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REVIEW

Advancing Drug Delivery with Biodegradable Molecularly Imprinted Polymers: From Design to Clinical Prospects

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Abstract: Molecularly imprinted polymers (MIPs) have emerged as promising materials for drug delivery systems, offering various advantages in terms of selectivity, stability, modified/smart release properties, and targeted therapy. Despite decades of development, the clinical translation of MIP-DDS remains limited, mainly due to concerns regarding long-term safety, biodegradability, and regulatory acceptance. To overcome these limitations, current research focuses on designing MIP-DDS by incorporating degradable monomers, crosslinkers, and polymer architectures. The selection of monomers and crosslinkers, as well as polymerization strategies, critically influences not only the efficiency of the recognition sites formed but also the rate of degradation and drug release, which can occur through stimuli-responsive bond cleavage, hydrolysis, or surface erosion. Beyond synthetic considerations, systemic evaluation of the biocompatibility, toxicity, and degradation mechanisms of MIP-DDS is essential to support regulatory approval and clinical implementation. Therefore, this article discusses current advances, key design strategies, degradation mechanisms, and translational challenges of biodegradable MIP-DDS, highlighting the development of clinically viable imprinted drug delivery platforms.

Keywords: molecularly imprinted polymer, drug delivery system, biodegradable MIP, modified release, stimuli-responsive

Introduction

Conventional drug delivery via oral or parenteral routes still has many limitations, such as non-specific distribution, low bioavailability and drug accumulation, plasma level fluctuations, and undesirable side effects due to uncontrolled drug release.[1,2] The limitations of conventional drug delivery highlight the urgent need for a more selective, targeted, and controlled drug delivery system to obtain optimal therapeutic concentrations and effects with minimal toxicity risk. To overcome these limitations, researchers in the pharmaceutical and biomedical fields have been developing novel drug delivery systems for several decades, including modified-release delivery systems, targeted delivery systems, and smart or stimulus-responsive drug delivery systems.[1,3] In the research and development of drug delivery system, polymers have been widely used as carriers. Polymer carriers are widely used because they provide more controlled drug release than conventional dosage forms. The mechanisms of drug release from polymer carriers include Fickian diffusion, diffusion through polymer matrix pores, and polymer matrix erosion.[4] The drug release mechanism from polymeric matrices depends on the composition of polymer, physicochemical properties of drug, crosslinking density, and environmental condition. Despite this controllable mechanism, the use of conventional polymeric carrier system may suffer from several limitations, such as poor drug loading, limited drug release control, and insufficient for targeted therapy; therefore, it is necessary to develop more advanced polymer materials as carriers in drug delivery.[5,6] In the development of selective, controlled, and effective drug delivery systems, molecularly imprinted polymers (MIPs) have emerged as a fascinating material with significant potential in renewable drug delivery. Moreover, the MIP application as a drug delivery system

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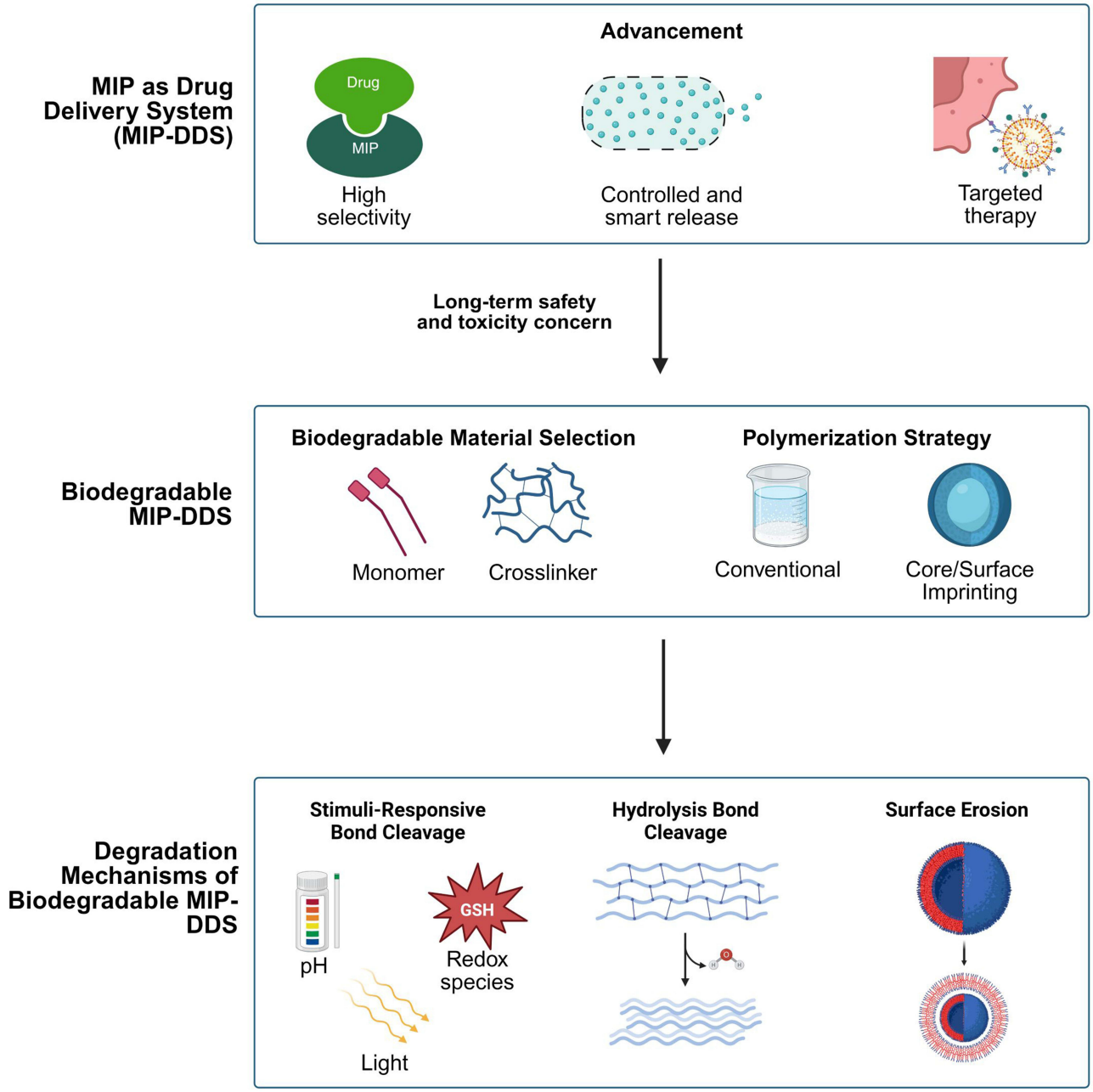
Graphical Abstract



was developed to overcome the limitations of conventional polymers, particularly uncontrolled and rapid drug release (burst release), which increases the risk of patients experiencing side effects or toxicity.[7,8]

MIPs are promising polymers as drug delivery systems because of their ability to improve drug release profiles and maintain drug effect in the body. MIPs are synthetic polymers prepared in the presence of template molecule, which create specific antibody-like recognition cavities that complementary in size, shape, and functional group to the template molecule. MIPs can provide specific recognition characteristics for a molecule due to the molecular imprinting process that occurs during polymerization.[9,10] Additionally, MIPs exhibit more several advantages, including high stability, high selectivity, high reusability, ease preparation, and wide range of applications.[9,10] During its early development, MIP was widely applied in

analytical separations and sensors. However, with the expansion of material development for drug delivery systems, MIP attracted attention for its several advantages, leading to the development of MIP as a drug delivery system (MIP-DDS) several decades ago.[9] The development of MIP-DDS has been widely explored for various types of preparations, including topical, transdermal, ocular, oral, and parenteral preparations.[11–16] MIP-DDS has also utilized several drugs as template molecules, including anti-cancer,[17,18] anti-arrhythmic,[19,20] anti-inflammatory,[21,22] antibacterial,[23,24] and antifungal agents.[25] Despite several advantages for drug delivery systems, conventional MIP-DDS remains based on highly crosslinked, non-degradable structural polymers, resulting in an insufficient understanding of its safety profile, degradation behavior, and long-term accumulation risks. Material of MIP-DDS can be absorbed into the body and tend to be difficult to degrade and eliminate naturally, thereby increasing the risk of bioaccumulation and long-term toxicity. Moreover, partial degradation of MIP-DDS has the potential to release polymer fragments with undesirable chemical properties that may cause inflammation, immune responses, and tissue damage. Although MIP-DDS are generally considered biocompatible, the long-term safety and potential toxicity of these materials have not been sufficiently studied, especially for in vivo and clinical applications. These limitations and issues of biocompatibility and biodegradability are major hindrances to the widespread application of MIP-DDS.[8,11,26]

To overcome the issue of biodegradability and biocompatibility of MIP-DDS, biodegradable molecularly imprinted polymers for drug delivery systems (biodegradable MIP-DDS) have been developed. Biodegradable MIP-DDS is a material for MIP-based drug delivery that focuses on the use of biodegradable, non-toxic, safer, and biocompatible materials, such as biopolymers or synthetic polymers composed of degradable compounds. Contrary to conventional MIP-DDS, which still relies extensively on non-degradable materials and highly crosslinked polymer networks, biodegradable MIP-DDS is designed with degradable polymer via cleavable linkages, such as ester and disulfide bonds, enabling control over the degradation rate while maintaining structural integrity for molecular recognition. Biodegradable MIP-DDS represents a significant advancement in drug delivery system development, combining molecular imprinting technology with controlled release from MIPs using biodegradable monomers or crosslinkers.[27–30] Biodegradable MIP-DDS is designed to deliver drugs specifically to target sites in a controlled and sustained way, ensuring that the polymer material breaks down into low-toxic and safe by products that can be excreted. The integration of biodegradability into MIPs paves the way for creating drug delivery systems that retain the advantages of MIPs while addressing the biodegradable issue associated with them. However, the lack of research and data related to the clinical use of MIP-DDS, regulatory agency approval, and strategies for preparing biodegradable MIP-DDS are limitations and obstacles to the clinical use of MIP-DDS. Currently, several articles have discussed biodegradable MIPs for drug delivery systems. However, these articles have not focused on the design and degradation mechanism of biodegradable MIP-DDS.[28] In this review article, the discussion also focuses on strategies for developing biodegradable MIP as a drug delivery system, the urgency and regulations regarding the use of biodegradable materials for drug delivery systems, and the degradation mechanism of biodegradable MIP-DDS. Therefore, this article can provide in-depth insights into the opportunities and challenges of biodegradable MIP as a new generation material for selective, controlled, and safe drug delivery.

Molecularly Imprinted Polymer and The Potential of Molecularly Imprinted Polymer as a Drug Delivery System

Basic Concept of Molecularly Imprinted Polymer

Molecular imprinting is a technique used to provide specific recognition characteristics to a material. MIPs are synthetic materials designed to recognize and bind target molecules specifically with high selectivity; therefore, MIPs are also known as synthetic antibodies. In MIPs, the molecular imprinting process occurs when monomers interact with template molecules, to form pre-polymerization complex, and linked by crosslinkers to form a cavity that is complementary to the template compound in terms of shape, size, dimensions, and chemical characteristics.[9,28,31] In the MIP synthesis process, template molecules, monomers, crosslinkers, and solvents are crucial components that can significantly impact the characteristics and performance of the MIPs. In general, the MIP synthesis process involves three main stages, ie., (1) the formation of a pre-polymerization complex between functional monomers and template molecules; (2) the polymerization process in which a crosslinker links together monomers to produce a stable polymer matrix; and (3) the removal of template molecules from the cavity to leave a specific cavity that is complementary to the template molecule (Figure 1).[32–34]

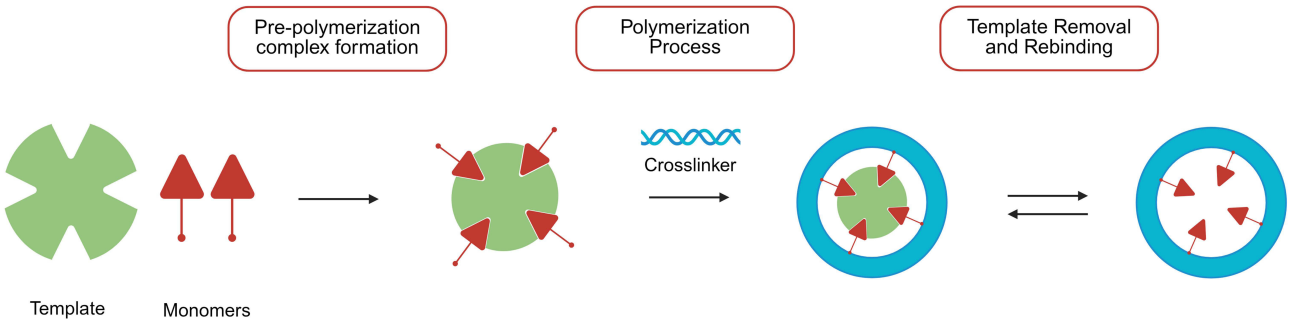


Figure 1 Illustration of the MIP synthesis process.

The MIP synthesis process has been achieved using various polymerization methods, including bulk polymerization, suspension polymerization, precipitation polymerization, surface polymerization, and emulsion polymerization.[33,35–38] In the successful synthesis of MIPs, several parameters in the polymerization process must be considered, including the molecular imprinting approach or strategy, the composition ratio of template molecules, monomers, and crosslinkers used, as well as the effects of solvents and polymerization temperature.[39] Molecular imprinting in MIP can occur during the polymerization process through three approaches based on the interaction between the monomer functional group and the template molecule, which are covalent, noncovalent, and semicovalent approaches. The covalent molecular imprinting approach can be applied when the template molecule is bound to the monomer by a reversible covalent bond. The reversible covalent bond, such as (boronic esters, esters, or imines) formed between the monomer and the template during the polymerization process can be dissociated through acid or base hydrolysis, resulting in a polymer that can rebind with the template molecule through covalent interactions. The noncovalent molecular imprinting approach can occur through hydrogen bonds, π-π stacking interactions, and electrostatic forces between the monomer and the template molecule during the pre-polymerization process. The semicovalent approach is a method that combines covalent interactions during the polymerization process with noncovalent interactions during the rebinding process.[35,40,41] In addition, MIPs also have several other advantages, including high stability under extreme conditions, flexibility in synthesis design, high reproducibility, and relatively low production costs compared to natural biomacromolecules.[10,34,42] Therefore, as MIP continues to develop, its use is also expanding in various fields, ranging from analysis and separation,[43,44] chemical sensors and biosensors,[45,46] compound purification,[47] and drug delivery systems.[23,48]

Molecularly Imprinted Polymer as Drug Delivery System (MIP-DDS)

In drug delivery systems, it is well known that polymers are one of the most useful drug carriers and have great potential for further development. Drug molecules dispersed within polymers can be released at a controlled rate over a specific period or under specific physical conditions. This can increase the success of therapy and reduce the risk of side effects or toxic effects in patients. However, because burst release still occur quite frequently in conventional polymer matrices, MIP was developed as an alternative to conventional polymers for drug delivery systems (MIP-DDS). In the field of drug delivery, MIP offers several advantages that are not found in conventional polymers. Specific cavities can be formed during the polymerization process using drug molecules as template molecules, allowing for high-affinity binding, high drug loading, and controlled drug release.[23,49] MIP-DDS also features a stable and flexible cavity, facilitating balanced and rapid drug loading and release. Additionally, MIP-DDS exhibits stability or resistance to undesirable enzymatic attacks.[50]

The use of MIP as a drug delivery system was first developed by Norell et al in 1998 for the sustained release of theophylline. Norell et al stated that MIP synthesized using theophylline as a template molecule provided good selectivity for theophylline compared to caffeine.[51] Additionally, the release profile of theophylline from MIP is more sustained compared to non-imprinted polymers (NIP). Studies related to the development of MIP-DDS are ongoing, with several examples listed in Table 1. Currently, using appropriate monomers, crosslinkers, or polymerization techniques, MIP-DDS has been designed as a stimuli-responsive DDS so that it can release drugs in response to certain stimuli, such as pH, temperature, and the presence of enzymes or other biomarkers.[8,52–56]

Table 1 Several Studies on Molecularly Imprinted Polymers as Drug Delivery Systems (MIP-DDS)

No	Drug Substances	Monomer	Polymerization Method	Drug Release Mechanism	Ref
1	Methotrexate	Acrylamide	Precipitation polymerization	pH-responsive	[57]
2	Aminoglutethimide	Methacrylic acid	In-situ polymerization	Controlled-release	[58]
3	S-sulpiride	N-acryloyl-tryptophan	Bulk polymerization	Controlled-release	[59]
4	Amitriptyline hydrochloride	Methacrylic acid	Precipitation polymerization	pH-responsive	[60]
5	Gallic acid	4-Vinylpiridine	In-situ polymerization	Controlled-release	[61]
6	Erythromycin	Methacrylic acid	Precipitation polymerization	Sustained-release	[62]
7	Sunitinib	Methacrylic acid	Precipitation polymerization	Controlled-release	[63]
8	Gentamicin	Polyvinyl alcohol	Emulsion cross-link polymerization	Wound dressing	[64]
9	Ciprofloxacin	Lactic acid; methacrylic acid	Emulsion polymerization, bulk polymerization, co-precipitation polymerization	Local controlled-release	[65]
10	Andrographolide	β-Cyclodextrin; 4-amino-4′-Methacrylamide azobenzene	Reverse atom transfers radical polymerization	pH/redox/light-responsive	[66]
11	5-Fluorouracil	Methacrylic acid	Bulk polymerization	Targeted-therapy	[67]
12	Clindamycin	Methacrylic acid	Precipitation polymerization	Controlled-release	[68]
13	Doxorubicin	Methacrylamide	Precipitation polymerization	Sustained-release	[69]
14	Cefixime	2-Hydroxyethyl methacrylate	Precipitation polymerization	Sustained-release	[48]
15	Tenofovir	*N1*-[(2-methacryloyloxy)ethyl] thymine and 2-(dimethylamino) ethyl methacrylate	Precipitation polymerization	Sustained-release	[25]

Although MIPs have great potential as drug delivery systems, MIPs still have fundamental limitations for application in drug delivery systems. MIP-DDS are generally synthesized using methacrylate or vinyl derivative monomers and crosslinkers with sufficiently high concentrations to ensure the strength and rigidity of the MIP structure. However, this leads to MIP-DDS having a very slow degradation rate in biological environments. Some MIP-DDS cannot be broken down through normal physiological metabolic pathways, so they tend to accumulate in tissues after entering the body.[29,70] The accumulation of MIP components poses a risk of long-term side effects, including local or systemic toxicity and tissue inflammation. In addition, several in vivo test results indicate that MIP allows for partial degradation, depending on the chemical structure, degree of crosslinking, and the presence of biodegradable linkages. Partial degradation of MIP-DDS can reduce the risk of long-term accumulation and toxicity. However, fragments resulting from partial degradation can induce an immune response that increases the risk or severity of inflammation.[11,71]

The urgency of developing MIP-DDS to be more suitable for clinical applications and drug delivery is increasing. Current MIP-DDS development is carried out using monomers or crosslinkers that are more biodegradable and biocompatible, thereby encouraging the use of biodegradable MIPs for drug delivery. The use of biodegradable materials has been widely adopted in various fields, including food, packaging, tissue engineering, agriculture, and drug delivery systems.[72–76] Biodegradable MIP-DDS is an innovation of MIP-DDS that addresses the limitations and issues of biodegradability and biocompatibility of conventional MIP-DDS, without compromising the selectivity, drug delivery, and stability of conventional MIP-DDS.

Urgency of Biodegradable Material for Molecularly Imprinted Polymer as Drug Delivery System (MIP-DDS)

MIP-DDS, which has been developed over several decades, has demonstrated its success in controlling and prolonging drug release,[21,77] targeted drug delivery,[27,78] and drug delivery in response to specific stimuli.[79,80] However, to date, further research on MIP-DDS in clinical trials has not been conducted. This is due to the limited application of MIP-DDS in clinical trials, primarily because of a lack of long-term biocompatibility data, regulatory approval, and the need to meet pharmaceutical requirements for patient use. The requirements for MIP to be used as a drug delivery system include (Figure 2):[7,8,81]

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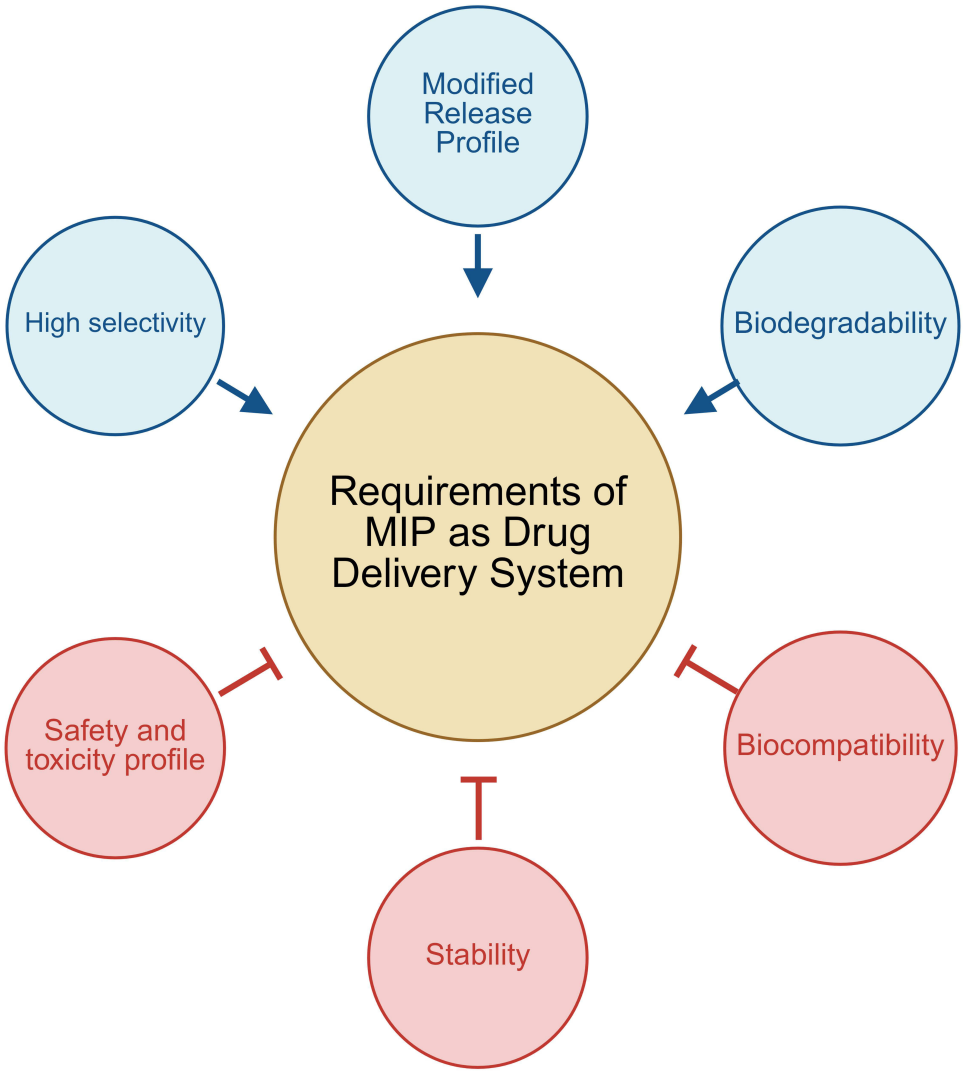

Figure 2 Pharmaceutical requirements of MIP as drug delivery system (MIP-DDS) for clinical applications.

1) High selectivity: the drug molecules can bind to the recognition site with high specificity and improved drug release control;
2) Modified release profile: MIP can be engineered for modified drug release, such as stimuli-responsive, controlled, and sustained release;
3) Biodegradability and biocompatibility: the incorporation of biodegradable materials in MIP-DDS may overcome the long-term accumulation and toxicity risks;
4) Stability: MIP-DDS must provide good thermal and chemical stability, thereby facilitating handling and storage processes;
5) Safety and toxicity profile: ensure that the materials or degradation byproducts of MIP-DDS do not cause side effects or long-term toxicity.

In addition, the synthesis of MIP-DDS, which has been extensively researched, still uses many non-degradable materials, making it difficult to apply MIP-DDS clinically. MIP-DDS is synthesized using a crosslinker that is suitable and sufficient to maintain its shape and recognition site. Still, the use of crosslinkers can also cause biocompatibility issues with MIP.[28] Furthermore, acrylate, methacrylate, or pyridine derivative monomers, which are widely used in MIP-

DDS synthesis, are generally safe at certain exposure levels, but still pose a risk of local irritation and systemic toxicity if they accumulate in the body.[82,83]

Research and development related to biodegradable MIP-DDS is still limited. This highlights the challenges in designing biodegradable MIP-DDS, as the biodegradability of MIP-DDS is influenced by the overall composition of the MIP and its structural architecture. However, current research still focuses heavily on developing biodegradable monomers and crosslinkers to form degradable imprinted networks. In recent years, certain biodegradable polymers have attracted considerable attention in the development of drug delivery due to their degradation behaviour and physicochemical properties can be engineered to influence drug release kinetics.[72,84] Therefore, several studies have combined biodegradable polymers with imprinting techniques to produce ideal biodegradable MIP-DDS for drug delivery systems. Biodegradable polymers can be combined to synthesize biodegradable MIP-DDS, which may include natural polymers or biodegradable synthetic polymers. Natural polymers, such as chitosan and cyclodextrin, have been widely used in medical applications and offer advantages in terms of biodegradability and biocompatibility.[15,66,85–87] In addition, biodegradable synthetic polymers, such as poly(3-hydroxybutyrate), poly(ε-caprolactone), and poly(lactic acid) also have been explored for MIP-DDS applications due to their degradable backbones and tunable physicochemical properties. Polyethylene glycol (PEG), although not strictly biodegradable, also widely incorporated because its biocompatibility, solubility in water, and excretability, that improve the overall safety profile of the MIP-DDS systems.[29,88–91] Biodegradable polymers used in the development of MIP-DDS are expected to undergo degradation under physiological conditions, producing low-toxic or metabolizable byproducts, thereby reducing toxicity risk and improving long-term safety. The degradation mechanisms of biodegradable polymers include hydrolytic cleavage, enzymatic degradation, surface erosion, and bulk erosion.[92] However, advanced mechanisms such as stimuli-responsive degradation (eg., pH, temperature, and light) have also been widely developed for the preparation of MIP-DDS using several synthetic biodegradable polymers.[66,93] The degradation rate of biodegradable polymers greatly affects drug release from MIP-DDS. More faster a degradation rate can cause premature drug release, while a slower degradation rate can inhibit drug release.[94] Therefore, the design of MIP-DDS preparation needs to be considered to achieve the expected polymer degradation and drug release rates.

Besides monomers, the substitution of crosslinkers commonly used in MIP-DDS synthesis, such as ethylene glycol dimethacrylate (EDGMA) and trimethylolpropane trimethacrylate (TRIM), with biodegradable crosslinkers is also urgent in the development of biodegradable MIP-DDS. Biodegradable crosslinkers can be either natural or biodegradable synthetic crosslinkers. Natural crosslinkers that can be used for the synthesis of biodegradable MIP-DDS can be peptide-based crosslinkers or bio-based polymers.[95,96] Meanwhile, biodegradable synthetic crosslinkers, such as acryloyl-terminated poly(lactide-co-glycolide) (PLGA) and dimethacryloyl hydroxylamine, are also known to degrade well through hydrolysis while maintaining the structure and recognition site of MIP-DDS.[18,97,98] The strategy of using biodegradable monomers and crosslinkers in the development of biodegradable MIP-DDS is discussed in more detail in sub-discussion *Design and Synthesis Strategy of Biodegradable MIP-DDS*.

The use of biodegradable materials in the synthesis of biodegradable MIP-DDS can also directly address the regulatory requirements of several drug regulatory agencies worldwide, including the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). The FDA and EMA frameworks and regulations evaluate the safety, biocompatibility, clearance, and long-term tolerability of residual polymer components from polymeric drug delivery systems.[99,100] When approving biodegradable materials for use in drug delivery systems, regulatory agencies consider and evaluate several key factors, including biocompatibility, degradation rate, drug release profile, and stability during clinical use. Several biodegradable polymers, such as poly(lactic-co-glycolide) (PLGA), poly(glycolic acid) (PGA), and poly(lactic acid) (PLA), have been approved by the FDA for use in several medical applications, such as implants, sutures, wound dressings, and drug delivery.[101,102] The use of these polymers has not yet been directly applied in the preparation of MIP-DDS. However, with the approval of biodegradable polymers for medical use, there is potential for their use in the preparation of MIP-DDS, which could accelerate the application of MIP-DDS in clinical field. The use of biodegradable polymers approved by regulatory agencies for the synthesis of biodegradable MIP-DDS can strengthen compliance with regulatory requirements for safety and efficacy, thereby accelerating the progress of biodegradable MIP-DDS for clinical use.

Design and Synthesis Strategy of Biodegradable MIP-DDS

The rational design and selection of synthesis techniques for biodegradable MIP-DDS require the careful integration of molecular recognition principles with biodegradable materials. Contrary to conventional MIPs, which use monomers and crosslinkers that are not easily degraded under physiological conditions, biodegradable MIP-DDS must be engineered with materials that can be safely and predictably degraded under physiological conditions. Therefore, strategies for selecting suitable monomers and crosslinkers, as well as synthesis techniques that enhance molecular recognition efficiency, need to be determined and well-organized to produce biodegradable MIP-DDS with optimal performance and characteristics.

Design Strategy of Biodegradable MIP-DDS

Monomer and Crosslinker Selection of Biodegradable MIP-DDS

The selection of suitable monomers and crosslinkers is a crucial step in designing biodegradable MIP-DDS, as they not only determine the imprinting efficiency and binding specificity to template molecules but also influence the biodegradability and biocompatibility behavior of biodegradable MIP-DDS. In previous studies on the synthesis of MIP-DDS, the use of methacrylate-based monomers and rigid crosslinkers, such as EGDMA or TRIM, was widely used to provide good mechanical stability and molecular recognition.[13,20,21,103] However, these materials still raise concerns and issues regarding bioaccumulation and long-term toxicity due to their lack of biodegradability.

To overcome these concerns and issues, the use of biodegradable materials has been introduced, such as natural polymer derivative monomers (chitosan, gelatin, and cyclodextrin) or biodegradable synthetic polymers (polylactic acid, polycaprolactone, and poly(lactic-co-glycolic acid)).[90,91,102] In addition, the use of biodegradable crosslinkers with ester, anhydride, and peptide bonds can also be employed to enhance the biodegradability of MIP-DDS, as they enable control over hydrolysis or enzymatic degradation under physiological conditions.[18,104] Several studies related to biodegradable MIP-DDS using biodegradable monomers and crosslinkers are listed in Table 2. By selecting the appropriate monomer-crosslinker combination, biodegradable MIP-DDS with molecular recognition, structural stability, and safe degradation can be achieved.

In several related studies, as shown in Table 2, the synthesis of biodegradable MIP-DDS can be achieved using synthetic monomers or natural polymers to impart biodegradable characteristics. One example of a synthetic monomer used in the

Table 2 Several Studies of Biodegradable Molecularly Imprinted Polymer as Drug Delivery System (MIP-DDS)

No	Template	Monomer	Crosslinker	Polymerization Technique	Type of MIP-DDS	Ref
Drug Molecule as Template						
1	Methotrexate	Methacrylic acid	N,O-dimethacryloyl hydroxylamine	Mini-emulsion	Controlled-release	[18]
2	Irinotecan	2-N,2-N-Diethyl-6-prop-1-en-2-yl-1,3,5-triazine-2,4-diamine (metformin HCl derivative)	Serotonin-conjugated fructose	Mini-emulsion	Self-targeted therapy	[104]
3	Docetaxel	Methacryloxypropyl trimethoxysilane	Glucose derivative	Microemulsion	Targeted therapy	[27]
4	Olanzapine	Methacryloxypropyl trimethoxysilane	Fructose derivative	Co-precipitation	Targeted therapy	[70]
5	5-Fluorouracil	Methacryloxypropyl trimethoxysilane	Tannic acid derivative	Mini-emulsion	Targeted therapy, sustained and controlled-release	[105]
6	Furosemide	Acrylamide	Cellulose acrylate	Radical polymerization	Controlled-release	[106]
7	Theophylline	Acrylic acid	Diacrylated PCL	UV photopolymerization	NA	[29]
8	Riboflavin	Low molecular weight chitosan	NA	NA (assembly of polymers)	Controlled-release	[107]
9	S-propranolol	Methacrylic acid	Bis(2-methacryloyloxyethyl) disulfide (DSDMA)	Bulk polymerization	Reduction responsive-release	[108]
10	Methotrexate	Acrylamide	1,4-Bis(acryloyl)piperazine	Core-shell polymerization	pH-reponsive	[57]

(*Continued*)

Table 2 (Continued).

No	Template	Monomer	Crosslinker	Polymerization Technique	Type of MIP-DDS	Ref
Biomarker Molecule as Template						
11	Sialic acid	Self-made monomer (glycerol + lactide) and dopamine	NA	Core-shell polymerization	Targeted therapy; controlled-release	[109]
12	Epitope CD59 Cell	Dimethylaminoethyl methacrylate	N,N′-Diacrylylcystamine	Core-shell polymerization	Targeted fluorescent imaging; GSH/pH dual-responsive release	[110]
13	Sialic acid and transferrin	2-Amino-N-(3,4-dihydroxyphenethyl)-3-mercaptopropanamide; 4-Mercaptophenylboronic acid	NA	Surface imprinting	Multiple targeted therapy; pH/redox responsive-release	[111]
14	Sarcosine	2-Acrylamido-2-methyl-1-propanesulfonic acid; 1-Vinylimidazole	Hyaluronic acid	Core-shell polymerization	Targeted therapy; controlled-release	[112]

synthesis of biodegradable MIP-DDS is a modified monomer from metformin HCl for the delivery of irinotecan.[104] Metformin HCl was chosen as a component of the monomer because it has a proven safety and toxicity profile and is known to have potential anticancer effects that support targeted therapy of MIP-DDS.[113] Modification of metformin HCl as a monomer was carried out by adding methacryloyl chloride, which serves as a functionalization agent. The addition of methacryloyl chloride to metformin HCl provides a vinyl double bond group to metformin HCl, enabling free radical polymerization between them.[104] The use of synthetic monomers with materials or compounds that have proven biodegradability, safety, and toxicity characteristics is one strategy in the synthesis of biodegradable MIP-DDS.

Apart from synthesizing biodegradable MIP-DDS using monomers, biodegradable MIP-DDS can also be prepared using imprinting techniques on pre-formed polymers such as chitosan or cyclodextrin. In one study, MIP-DDS was synthesized for riboflavin delivery using low-molecular-weight chitosan, which is non-toxic, biodegradable, and hydrophilic.[114] In the preparation of riboflavin MIP-DDS from pre-formed polymers conducted by Mokhtari and Ghaedi, no crosslinker chemicals were used, which could reduce the problems of biocompatibility and toxicity of the resulting MIP-DDS.[107] Chitosan-based MIP-DDS for riboflavin delivery was prepared by dispersing and combining chitosan with riboflavin, followed by stirring at 60°C overnight, which resulted in a thick polymer solution. This study demonstrated that utilizing natural polymers as a backbone for the preparation of biodegradable MIP-DDS is a viable strategy.

The selection of biodegradable crosslinkers is also a consideration in the preparation of biodegradable MIP-DDS. New crosslinkers containing hydrolysable groups have been synthesized in several studies, increasing the biodegradability of MIP-DDS. For example, the crosslinker N,O-dimethacryloyl hydroxylamine was synthesized from methacryloyl chloride with hydroxylamine, resulting in a hydrolysable functional group, CO-O-NH-CO group. The synthesized N,O-dimethacryloyl hydroxylamine crosslinker was then used to prepare controlled-release methotrexate MIP-DDS. The use of N, O-dimethacryloyl hydroxylamine crosslinker could increase the degradation rate of MIP-DDS in alkaline conditions, when compared to MIP-DDS prepared using EGDMA crosslinker. This occured because the functional groups in N, O-dimethacryloyl hydroxylamine could accelerate the hydrolysis process of the crosslinker, thereby rapidly reducing the structure and rigidity of the polymer.[18]

Besides the addition of hydrolysable groups to the crosslinker, the use of crosslinkers with disulfide bonds can also increase the degradability of MIP-DDS in response to the presence of reducing agents (reduction-responsive). Crosslinkers with disulfide bonds, such as N,N′-diacrylylcystamine and bis(2-methacryloyloxyethyl)disulfide (DSDMA), can be used for cancer drug delivery, where MIP-DDS with these crosslinkers can be degraded in the cancer microenvironment due to high glutathione concentrations.[108,110] Preparation of MIP-DDS with N,N′-diacrylylcystamine crosslinker was used for doxorubicin delivery systems.[110] The doxorubicin-loaded MIP-DDS framework will break down under the stimulation of the tumor microenvironment, where glutathione concentrations are high and pH conditions are slightly acidic. This induces the release of doxorubicin and further degradation of the MIP-DDS. In addition to anticancer drug delivery, MIP-DDS preparations with crosslinkers that have disulfide bonds can also be made for other drugs, such as S-propranolol MIP-DDS preparations using

DSDMA crosslinkers.[108] The release and degradation of S-propranolol are facilitated by different reducing agents, including glutathione, dithiothreitol (DTT), and sodium borohydride ($NaBH_4$). From MIP-DDS reductive responsive studies, it can be conclude that the presence of reducing agents can induce degradation of the polymer structure, thereby inducing the drug release and increasing the degradability of MIP-DDS.

Another strategy that can be implemented is the modification of biomolecular derivatives, such as glucose and fructose, to obtain biodegradable crosslinkers with good water-compatibility characteristics, which helps improve drug release under physiological conditions.[27,70,104] In addition, using biomolecular derivatives may improve biocompatibility and reduce the risk of long-term accumulation compared to MIP-DDS synthesis using synthetic crosslinkers such as EGDMA or TRIM. The modification of glucose and fructose to act as crosslinkers can be achieved by substituting the hydroxyl (−OH) group in glucose and fructose with functional groups that are more susceptible to undergo free radical polymerization, such as methacrylate, divinyl, or aldehyde derivative functional groups. A common modification involves reacting methacryloyl chloride with glucose or fructose to obtain a modified crosslinker.[27,70]

Preparation of biodegradable magnetic MIP-DDS for docetaxel was carried out using a modified glucose crosslinker for targeted cancer therapy. The evaluation of adsorption capacity, drug release, and degradability showed that the biodegradable magnetic MIP-DDS with a modified glucose-based crosslinker exhibited excellent performance, indicating its potential suitability as a drug delivery system for cancer therapy.[27] Additionally, biodegradable MIP-DDS with a modified fructose crosslinker was also prepared for the targeted delivery of olanzapine to brain tissue. The selection of fructose as a crosslinker was based not only on its biodegradability, but also on the fact that fructose compounds are needed by the brain as fuel, so that the degradation products of MIP-DDS in the form of fructose can be reused by the body and do not leave behind harmful degradation products.[70,115]

In summary, rational selection strategies and modification of monomers or crosslinkers play a crucial role in the development of biodegradable MIP-DDS, resulting in excellent performance, imprinting, and favorable degradation behavior. Each degradable material has its own advantages and limitations in the preparation of biodegradable MIP-DDS. The use of synthetic biodegradable monomers, such as self-made dopamine- and metformin-based monomers, offers greater flexibility and the possibility of structural modification. Self-made monomers usually require modification or the addition of active functional groups that facilitate strong interactions with template molecules during the imprinting process. For example, in self-made metformin monomers, functionalization with vinyl groups is required for efficient polymerization, enabling the formation of well-defined and efficient imprinting cavities. However, this functionalization itself becomes an additional step that can increase the complexity of the biodegradable MIP-DDS synthesis process, which needs to be considered. In contrast, the use of pre-formed degradable polymers, such as chitosan and cyclodextrin, as polymer networks for biodegradable MIP-DDS can provide advantages in terms of biocompatibility, biodegradability, and reduced toxicity risk. The use of chitosan and cyclodextrin has also been widely applied in the biomedical field, thereby strengthening regulatory considerations. In addition, pre-formed degradable polymers are abundant in active functional groups, such as hydroxyl and amine, eliminating the need for functionalization. However, pre-formed degradable polymers have lower rigidity than self-made monomers, potentially reducing the structural rigidity, stability, and fidelity of the MIP-DDS recognition site.

The transition from conventional rigid crosslinkers, such as EGDMA and TRIM, to biodegradable synthetic or natural-based crosslinkers addresses concerns related to bioaccumulation and long-term toxicity. Incorporating biodegradable functional groups, such as esters, anhydrides, peptides, and disulfides, enables controlled degradation under physiological or pathological stimuli, thereby enhancing safety and therapeutic efficiency. Moreover, the introduction of biomolecule-derived crosslinkers, such as glucose- and fructose-based derivatives, offers additional advantages in terms of water-compatibility, biocompatibility, and environmental sustainability. These strategies demonstrate that careful tailoring of monomer–crosslinker combinations can ensure the structural integrity and molecular recognition capacity of MIP-DDS, while also providing safe degradation pathways that meet the requirements for advanced and targeted drug delivery applications.

Template Selection of Biodegradable MIP-DDS

The selection of template molecules for the preparation of biodegradable MIP-DDS is a fundamental step because template molecules not only define the recognition sites in the matrix polymer but also directly influence the specificity, sensitivity, and overall clinical performance of MIP-DDS.[42,116] As a whole, several requirements or characteristics must be considered when selecting a template molecule for MIP synthesis. Essential attributes of a template molecule include a structure and functional

groups complementary to the functional monomer, good chemical and thermal stability under polymerization conditions, solubility in the solvent used for polymerization, and the availability and safety of the template.[117] In the preparation of biodegradable MIP-DDS, the template molecules can be drug molecules, biomarker fragments, or receptor fragments, each of which plays a distinct role. While drug molecules are used to create imprints that enable controlled and sustained release, biomarker and receptor fragments act as recognition targets, allowing the system to respond to specific physiological signals and thereby enabling more precise and responsive drug delivery.[18,106,109,110,118] Several studies on biodegradable MIP-DDS with drug molecules and biomarkers or receptor fragments as template molecules are shown in Table 2.

Sialic acid is a monosaccharide commonly found on the surface of cancer cells and is an important biomarker that indicates the presence of cancer cells.[119] The development of biodegradable MIP-DDS for targeted cancer therapy can use sialic acid as a template molecule, so that the resulting MIP-DDS can recognize cancer cells, like the antigen-antibody principle.[109] The use of sialic acid as a template molecule for the preparation of targeted MIP-DDS has been done before, but the use of biodegradable materials has not been the main focus.[118] Biodegradable MIP-DDS with sialic acid templates were prepared using magnesium ion-doped silica nanoparticles (Mg-SMSNs/DOX-Ce6) as the MIP-DDS framework.[109] Stellated mesoporous silica nanoparticles (SMSNs) possess high surface area and drug loading efficiency; however, their degradation rate is slow due to the presence of silicon and oxygen atoms. Therefore, the use of Mg^{2+} doping can increase the biodegradability of mesoporous silica nanoparticles because the Mg-O bond is pH-sensitive, so it can be broken in the microenvironment of cancer, which has a slightly acidic pH.[109,120,121] In addition, MIP synthesis on the Mg-SMSNs/DOX-Ce6 surface was carried out using self-made biodegradable monomers containing numerous ester bonds and 4-aminophenylboronic acid as an auxiliary monomer. Self-made biodegradable monomers with ester bonds can be easily degraded under the acidic conditions of the tumor environment and break down the MIP layer on the Mg-SMSNs/DOX-Ce6 surface.[109]

The preparation of biodegradable MIP-DDS can also be achieved using sialic acid and transferrin as multitemplates, in addition to using sialic acid as a single template.[111] Transferrin is a biomarker that plays a role in cell growth and is overexpressed in cancer cells.[122,123] Disulfide-bridged dendritic mesoporous organosilica nanoparticles (SS-DMONs) are utilized as the framework of biodegradable MIP-DDS due to their several benefits, including enhanced drug loading, a large surface area for the imprinting process, and the presence of disulfide bonds that can be broken in the tumor microenvironment, thereby facilitating the degradation of MIP-DDS. Doxorubicin-chlorin e6 loaded SS-DMONs (SS-DMONS/DOX-Ce6@MIPs) were imprinted on their surface using monomers 2-amino-N-(3,4-dihydroxyphenethyl)-3-mercaptopropanamide and 4-mercaptophenylboronic acid, as well as the multitemplate sialic acid and transferrin. Therefore, the use of multitemplate sialic acid and transferrin can enhance the precision of targeted therapy and enable effective drug release in response to dual stimuli (chemical and photodynamic).[111]

The use of epitopes from a cell as template molecules for biodegradable MIP-DDS has also been attempted. Fluorescent zeolitic imidazolate framework-8 nanoparticles loaded with doxorubicin (FZIF-8/DOX) were used as the core, which were then coated with biodegradable MIP-DDS for targeted drug delivery. In the imprinting process on the surface of FZIF-8/DOX, the CD59 cell membrane glycoprotein epitope was used as a template, allowing FZIF-8/DOX-MIPs to recognize cancer cells that express CD59. Additionally, in line to obtain biodegradable MIP-DDS, crosslinkers and monomers with biodegradable characteristics were used to get a MIP-DDS framework that could be destroyed by tumor microenvironment stimulation.[110]

The selection of suitable template molecules, whether drug molecules or biomarker and receptor fragments, is the core of designing biodegradable MIP-DDS with high therapeutic potential. The selection of templates not only determines the selectivity of recognition sites but also determines the capability of MIP-DDS to be used as targeted therapy and the effectiveness of the therapy. Template molecules from disease biomarkers, such as sialic acid, cell epitopes, and transferrin, enable MIP-DDS to selectively recognize cancer cells, thus playing an important role in the specificity of targeted therapy. Furthermore, integrating a biodegradable framework or a stimuli-responsive material ensures that the MIP-DDS system can undergo controlled degradation under physiological conditions or in the tumor microenvironment, minimizing the risk of side effects and systemic toxicity. In addition, the use of drug molecules as templates remains a widely used and developed strategy for MIP-DDS preparation, providing a controlled and smart drug-release profile. Collectively, these strategies highlight how rational template selection combined with degradable materials can synergistically improve the specificity, responsiveness, and clinical performance of MIP-DDS, opening the door to more effective and safer targeted drug delivery systems.

Synthesis Strategy of Biodegradable MIP-DDS

Developing biodegradable molecularly imprinted polymer drug delivery systems (MIP-DDS) requires careful selection of polymerization methods to ensure both imprinting efficiency and biodegradability. Recent advances focus on green chemistry, surface modification, and the use of novel monomers and cross-linkers.[16,91,124] From several studies related to biodegradable MIP-DDS listed in Table 2, the preparation of biodegradable MIP-DDS can be performed using various polymerization methods, including emulsion polymerization,[18,27,104,105] precipitation polymerization,[70] bulk polymerization,[108] core-shell polymerization,[110] and surface polymerization.[111] The selection of the polymerization method is also based on the desired physicochemical characteristics and release behavior of biodegradable MIP-DDS.

Emulsion Polymerization

Emulsion polymerization is a polymerization process in which monomers, crosslinkers, and templates are dispersed in a continuous phase (typically water), forming micelles or droplets with the aid of surfactants. Emulsion polymerization can produce spherical MIP-DDS particles with controlled sizes (Figure 3a).[125] Several biodegradable MIP-DDS preparations have been carried out using mini-emulsion or microemulsion polymerization techniques, especially for the preparation of MIP-DDS nanoparticles.[27,51,104] The mini-emulsion method can produce droplets with larger sizes, around 50–500 nm, compared to microemulsion (about 10–100 nm).[126] The preparation of biodegradable material-based MIP-DDS nanoparticles for irinotecan delivery was carried out using the mini-emulsion method to obtain MIP-DDS with a homogeneous monodisperse

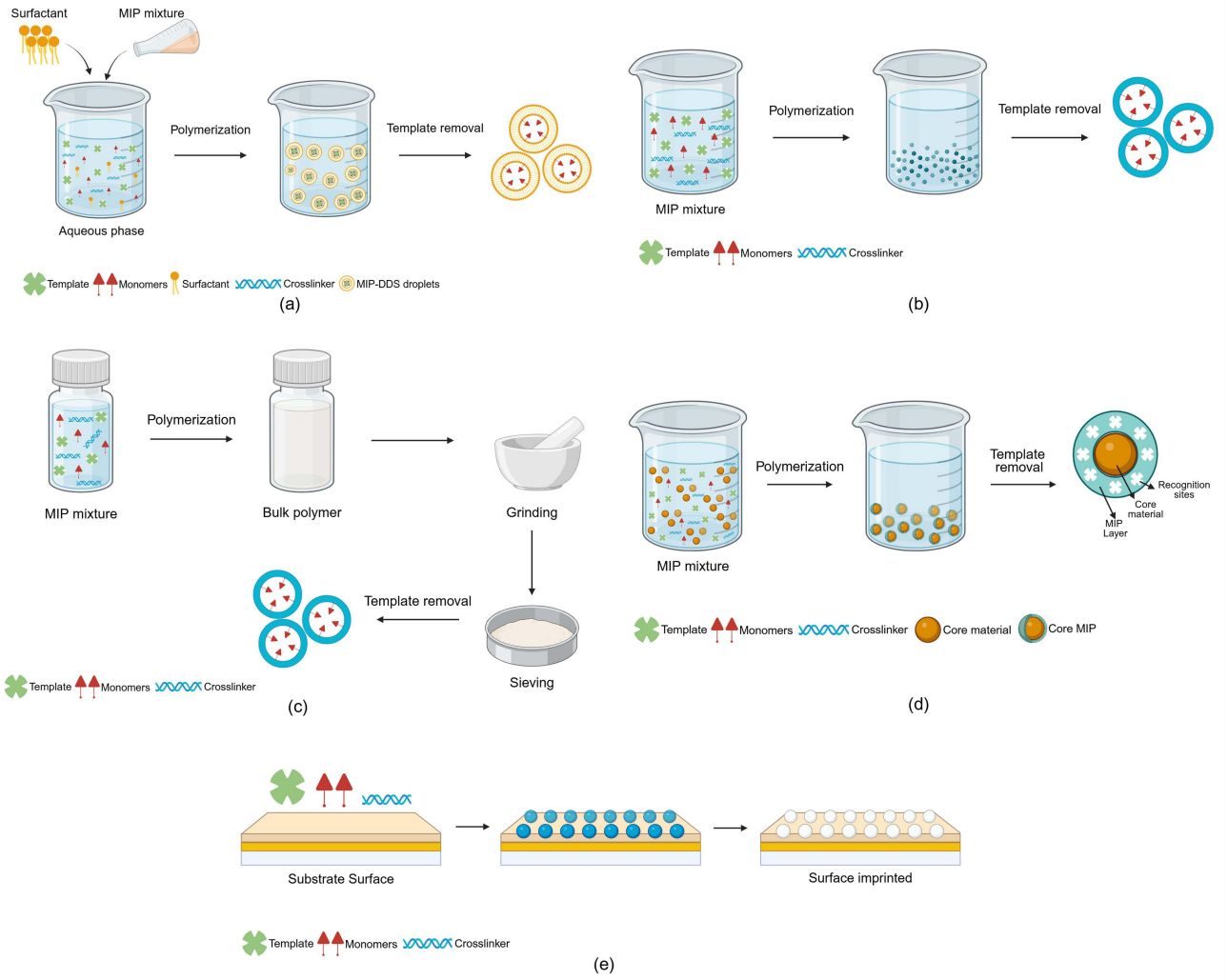

Figure 3 Illustration of biodegradable MIP-DDS preparation techniques by (**a**) emulsion polymerization, (**b**) precipitation polymerization, (**c**) bulk polymerization, (**d**) core-shell imprinting, and (**e**) surface imprinting.

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morphology. Additionally, the nanoparticle shape was selected based on its large surface area, which can increase the rate of degradation and drug release as desired. The use of modified metformin chloride monomer and serotonin-conjugated fructose crosslinker in the synthesis of irinotecan MIP-DDS nanoparticles is expected to ensure complete degradation of the nanoparticles under physiological conditions.[104] Additionally, the microemulsion polymerization method has been employed to modify fluorescent magnetic nanoparticles for the delivery of docetaxel. The preparation began with the synthesis of fluorescent magnetic nanoparticles, which were then coated with a biodegradable MIP-DDS matrix composed of a complex of monomers, glucose crosslinkers, and docetaxel. This preparation was carried out to produce MIP-DDS with the ability to release drugs and detect the presence of drugs in the body by fluorescence, by replacing harmful crosslinkers with biodegradable crosslinkers.[27]

Precipitation Polymerization

Precipitation polymerization is a polymerization technique in which the growing polymer chains become insoluble in the reaction medium and spontaneously precipitate, forming uniform suspended particles. In precipitation polymerization, the solvent serves as the reaction medium, but some solvents can also affect the morphology and porosity of the resulting MIP-DDS. Precipitation polymerization can be used to prepare uniform nanoparticles with porous microspheres, which can enhance selectivity and binding efficiency (Figure 3b).[36,127] For example, biodegradable magnetic MIP-DDS for targeted delivery of olanzapine to the brain was prepared using a sucrose-based biodegradable crosslinker. In the synthesis of biodegradable magnetic MIP-DDS, magnetic nanoparticles were synthesized and modified with citrate functional groups. The resulting nanoparticles were then coated with silica to improve the dispersion of the magnetic core in the polymer matrix. The magnetic nanoparticles then served as the base material for the synthesis of magnetic fluorescent nanoparticles, which were achieved by adding a fluorescent agent. The preparation process continued with the fabrication of magnetic MIP-DDS using the co-precipitation polymerization method. The co-precipitation polymerization yielded uniform biodegradable magnetic MIP-DDS with an average size of approximately 20 nm and a MIP layer thickness of around 5–7 nm on the surface of the magnetic fluorescent nanoparticles.[70]

Bulk Polymerization

Bulk polymerization is a polymerization method that produces polymers with irregular shapes and large particle sizes, requiring grinding and sieving processes to obtain particles with homogeneous particle sizes (Figure 3c). Bulk polymerization is a simple polymerization method that is widely used to produce polymers with a wide range of applications, including drug delivery systems.[36,127,128] One of the biodegradable MIP-DDS synthesized by bulk polymerization is a biodegradable MIP-DDS for S-propranolol delivery, utilizing a crosslinker with a disulfide group, bis(2-methacryloyloxyethyl)disulfide (DSDMA). The MIP-DDS synthesized by bulk polymerization exhibited irregular and rough shapes, with particle sizes exceeding 1 μm, as determined by scanning electron microscopy (SEM) analysis. However, polymers synthesized by bulk polymerization yield uneven binding sites on the polymer matrix. In addition, the bulk polymerization method made it challenging to control the size and shape of MIP-DDS particles, so other polymerization methods were preferred.[108]

Core-Shell and Surface Polymerization

Core-shell and surface polymerization strategies are at the forefront of designing advanced, biodegradable MIP-DDS. These approaches enable precise control over drug loading, release, and targeting, while ensuring biocompatibility and degradability. Core-shell MIP-DDS typically utilizes a biodegradable core loaded with drugs, such as metal-organic frameworks, silica, or biopolymers, which is then coated with MIP to provide molecular recognition and modified release characteristics (Figure 3d).[112,129] Meanwhile, in surface polymerization, the imprinting process occurs directly on the surface of the carrier, such as nanoparticles, silica, or drug crystals, resulting in recognition sites exposed on the outer surface (Figure 3e).[130] In the core-shell/surface polymerization process, the surface of the core material or substrate can be modified by adding reactive functional groups (eg., hydroxyl, amine, and carboxylate) to enhance interaction between the core material or substrate and the monomer. In addition, surface modification with reactive functional groups is preferred and widely used to help control the synthesis process and the thickness of the resulting MIP shell. For example, silica nanoparticle core materials are often modified by adding silanol (Si-OH) functional groups using modification

agents such as (3-Aminopropyl) triethoxysilane (APTES). The functional monomers used to synthesize the MIP layer on the surface of the core material or substrate will interact with the reactive functional groups resulting from the modification, and the MIP layer will be synthesized after thermal/photochemical/electro-initiation.[131]

Core-shell polymerization was applied in the coating of fluorescent zeolitic imidazolate framework-8 nanoparticles loaded with doxorubicin (FZIF-8/DOX) as a tumor-targeted biodegradable MIP-DDS. In the preparation of FZIF-8/DOX-MIP, MIP was synthesized on the surface of the FZIF-8/DOX core using the CD59 glycoprotein epitope as a template molecule to provide targeted therapeutic capabilities to cancer cells. In addition, the core-shell synthesis process was carried out using N,N′-diacrylylcystamine crosslinker with disulfide bridges, ensuring that FZIF-8/DOX-MIP would degrade in the tumor microenvironment.[110] Meanwhile, surface polymerization was applied in the preparation of sialic acid-transferrin imprinted biodegradable organosilica (SS-DMONS/DOX-Ce6@MIPs) for the delivery of doxorubicin and chlorin e6. The use of mesoporous organosilica with a large surface area can increase the success of the imprinting process on the surface of organosilica nanoparticles. Similar to the preparation of FZIF-8/DOX-MIP, the use of a crosslinker containing a disulfide bridge can induce the degradation of biodegradable MIP-DDS nanoparticles, allowing them to disintegrate under physiological conditions, particularly in the tumor or cancer microenvironment.[111]

The selection of polymerization methods plays an essential role in determining the efficiency, biocompatibility, and degradation behavior of biodegradable MIP-DDS. While bulk polymerization is a simple polymerization method, it has limitations in terms of morphology and particle size. In contrast, emulsion and precipitation polymerization offer better control over particle size and morphology, enabling the production of nano-sized polymer particles. Moreover, advanced methods such as core-shell and surface polymerization can also be employed as strategies to produce biodegradable MIP-DDS with improved size control, targeting, and biodegradability, which can facilitate further development of biodegradable MIP-DDS.

The choice of polymerization technique also affects the degradation behavior of MIP-DDS. In general, there are two approaches to preparing biodegradable MIP-DDS, which are bulky imprinting to produce completely degradable MIP-DDS and core-shell and surface imprinting to produce partially degradable MIP-DDS.[28] In the bulky imprinting process using biodegradable materials, the matrix or framework of MIP-DDS can be completely degraded, leaving no residual scaffold. This occurs because the imprinting site and degradable materials are distributed throughout the polymer matrix. Completely degradable MIP-DDS is excellent for loading high amounts of drugs and prioritizing the biodegradability of the polymer framework.[11,28,29] Meanwhile, in core-shell and surface imprinting, the MIP layer is synthesized on the surface of the particle core, which is usually inorganic or non-biodegradable, such as carbon microspheres, metal-organic frameworks, and magnetic nanoparticles. Thus, the degradation process only occurs on the MIP surface layer and leaves the particle core undegraded, requiring further elimination. However, the partial degradation process can provide advantages by offering faster binding kinetics and better control over drug release from the MIP-DDS matrix.[28,109,111,132]

Degradation Mechanism of Biodegradable MIP-DDS

The degradation mechanism of biodegradable MIP-DDS is a crucial aspect that determines the level of biocompatibility and biodegradability, safety, and efficiency of drug release. Understanding how the process and mechanism of biodegradable MIP-DDS degradation occur in a physiological environment can provide insight into the drug release profile and the design of MIP-DDS preparations. In general, the degradation mechanism of MIP-DDS can be influenced by several factors, such as polymer composition, degree of crosslinking, and environmental stimuli.[133,134] Based on several studies, the degradation of biodegradable MIP-DDS can be categorized into three mechanisms: stimuli-responsive bond cleavage,[108,110,135] hydrolysis,[18,70] and MIP surface erosion.[92,136] These mechanisms often act simultaneously or sequentially, ultimately ensuring that biodegradable MIP-DDS release the drug at a controlled rate while degrading into nontoxic metabolites. Drug release from biodegradable structures consists of two main complex processes. First, drug molecules diffuse through the polymer network, and second, the drug is released into the body, followed by destruction of the polymer matrix (Figure 4).

Stimuli-Responsive Bond Cleavage

Bond cleavage in biodegradable MIP-DDS frameworks occurs in bonds that are labile or sensitive to physiological or pathological triggers. Stimuli that often trigger bond cleavage in biodegradable MIP-DDS are the presence of reducing agents or pH conditions that are more acidic or basic than normal conditions. Disulfide bonds are an example of bonds

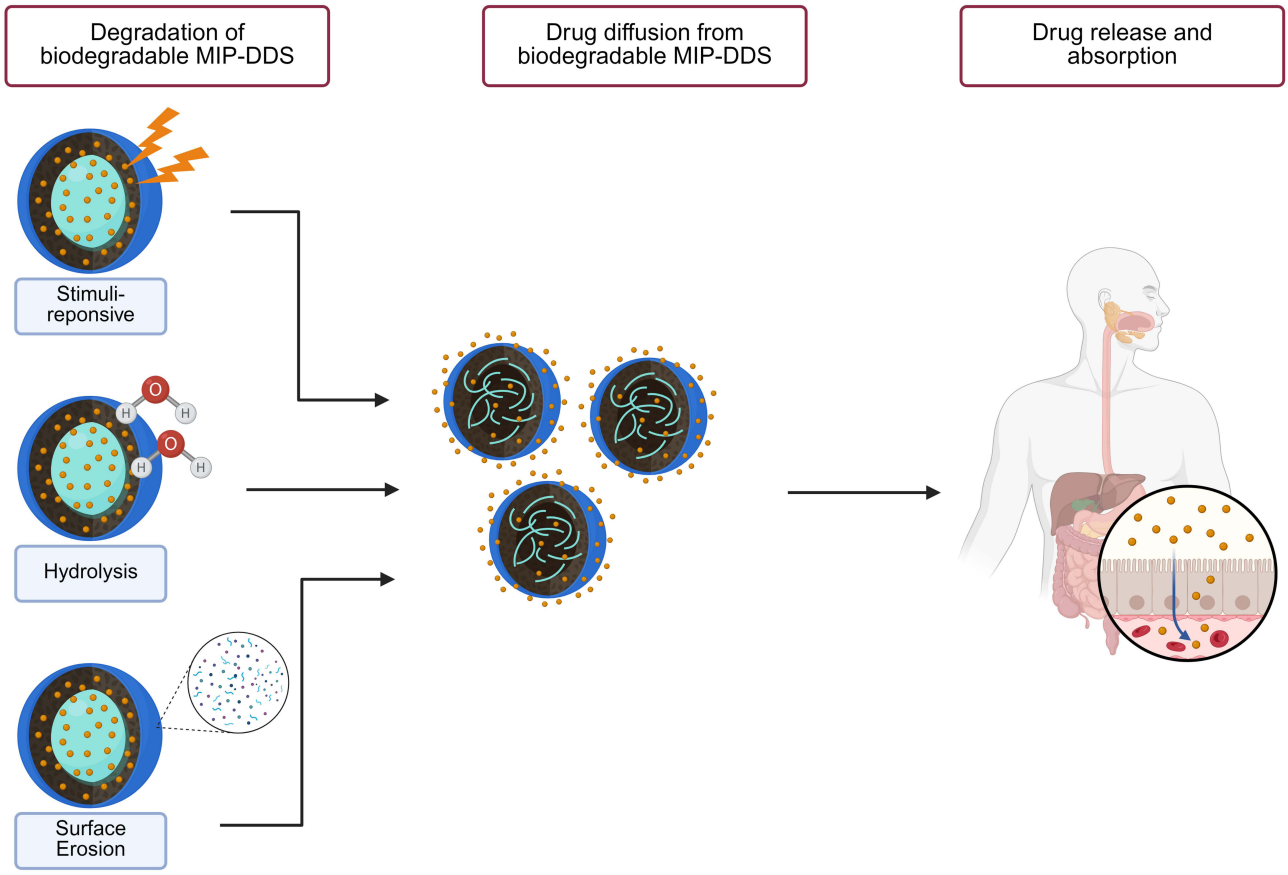

Figure 4 The degradation mechanism of biodegradable MIP-DDS.

that are easily broken in the presence of reducing agents, such as glutathione in the tumor microenvironment. Biodegradable MIP-DDS that use monomers or crosslinkers with disulfide bonds can undergo degradation and drug release if the disulfide bonds break and the polymer matrix is destroyed.[108,110,111] In addition to reducing agents, changes in pH from normal physiological conditions can also trigger bond breaking and destruction of the biodegradable MIP-DDS matrix. Ester bonds present in biodegradable MIP-DDS can undergo bond breaking in slightly acidic physiological environments, such as those found in cancer cells or within the intracellular environment. Ester bonds can undergo protonation in acidic environments, allowing the biodegradable MIP-DDS framework to be exposed to physiological environments for further degradation.[27,109]

The degradation mechanism of bond cleavage due to reduction/pH-sensitivity can occur simultaneously in biodegradable MIP-DDS. pH-responsive biodegradable core nanoparticles, such as zinc-based metal-organic frameworks, can be coated with MIP containing disulfide bonds. In a cancer cell environment, the MIP layer on the surface of the core nanoparticle degrades first due to the presence of reducing agents. Degradation of the MIP layer exposes the pH-sensitive core nanoparticle to the slightly acidic environment of cancer cells, allowing the core nanoparticle to also degrade and induce drug release.[110,111]

Overall, stimuli-responsive bond cleavage provides an effective strategy for integrating molecular recognition with degradation in biodegradable MIP-DDS. The incorporation of labile bonds, such as disulfide bonds, allows MIP-DDS to remain stable under normal physiological conditions but undergo degradation under specific pathological microenvironment conditions, such as the presence of glutathione (GSH) and slightly acidic conditions in tumor tissue. This characteristic provides a particular advantage for improving drug-release selectivity and minimizing premature drug leakage during systemic circulation. However, the effectiveness of stimuli-responsive bond cleavage strongly influences the balance between structural stability and responsiveness of the MIP-DDS network. An excessive number of labile

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bonds compromises the mechanical stability of MIP-DDS and reduces the fidelity of the recognition cavities, thereby limiting degradation efficiency and delaying drug release. In addition, variations in pH and glutathione concentration also affect the diversity of MIP-DDS degradation behavior.[110,111] Therefore, the selection of monomers or crosslinkers that can provide stimuli-responsive characteristics needs to be considered and ensured to be suitable for the desired drug release design.

Hydrolysis and Enzymatic Degradation

Hydrolysis is the most fundamental degradation pathway of biodegradable MIP-DDS. Hydrolysis is achieved through the interaction between water molecules and hydrolyzable functional groups in the MIP-DDS framework, which can be derived from modified monomers or crosslinkers. Ester, amide, anhydride, and carbonate functional groups are particularly susceptible to hydrolysis under physiological conditions, allowing MIP-DDS chains to break down into smaller and more soluble fragments.[137,138] Under physiological conditions, biodegradable MIP-DDS that is susceptible to hydrolysis will undergo hydrolysis, forming water-soluble polymers. In addition, modification of biodegradable MIP-DDS by incorporating hydrolyzable groups into the polymer framework can enable polymer degradation in different pH environments.[18] Biodegradable MIP-DDS that has undergone hydrolysis and polymer framework degradation promotes the release of drugs loaded within the system. Biodegradable MIP-DDS can also undergo degradation due to enzymatic reactions. Systems incorporating crosslinkers derived from modified glucose or fructose are highly susceptible to crosslinker bond cleavage by glycosidic bond-cleaving enzymes, such as glycosidases.[27,70,104] Other enzymes, such as lipases and proteases, may also cause enzymatic degradations depending on the compositions of the biodegradable MIP-DDS.[139,140]

Surface Erosion

Surface erosion is a physical degradation that often occurs in polymers, characterized by the loss of material as monomers remove themselves from the surface or polymer framework. Several factors, such as hydrophilicity, morphology, and drug loading, can influence the erosion mechanism in biodegradable MIP-DDS. Layer-by-layer surface erosion is also crucial in controlling the release of drugs from MIP-DDS. Surface erosion often occurs in biodegradable MIPs that are synthesized or imprinted on the surface of a nanoparticle core. Water or enzymes from the physiological environment can react with the biodegradable MIP layer exposed on the surface, thereby breaking down the biodegradable MIP layer and converting it into fragments that are soluble in the surrounding environment. In surface erosion, the particle size of biodegradable MIP-DDS becomes smaller even though its shape or morphology remains the same. The rate of surface erosion can also affect the rate of drug release, so it is very important to ensure that the surface erosion process can release the drug with a rapid onset and prolonged duration.[92,136,141,142]

The degradation mechanism of biodegradable MIP-DDS has a significant impact on drug release performance. In addition to ensuring the safety and breakdown of the polymer matrix into non-toxic products, the degradation of biodegradable MIP-DDS also influences the rate and duration of drug release. Degradation pathways or mechanisms, such as stimuli-responsive bond cleavage, hydrolysis, and enzyme degradation, as well as surface erosion of biodegradable MIP-DDS, can ensure that the polymer framework undergoes a controlled breakdown into non-toxic and biocompatible byproducts. A comprehensive understanding of the degradation mechanism of biodegradable MIP-DDS is crucial in designing its preparation, particularly for selecting and modifying materials that will undergo degradation.

Key Challenge and Future Prospects of Biodegradable MIP-DDS

Biodegradable MIP-DDS offers innovation and potential for targeted therapy and controlled drug release, along with selectivity for specific drug molecules or pathological biomarkers. However, biodegradable MIP-DDS also has several limitations and challenges, especially for clinical applications. Currently, the selection and development of suitable biodegradable monomers or crosslinkers for MIP-DDS preparation are still limited, which restricts the design and performance of MIP as biodegradable drug delivery system.[18,28] Moreover, the template removal process, which typically employs solvents, can leave residues and increase the risk of residual toxicity, thereby affecting biocompatibility.[10,143] Scale-up and reproducibility of biodegradable MIP-DDS preparation to produce consistent quality and performance also remain obstacles to the extensive application of biodegradable MIP-DDS due to variability and complexity during batch-to-batch process.[94,143] The

physical stability and in vivo validation of biodegradable MIP-DDS require further investigation to ensure favorable pharmacokinetic profiles, long-term safety, and controlled biodegradation rate, thereby bringing clinical translation one step closer. Another limitation is the uncertainty surrounding the regulation and commercialization of biodegradable MIP-DDS, particularly the approval of biodegradable MIP-DDS materials for clinical use and drug delivery devices.[28,94,143]

Despite its limitations and challenges, there are still potential area for research and development of biodegradable MIP as drug carrier. Potential directions include the development of new biodegradable monomers or crosslinkers, green synthesis techniques, and stimuli-responsive properties, all of which could widen the design scope and safety profile of biodegradable MIP-DDS. The integration of smart stimuli, surface modification, and hybridization with target ligands could enable the use of biodegradable MIP-DDS as a smart and multi-responsive system, as well as for personalized or targeted therapy. Furthermore, further clinical studies of biodegradable MIP-DDS can clarify its safety, efficacy, and biodegradation, thereby supporting regulatory approval. Biodegradable MIP-DDS holds significant potential for targeted, controlled, advanced, and safe therapeutics. Overcoming current challenges through material innovation, improved manufacturing, and thorough in vivo validation will be crucial for their future clinical success.

Conclusion

MIP is a promising material for drug delivery systems because it offers various advantages, including high structural stability, high selectivity, good drug-loading capacity, and the ability to enable controlled and targeted drug release. Despite offering significant advantages for the development of drug delivery systems, the clinical translation of MIP-DDS is still limited, primarily due to concerns related to biodegradability, biocompatibility, long-term safety, and toxicity. The development of MIP-DDS using biodegradable materials, such as monomers and crosslinkers, has emerged as one of the strategies used to overcome these limitations and open the way for clinical applications of MIP-DDS. However, current research is still fragmented and has critical gaps that need to be addressed. In particular, a systematic design strategy is still needed to balance imprinting efficiency with controlled biodegradability, as excessive degradation risks compromising the stability of the recognition site, while insufficient degradation can inhibit drug release and safe elimination from the body. Future research should focus on the selection and rational engineering of biodegradable monomers and crosslinkers for the preparation of biodegradable MIP-DDS. In addition, the development of advanced polymerization strategies is also necessary to maintain high-precision imprinting while enabling predictable degradation under physiological conditions. Furthermore, comprehensive in vitro and in vivo evaluations, consisting of degradation kinetics, degradation product toxicity, pharmacokinetics, and long-term safety, are essential for establishing the safety profile of biodegradable MIP-DDS. These practical steps also require standardization, evaluation protocols, and regulations that encourage the clinical translation of MIP-DDS. By overcoming these challenges, biodegradable MIP-DDS can evolve from a promising experimental system into a viable drug delivery platform for safer and more precise therapeutic interventions.

Abbreviations

DSDMA, Bis(2-methacryloyloxyethyl)disulfide; DTT, Dithiothreitol; EDGMA, Ethylene glycol dimethacrylate; EMA, European Medicines Agency; FDA, Food and Drug Administration; FZIF-8/DOX, Fluorescent zeolitic imidazolate framework-8 nanoparticles loaded with doxorubicin; MIP, Molecularly Imprinted Polymer; MIP-DDS, Molecularly Imprinted Polymer Drug Delivery System; $NaBH_4$, Sodium borohydride; NIP, Non-imprinted Polymer; PGA, Poly (glycolic acid); PLA, Poly(lactic acid); PLGA, Poly(lactic-co-glycolic acid); SEM, Scanning Electron Microscopy; SMSN, Stellated Mesoporous Silica Nanoparticle; SS-DMONS/DOX-Ce6@MIPs, Doxorubicin-chlorin e6 loaded SS-DMONs; TRIM, Trimethylolpropane trimethacrylate.

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Disclosure

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