced permeability and retention effect (EPR). The EPR effect occurs in tissues with vasculature anomalies that cause blood leakage and a compromised hemodynamics. A EPR targeted delivery needs nanovector with a prolonged circulation time to allow the accumulation. On the other side, prolonged circulation times cause the accumulation of nanoparticles also in other districts, reducing the targeting properties of the system. Active targeting methods are thus preferable.

Active mechanisms can use external or internal stimuli, or signal molecules present at the site of the pathology. Recent active targeting approaches rely on mechanisms involving cell receptors. Pathological tissues often present altered conditions and cell receptor up-regulation. Up-regulated receptors can be the key factors in targeted drug delivery. Cell receptors selectively recognize their ligand, and often the ligand/receptor complex formation enables endocytic processes. Overexpressed receptors in pathological sites increase the number of interactions with corresponding ligands. Thus, conjugating the corresponding ligand to the active molecule or to the nanocarrier surface should be an excellent targeting strategy. This approach results promising for several applications [63,64] but, despite the promising results, targeting moieties can cause the immune system activation and seriously compromise drug circulation time [65]. The replacement of biological moieties with synthetic recognition properties should overcome this limitation. The molecular recognition pattern in ligand/receptor complex can be mimicked with MIPs [66]. Imprinted cavities are excellent candidates to accomplish this role, both with the direct recognition of the cell receptor (Fig. 3a) or by binding circulating molecules that can target cell receptors and act as a Trojan Horse (Fig. 3b).

MI nanoparticles were investigated in pre-clinical studies for targeted cancer treatment. Cancer cells show the up-regulation of several known receptors and their target can potentially lead to a targeted treatment. Among highly expressed cancer cell receptors, the most common is the folate receptor. Such receptors bind folic acid, the vitamin necessary for cell proliferation. Folate receptors were successfully targeted via molecularly imprinted particles imprinted toward the pteridine moiety [67] and obtained synthetic receptors have demonstrated a reduced non-specific binding in *in vitro* tests. Despite developed molecularly imprinted particles were promising, cell culture or *in vivo* tests were not yet performed and the clinical application for such synthetic receptors is still a concept.

Transferrin receptors (TfR), involved in cell growth, are also over-expressed in cancer cells. MI technology was developed to

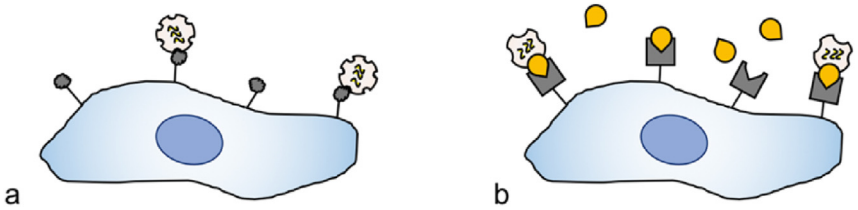

Fig. 3. Active drug targeting by using MI nanoparticles: **a** recognition cavities are imprinted against the receptor or a fragment thereof, thus nanoparticle can bind the receptor and can be internalized via a receptor-mediated mechanism; **b** imprinted nanoparticles bind *in vivo* a specific endogenous molecule that bind the receptor, exploiting a Trojan Horse mechanism to be internalized via a receptor-mediated mechanism.

selectively recognize the soluble part of TfR, to monitor the concentration of this molecule in ranges where commercial assays fail [68]. Also in this case, the significantly high sensitivity of molecularly imprinted particles toward TfR was not exploited in more advanced biological or medical applications. Other interesting targets for cancer cells are glycoproteins. An impressive application of MI in this field was recently reported [69] to obtain sensors with very high sensitivity but medical applications of this technology are still far away.

MI against large proteins can be difficult to be deeply understood and final recognition properties could be not optimal [70]. As previously outlined, the epitope approach is currently the most relevant strategy to recognize and bind large molecules with molecularly imprinted particles. The feasibility of epitope imprinting has only recently been demonstrated. The epitope approach was demonstrated for a few large molecules, like lysozyme [71], albumin [72], oxytocin [73], and melittin with *in vivo* demonstration [74]. More recent works report the multi-epitope approach, used to obtain polymers imprinted against various target proteins [75].

Targeting conformational epitopes confer to particles a higher affinity than that obtained with the linear counterpart of the same fragment [76]. It is because the 3D shape of the epitope endows imprinted cavities not only with a complementary chemical specificity but also a characteristic topology, and this combination is unique for the protein to bind. The conformational epitope approach can be suitable also in intrinsically disordered proteins. This class of proteins are composed of unstructured peptide chains and their targeting is more difficult. However, molecularly imprinted particles can induce the required binding site and exploit the conformational epitope mechanism to target the cells of interest [77]. The refinement of MI techniques to obtain recognition properties toward complex motifs is a potential way to target specific cell types [78].

4. Molecularly imprinted particles for drug delivery

Molecularly imprinted particles as drug carriers are particularly appealing for their crosslinked structure. Crosslinked structures are good reservoirs for active principles, in particular for low molecular weight molecules. The interconnected structure of crosslinked particles provides a slow delivery rate, enabling a prolonged administration. The slow release provided by crosslinked particles is favorable for the administration of drugs with narrow therapeutic windows. The sustained and prolonged drug delivery provided by molecularly imprinted particles is the main benefit achievable. Molecularly imprinted particles were successfully tested with antibiotics [79–81], antipsychotics [82], anti-inflammatories [83] and genes [84] with different applications.

The MI technology was recently applied to liquid crystalline polymers for gastric delivery [85]. This work reported the feasibility of the imprinting process onto liquid crystalline polymers and their improved functional behavior as drug delivery systems, with a prolonged residence time and a zero-order drug release rate, resulting 7–8 times higher than that obtained with the non-imprinted reference system.

Imprinted particles were tested *in vivo* for the oral administration of insulin in diabetic rats [86]. *In vitro* tests on such system have demonstrated that molecularly imprinted particles provided a slower protein release than non-imprinted particles at gastric pH. This result was confirmed with tests in rats, which showed a fast decrease of the systemic glucose level after the oral administration of insulin with molecularly imprinted polymers while no effects were detected after the same administered dose via non-imprinted particles.

Imprinted cavities recognize and rebind their homologous more efficiently in structurally stable materials. On the other hand, soft particles and micro- or nanogels, with a limited crosslinking density, are more suitable for drug delivery applications and strictly stable imprinted cavities are not strongly required for long times. This aspect is relevant in swellable particles, which may show a surface or volume variation in specific environments or under the influence of an external stimulus.

Another valuable application of molecularly imprinted polymers is the enantioselective release of active molecules. After synthesis, some drugs are obtained as racemic blends in which only one enantiomer has a pharmacological activity. If the racemic separation fails or is too difficult to be performed, molecularly imprinted polymers can be successfully used to release only the enantiomer of interest while entrapping the other form in a permanent way. This application was demonstrated for the first time by Suedee and coworkers [87,88] that developed a delivery system of a β-blocker and two non-steroidal anti-inflammatory drugs.

4.1. Drug delivery mechanism in molecularly imprinted particles

Drug delivery kinetics from polymer particles is governed, in most cases, by the Fick's law. The driving force of the diffusion is the concentration gradient between particles and external environment. In crosslinked hydrogels, drug delivery is governed by swelling and macromolecular relaxation upon water absorption. In this case, drug delivery can be tuned by varying the crosslinking degree. Drug delivery kinetics obtained with molecularly imprinted particles is generally anomalous and does not follow conventional pathways.

Drug delivery kinetics in molecularly imprinted particles is generally less diffusion-mediated than non-imprinted devices [89] and release profiles tend to a zero-order kinetics. Some works report a slower release kinetics in molecularly imprinted polymers compared to non-imprinted materials, attributing differences to the effect of crosslinking [90]. The increase in crosslinking degree results in slower release kinetics but it may be an indirect effect. It was demonstrated that higher crosslinking degrees lead to better recognition performances [91]. Consequently, effects on delivery

kinetics can be attributed to recognition cavities. The effect of stronger interactions between recognition cavities and eluted drug molecules were reported in the work of Asadi and co-workers [92]. In the cited work, the authors have developed a cyproterone-imprinted system in which the slower release kinetics than in non-imprinted system was attributed to the interactions between drug functional groups and carboxylic groups in the polymer nanoparticles. This hypothesis was confirmed also for different drugs [93]. The mechanism under this behavior can be explained with a theoretical approach. The populations of recognition cavities distributed in the material can lead to a *tumbling* effect. The tumbling effect is the transfer of the molecule to be eluted from one cavity to another, with the continuous decomposition and formation of stable complexes. This migration generates multiple interaction patterns, which are as complex as the number of recognition cavities increases. The tumbling effect hypothesis was confirmed for acrylic-based hydrogels imprinted against ketotifen fumarate [94]. The cited study demonstrated the retarded release of the solute molecules, and the diffusion coefficient for MI hydrogels was quantified to be one order of magnitude lower than that calculated for non-imprinted crosslinked materials with comparable mesh size.

4.2. Covalent molecularly imprinted polymers as drug-delivery systems

Covalent molecularly imprinted polymers, imprinted against the drug to release, provide a more controlled delivery rate than non-covalent systems, due to the strong template/matrix bonds.

Despite this advantage, the use of covalent molecularly imprinted polymers for drug delivery is not recommended because covalent links could irreversibly retain part of the loaded drug. Linking the active molecule to the polymer matrix with cleavable linkers can overcome this limitation [95]. This approach was already demonstrated for antibody-drug conjugates [96], but their exploitation was limited by the potential leakage of side products arising from bond cleavage. For these systems, the biocompatibility of side products must be carefully checked.

4.3. Zero-order release kinetics MI systems

In zero-order release kinetics the release of the active molecule is constant with time. Such kinetic rate is the desired goal for a variety of applications. A zero-order kinetics offers the advantage to limit over- or under-dosage, improving patient compliance. The development of zero-order drug delivery systems is tricky but molecularly imprinted polymers have a high potential and some strategies are already under investigation.

The recent literature reports the preparation of molecularly imprinted particles with an almost zero-order release kinetics. Tang et al. [97] have reported a very simple method, based on macromolecular crowding, to modify the delivery kinetics. This method is based on the addition of a macromolecular co-solute (polystyrene) during particle synthesis obtaining a reduction of the diffusion coefficient by two orders of magnitude. More recently, Jia et al. [98] have reported the effect of heterogeneous macromolecular crowding, by adding to the main co-solute a low-molecular weight compound (polyethylene glycol) to further control release properties.

5. Stimuli-responsiveness and molecularly imprinted polymers

Stimuli-responsive polymers are able to change their properties under the effect of a stimulus. More relevant stimuli for drug delivery systems are related to specific pathological conditions, such as changes in temperature, pH and ionic strength, or presence/absence of a specific chemical specie. This feature was already reported for molecularly imprinted polymers, combining selective recognition with the capability to respond to external stimuli [99].

5.1. Thermo-responsive behavior

The majority of biochemical processes are highly sensitive to temperature changes. Temperature-active molecularly imprinted polymers can be obtained by preparing particles from thermo-responsive polymers.

The most common thermo-responsive biopolymer is the poly(*N*-isopropylacrylamide) (PNIPAam), which undergoes a reversible sol-to-gel transition by increasing the temperature over 32 °C in aqueous solution. The sol-to-gel transition involves the increase of hydrophobic interactions, the collapse of macromolecules and the squeezing of the water content. One of the first examples of PNIPAam-based imprinted hydrogel has been reported by Watanabe et al. [100]. This study confirmed that recognition properties and thermo-responsive properties can co-exist. In fact, the developed MI gel maintained its recognition properties after shrinking over the transition temperature. Moreover, such gel showed a molecular recognition state in which volume changes were attributed to the concentration of the template molecule in a solution in contact with the gel. Recognition properties in PNIPAam-based MIPs are mainly based on hydrogen bond interactions [101]. Small modifications to the PNIPAam composition increased recognition properties via multiple-point electrostatic interactions [102], and this approach resulted promising to obtain reversible recognition properties towards different groups of molecules [103,104]. The sharp sol-to-gel transition showed by PNIPAam-based MIPs can be also exploited to obtain switchable systems [105]. PNIPAam-based MIPs were also prepared for large protein recognition and release [106,107] with interesting results. Recently, the same polymer was used in the preparation of surface imprinted nanoparticles for the adsorption and release of blood proteins for human plasma [108]. The developed system was able to remove the target protein at high temperature (45 °C), and following release the same molecule at low temperature (4 °C). Despite the basic concept of the system is significantly interesting, temperature range is out of physiological conditions and a refinement of the thermo-responsive behavior of such MIPs is needed before a potential *in vivo* application. Recently, a hybrid copolymer poly(amino acid)-based was used for the surface imprinting on magnetic nanoparticles for lysozyme recognition and release [109]. In this case, rebinding and delivery kinetics were completely modulated by temperature changes, finding potential applications in the selective enrichment of an environment in target proteins. As a further enhancement, thermo-responsive MIPs are simple to be extracted after the preparation. This aspect was underlined in the study of Li et al. [110], indicating that the template was easily removed from oligo(ethylene glycol)-based MIPs imprinted against lysozymes by changing the temperature during particle washing.

5.2. pH-responsive behavior

pH-responsive materials are generally weak polyelectrolytes that can exchange protons at specific pH values. pH-responsive polymers can change their conformation in environments in which pH variations occur and this characteristic is suitable to obtain smart materials for controlled drug delivery.

The successful combination of imprinting and pH-responsive materials was already demonstrated [111,112], and two

exploitable mechanisms to obtain pH-controlled drug release from MIPs have been identified.

The first mechanism is based on the swelling or the shrinking of imprinted materials by changing pH. Functional monomers can be selected to form macromolecular segments that can modulate their hydrophilic/hydrophobic interactions in aqueous environment by changing pH. A good example of such systems has been reported by Kanekiyo and coworkers [113], which selected acryloyl amylose as functional monomer and bisphenol-A as template. The functional monomer formed helical inclusion-complex with the bisphenol-A after the occurrence of hydrophobic interactions in water. Formed complexes were labile and showed a reversible structural change upon pH variation, modulating the strength of polymer/template interactions.

The second mechanism involves changes in the chemistry of imprinted cavities. MIPs are generally obtained from polar monomers, like maleic, acrylic or methacrylic acid, which polarities increase interactions with the template. This class of monomers can also respond to pH variations donating or accepting protons. Being functional monomers involved in the formation of imprinted cavities and the same topologies accommodate drug molecules, the protonation or deprotonation of pH-responsive groups can trigger drug release. This mechanism was demonstrated by Puoci et al. with methacrylic acid-based molecularly imprinted particles imprinted against sulfasalazine [114]. The system provided a fast release of the active molecule when pH increased over 6.8, which was the average pKa of carboxylic groups in the system. Applications of MIPs based on the same design were extended to the delivery of paracetamol [115], dexamethasone phosphate [111], and doxorubicin [116].

5.3. Biochemical-responsive behavior

Biochemistry-responsive imprinted polymers can completely exploit their two main properties, controlled drug delivery and sensing. In these systems, entrapped active molecules are released with a specific timing and rate, only in the presence of a molecule, which modulate delivery profiles with its concentration. With this premise, biochemistry-responsive MIPs could enable a very smart and targeted drug delivery. Some relevant examples have been reported in the literature to confirm the feasibility of such controlled delivery. One of the first studies was reported by Sreenivasan et al. [117]. They developed a MIPs composed of 2-hydroxyethylmethacrylate, imprinted against hydrocortisone, for the controlled release of testosterone. The release rate of testosterone in water was very slow but, in the presence of the template molecule, this release rapidly increased.

6. Degradable MIPs

Polymer-based drug delivery systems are micro- or nanoparticles designed to transport the drug and, once the drug is released, empty particles should be eliminated from the body to avoid bioaccumulation. Particles can be excreted through biological fluids or biodegraded in smaller products to facilitate their clearance. In the last decade, drug-releasing systems are mainly prepared from degradable materials. Despite the relevance of MIPs as drug-delivery systems, MI is mostly applied to non-degradable polymers. It is a severe limitation to MI because non-degradable nanocarriers are accumulated in tissues and organs, and might be dangerous to living bodies [118].

Molecularly imprinted particles must be crosslinked to maintain their topology but crosslinking limits their degradability. The combination of degradation and molecular imprinting in particle-based systems was not explored for a long time, due to technological limitations. Only recently some studies on this topic have been reported in the literature.

To date, there are two different approaches to prepare degradable MIPs: i. completely degradable bulky MIPs and ii. partially degradable core/shell MIPs.

The literature reports only few examples of completely degradable polymer-based MIPs. An interesting approach to obtain degradable MIPs is the use of a degradable polymer as crosslinker, as reported in Ref. [119]. In the cited work, a branched oligomer, composed of poly(D,L-lactide-*co*-glycolide) was synthesized and modified to be used as functional macromer. Nanoparticles were imprinted against biotin, showing good recognition properties not only towards the template but also towards a biotin-labeled large protein. Nanoparticle degradation was confirmed in aqueous environment. Recognition properties were exploited to bind biotin molecules involved in the formation of a complex with their cell receptors. Nanoparticle internalization in HeLa cells was higher in imprinted particles than in the reference non-imprinted system.

Another approach is the use of a degradable low-molecular-weight crosslinker and water-soluble monomers to obtain degradable nanoparticles, as reported in Ref. [120]. In this case, MIPs were obtained with methacrylic acid as monomer and dimethacryloyl hydroxylamine as crosslinker. The template used for the synthesis was methotrexate, with application in breast cancer treatment. *In vitro* results on MCF7-breast cancer cells indicated higher cytotoxicity than free anticancer the cytotoxicity was investigated. With a similar approach, an imprinted degradable nanogel composed of methacrylic acid as functional monomer and the crosslinker, bis(2-methacryloyloxyethyl)disulfide containing disulfide bonds was imprinted toward S-propranolol and tested as drug carrier for intracellular delivery [121]. The system was able to modulate the release properties in the presence of glutathione as reducing agent.

Among partially degradable MIPs, Culver and co-workers have developed a method to obtain a surface imprinting on biodegradable poly(ε-caprolactone) core/shell nanoparticles [122]. The selected template molecule was lysozyme as a model protein. This was the first work in which degradable nanoparticles were used to support MI. PCL core was coated with a poly(maleic anhydride-*alt*-1-octadecene)-*g*-poly(ethylene glycol) methacrylate brushes to provide sites for polymerization of a molecularly imprinted coating.

Partially degradable magnetic MIPs were developed by Asadi and coworkers [123]. In their work, the crosslinker was obtained by derivatization of the natural fructose with methacryloyl chloride. Imprinted multi core/shell particles were obtained around a not degradable magnetic core composed of iron oxide and silica. The imprinted shell provided recognition sites toward Olanzapine, with recognition cavities exposed to the external surface. In this study the active drug targeting was obtained with an external magnetic field and the imprinted shell had the double function to release the drug and provide an additional energy source after degradation. The same group developed a similar system starting from tannic acid imprinted against 5-Fluorouracil [124]. This system showed high accumulation under an external magnetic field and a drug delivery kinetics tuned by environmental pH.

More recently, degradable core/shell particles, composed of fluorescent zeolitic imidazolate framework-8 as a core and a MI shell, were proposed for the delivery of doxorubicin in solid tumor tissues [125]. The shell was imprinted against the epitope of CD59 cell membrane glycoprotein, to endow particles of actively targeting recognition of MCF-7 cancer cells, that are CD59-positive. Such strategy was proposed to enrich tumor sites of doxorubicin-loaded nanoparticles exploiting the recognition properties of the imprinted particle surface. The imprinted shell of the system was obtained by using dimethyl aminoethyl methacrylate as the main

Table 1
Degradable molecularly imprinted particles currently present in the literature.

MIP	Template	Structure	Application	Ref.
Poly(D,L-lactide-*co*-glycolide)	Biotin	Fully degradable, bulk imprinted	Active cell internalization (Trojan horse)	[119]
Poly(methacrylic acid)	Methotrexate	Water-soluble, bulk imprinted	Breast cancer, prolonged drug delivery	[120]
Poly(methacrylic acid)	S-propranolol	Water-soluble, bulk imprinted	Intracellular controlled drug delivery system	[121]
Poly(maleic anhydride-alt-1-octadecene)-*g*-poly(ethylene glycol) methacrylate over a poly (caprolactone) core	Lysozyme	Fully degradable, surface imprinted	Synthetic antibody	[122]
Fructose derivative	Olanzapine	Partially degradable, surface imprinted (magnetic non-degradable core)	Active drug targeting (driven by external magnetic stimulus)	[123]
Tannin acid derivative	Fluorouracil	Partially degradable, surface imprinted (magnetic non-degradable core)	Active drug targeting (driven by external magnetic stimulus)	[124]
Poly(dimethyl aminoethyl methacrylate)	Epitope of CD59 cell membrane glycoprotein	Partially degradable, surface imprinted (non-degradable core)	Tumor imaging	[125]
Poly(ethylene glycol dimethacrylate)	Doxorubicin	Partially degradable, surface imprinted (non-degradable core)	pH- and reducing environment-responsive drug delivery	[126]
Glucose derivative	Docetaxel	Partially degradable, surface imprinted (non-degradable core)	Tumor imaging (driven by external magnetic stimulus)	[127]

monomer and *N*,*N*′-diacrylylcystamine as the crosslinker. The presence of disulfide bonds in the MI shell ensured the degradation in the presence of glutathione, while the core can be degraded when exposed to a weakly acidic environment. Both glutathione and weakly acidic environment are typical of tumor tissues. The same combination of pH-responsiveness and degradability was explored in the work by Zhang et al. [126]. In the cited work, the degradation of the molecularly imprinted particles was accounted to provide a significant increased release. After 12 h of incubation in *in vitro* tests, the percent amount of doxorubicin (template molecule) released from nanoparticles ranged from 20% at pH 7.4 to more than 75% at pH 5.0 in the presence of glutathione.

The combination of recognition properties of degradable molecularly imprinted particles and the functional properties of different materials to improve drug delivery was demonstrated in a fluorescent and magnetic drug carrier [127]. In order to ensure the multifunctionality of the system, the structure of the proposed delivery system was a multicore-shell, and the imprinted polymeric component was obtained by using a synthesized glucose-based crosslinker. The system showed an improved release of docetaxel (template), and a faster degradation at acidic pH than in a neutral environment.

For the sake of clarity, all the cited works related to degradable MI systems cited in this Section are summarized in Table 1.

7. Conclusions and future perspectives

Molecular Imprinting technology is a consolidate way to obtain materials with recognition properties. Such recognition properties can be exploited in different ways. In nanomedicine, MIPs can prolong the releasing time of a drug, can be used in active drug targeting or to obtain *in situ* Trojan horses. Recognition properties can be obtained also in thermo- and chemo-responsive polymers, giving the opportunity to obtain multifunctional materials.

To date, several efforts were done in the field of molecularly imprinted particles but, despite the promising advances in MI technology, the potential of molecularly imprinted particles in drug delivery was not yet completely explored. In this field, the literature reports a very small number of examples in which recognition properties, sensing and controlled delivery rate are simultaneously exploited.

There are important evidences of the high performances of such devices in targeted and controlled drug delivery but clinical applications are still far. The prolonged drug delivery was only verified in *in vitro* tests, as well as the recognition properties towards biological targets [128]. The combination of these two characteristics seems to be difficult to obtain and a very limited number of *in vivo* tests were developed with interesting results. The use of non-biodegradable particles, representing the large part of analyzed systems, is probably the most important limitation in molecularly imprinted particles exploitation.

There is a large amount of work to do before thinking about clinical exploitation of MIPs and particles but the current bench approaches, which combine experimental and theoretical studies, go in the right direction and it is desirable that in the coming years a wider application of MIPs and particles will be possible, with a considerable improvement in targeted therapies.

Declaration of competing interest

None.

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