MIP-Based Drug Delivery Systems

Subjects: Cell & Tissue Engineering

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Despite the tremendous efforts made in the past decades, severe side/toxic effects and poor bioavailability still represent the main challenges that hinder the clinical translation of drug molecules. This has turned the attention of investigators towards drug delivery vehicles that provide a localized and controlled drug delivery. Molecularly imprinted polymers (MIPs) as novel and versatile drug delivery vehicles have been widely studied in recent years due to the advantages of selective recognition, enhanced drug loading, sustained release, and robustness in harsh conditions. This review highlights the design and development of strategies undertaken for MIPs used as drug delivery vehicles involving different drug delivery mechanisms, such as rate-programmed, stimuli-responsive and active targeting, published during the course of the past five years.

Keywords: molecularly imprinted polymers ; drug delivery systems

1. Introduction

1.1. Drug Delivery Systems

Certain categories of pharmaceuticals, such as peptides, gene-based drugs and small molecules with low solubility and/or lipophilicity, cannot be effectively delivered using conventional formulations, due to enzymatic degradation and/or insufficient absorption into systemic circulation because of molecular size and charge. A drug delivery system (DDS) refers to a device or a formulation that vehiculates a therapeutic agent into the body, with an adequate dosage and possibly in a targeted manner, at the desired rate and time to reduce adverse effects, improve patient compliance and extend the duration of pharmacological actions [1].

The loading capacity of different DDSs can significantly affect treatment efficiency and/or dosing frequency in various ways, mainly by a change of the pharmacokinetic and pharmacodynamic profile [2][3]. In particular, polymers as drug delivery vehicles have significantly advanced the progress of DDSs production [4][5]. For polymer-based DDSs, drug molecules are normally dispersed within a polymer matrix or behind a polymer membrane, aimed at releasing drugs at a controlled rate or under certain physiological conditions. Thus, various side/adverse effects of the drug can be reduced or even significantly overcome [6][7][8][9][10][11][12][13][14][15][16].

Nevertheless, a burst release of drug is frequently observed in conventional polymeric vehicles, thus resulting in potentially severe consequences for the patients such as toxicity issues and undesirable side effects caused by temporarily high-drug dosage [5]. To date, although improved polymeric vehicles have been developed, some key knowledge gaps in terms of toxicity, physicochemical instability and lack of stimuli-responsiveness have been limitedly addressed, thus hindering practical applications [17][18][19]. On average, only one of the 5000 polymer-based DDSs that enters preclinical studies turns into an approved dosage form after ~10 years (from the initial conception to the market approval) [20].

1.2. Molecular Imprinting: Advanced Synthetic Molecular Recognition

Many approaches have been investigated to overcome the limitations existing in conventional polymer vehicles [21][22][23]. Amongst these approaches, molecularly imprinted polymers (MIPs) represent promising polymeric carriers that could potentially ameliorate drug delivery due to their unique features. Molecular imprinting technology can generate polymers with the ability to recognize specific target molecules. In addition to this main molecular recognition feature [24], MIPs exhibit high stability in harsh conditions (including extreme pH, presence of organic solvents, high temperature and high pressure) [25][26]. Furthermore, they possess a number of advantages such as ease of preparation, cost-effectiveness, enhanced drug loading and even potential enantioselectivity [27][28][29]. Therefore, controlled and/or targeted drug delivery can be tailored for different routes of administration and pathological conditions.

The affinity of polymers for template molecules during polymerization was first demonstrated by the seminal work of Polyakov in 1931 [30]. However, it was not until the 1970s that the pioneering work of Wulff and Sarhan [31] and Arshady and Mosbach [32] brought MIPs back into focus. Indeed, there has been increasing interest in the rational design of polymer networks for molecular recognition in various fields, such as sensors [33][34][35], separation science [36], enzyme mimics [37], synthetic antibodies [38][39][40], drug discovery [41], and drug delivery [42].

MIPs are prepared in the presence of target molecules, called “templates”, used to generate specific and complementary binding sites within the polymer matrix. This allows MIPs to recognize the templates with antibody-like affinity and selectivity [36][43]. Generally, functional monomers, template molecules, cross-linkers, initiators and solvents are all essential components to the synthesis of MIPs [5][27]. The choice of the functional monomer(s) is driven by the template molecule, and polymeric matrices are mainly prepared by free radical polymerization [44]. Nonetheless, other polymerization techniques such as controlled radical polymerization [45] [e.g., reversible addition-fragmentation chain transfer (RAFT) and atom transfer radical polymerization (ATRP)] and ring-opening polymerization approaches [46][47] (anionic, cationic and radical ring-opening polymerization) have also been used. Despite the advantages, issues associated with industrial-scale manufacturing, such as the difficulty in automatic production, currently represent a significant obstacle to the translation of MIPs from academia to the commercial stage.

In the conventional preparation scheme of MIPs [29], the functional molecule(s) and the free template molecule(s) (Figure 1) initially form what is known as a pre-polymerization complex, which is then polymerized in the presence of a suitable cross-linker after addition of an initiator molecule. The crosslinking monomer is crucial to stabilize this three-dimensional structure into the polymeric material. To remove the template, usually manual washings or Soxhlet extraction performed using mild acids and organic solvents are used. The template binding cavities are thus generated in the polymeric matrix, and exhibit shape, size, orientation and chemical moieties complementary to the template molecules, thereby allowing for selective rebinding.

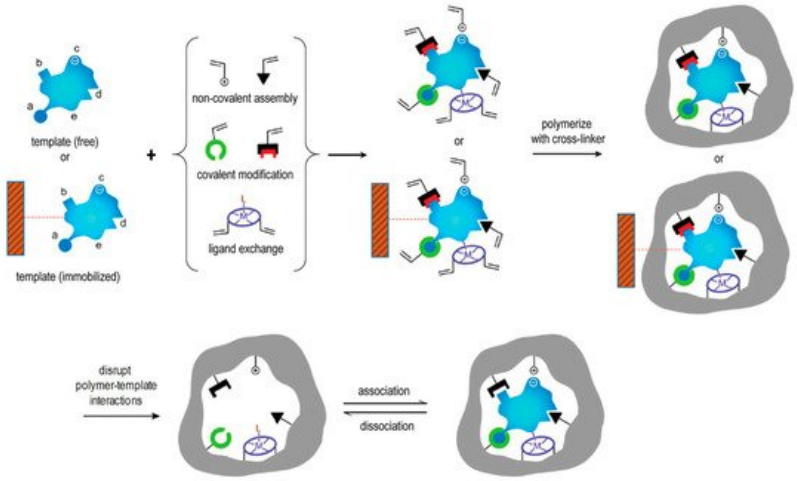

Figure 1. Scheme of the molecular imprinting process: the establishment of interactions between the template (free in solution or immobilized on a suitable solid support) and polymerizable groups interacting either covalently, non-covalently, or via co-ordination with a metal center with suitable functional groups or structural elements of the template. Subsequent polymerization in presence of a cross-linker develops a porous insoluble matrix containing the binding sites for the template. At this point, either the template is removed (if free), or alternatively the polymer is separated from the immobilized template in suitable washing/elution conditions. In all cases the target analyte can selectively rebind to the polymer into the sites formed by the template, or “imprints”. Reproduced with permission from Patel et al. [29].

However, the practical and commercial applications of MIPs prepared with free template molecules in solution have been limited by several issues, including template residues leftover in polymeric matrices, binding site heterogeneity and complex production processes [48]. To address these limitations, solid-phase synthesis approaches that rely on the template molecules immobilized on a solid surface have been recently developed (e.g., to prepare MIP nanoparticles, MIP NPs) (Figure 1). MIPs prepared in this fashion usually exhibit high affinity and selectivity for the target molecules and do not contain leftover template molecules, eventually leading to a final product with higher target affinity and selectivity than MIPs prepared in presence of free template molecules [49][50][51][52][53][54][55][56][57][58][59].

1.3. The Rationale of MIPs Used in Drug Delivery

The use of molecular imprinting technology in DDSs is a novel and attractive field of research, which can generate efficient polymeric DDSs with the high specificity to recognize target biomolecules and the ability to introduce stimuli-

responsiveness [60][61][62]. Although MIPs-based DDSs have not been translated to the clinic yet, the molecular imprinting technology has a great potential to create ideal dosage forms. A good proof is that publications devoted to the use of MIPs in the design of novel DDSs and devices are gradually increasing [63][64][65]. Although the number of studies on drug delivery related to molecular imprinting is still limited, the studies on MIP-based drug delivery have increased significantly in the past five years, with more than 50% of the papers on drug delivery related to molecular imprinting published on PubMed during this time span, which indicates the increasing interest in the use of molecular imprinting vehicles as DDSs (Figure 2).

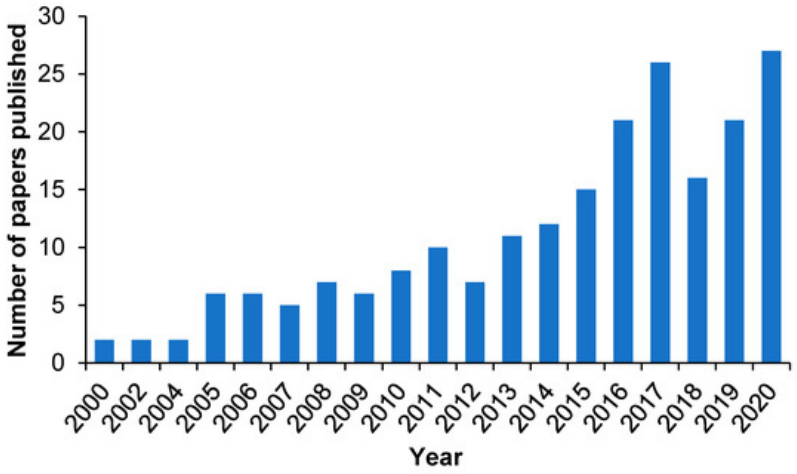

Figure 2. Number of published papers on MIP-based DDSs in the years 2000–2020. Source: PubMed.

Additionally, owing to the high stability and robustness of MIPs in harsh conditions, MIPs have shown fascinating potential in drug delivery. Indeed, MIPs can be stored in a dry state at room temperature without losing their recognition properties for several years [5]. Furthermore, the high stability and robustness render MIPs promising vehicles for drug delivery because the imprinted cavities can protect drug molecules from complex human body environments such as within the gastrointestinal tract [66].

The considerations for the safety and biocompatibility of MIP-based DDS are extremely important. Acrylic and methacrylic monomers have been widely used in various MIP applications, and they can also be used to develop DDSs because of their biocompatibility [67]. However, the long-term toxicity of these materials when introduced in the human body needs to be further investigated. To avoid the risk of long-term toxicity, there is no doubt that the use of natural biodegradable polymers can be considered in the development of MIP-based DDS. Besides, it is also important to consider the water-compatibility of MIPs, because drug delivery vehicles usually need to be able to work in an aqueous medium to ensure efficient drug release in the body.

Norell, Andersson and Nicholls firstly reported in 1998 that MIPs can be potentially used as sustained drug delivery vehicles to release theophylline [68]. They showed that the synthesized MIPs had a higher binding affinity to theophylline than towards caffeine and demonstrated a more sustained release than the corresponding non-imprinted polymers (NIPs).

The MIP matrices rely on a high degree of cross-linking to maintain complementary cavities that act as drug reservoirs [69], but the mobility of polymer chains is often limited due to the cross-linking process [60]. Therefore, MIPs with a lower degree of cross-linking are usually more advantageous for applications in drug delivery. Furthermore, the introduction of external materials such as thermosensitive polymers [70], magnetite [71] and specific moieties such as disulphide bonds [72] allows to MIPs to exhibit suitable changes in response to external stimuli, such as changes in pressure, pH, temperature, ionic strength, electric fields, chemicals and light.

Taking into account the above-mentioned aspects, as well as the exponential increase in literature examples of MIP-based DDSs during the course of the past five years, this review aims to highlight the design and development of strategies undertaken for MIPs used as drug delivery vehicles involving three main drug-delivery mechanisms: (i) rate-programmed drug delivery, where MIPs serve as excipients to control drug diffusion and/or enhance loading capacity for the system; (ii) stimuli-responsive drug delivery, in which some physical, chemical and/or biological factors can activate drug release from the system; (iii) active targeting drug delivery, where MIPs act as target delivery vehicles that provide spatial control of drug release to specific sites of the body. We will strive to provide comparisons with conventional and possibly commercial examples of polymeric DDSs, bearing in mind the administration routes, to identify the main challenges that need to be addressed in order to eventually actualize the commercial translation of MIP-based DDSs.

2. MIP-Based Drug Delivery Systems

2.1. Rate-Programmed Drug Delivery

Within the context of this release mechanism, MIPs are used as excipients to control drug release at a specific rate and/or time. Since Norell, Andersson and Nicholls first reported that MIPs could potentially serve as sustained drug delivery vehicles for theophylline release [68], it has been suggested that MIPs can be used as excipients to improve the precision of drug release, thereby reducing side/adverse effects and/or improving bioavailability.

2.2. Stimuli-Responsive Drug Delivery

An ideal stimuli-responsive DDS should be able to provide localized, dose-controlled and rate-controlled drug delivery through endogenous stimuli (e.g., reactive oxygen species, changes in physiological pH and temperature, overexpressed proteins and enzyme levels) or exogenous stimuli (e.g., changes in temperature, light, magnetic field, etc.) [67].

Indeed, endogenous- and exogenous-responsive polymer-based DDSs have been developed for the controlled release of various drugs, especially anti-tumor agents. Nevertheless, conventional polymer-based DDSs have limitedly addressed the need for cost-effectiveness, low systemic toxicity and controlled release of drugs [73][74].

2.3. Active Targeting Drug Delivery

Conventional DDSs usually deliver drugs to both healthy and unhealthy tissues, even though those drugs may damage the healthy cells and thus cause severe side effects, particularly if the drugs are highly toxic (e.g., anti-tumor drugs). Active targeting is another important feature of controlled DDSs, which can spatially control the release of drugs to the target sites within the body, thereby reducing the side effects associated with damage to healthy cells, thus improving the overall therapeutic profile.

The induction of external stimuli to activate the drug delivery vehicles loaded with toxic drugs is an effective method of site-targeting as described above. If external guidance is not used, however, these DDSs will be distributed all over the body.

Therefore, polymeric DDSs with active targeting have been employed to recognize specific cell markers and deliver drugs precisely to the target sites. Active targeting of conventional polymeric DDSs is normally achieved via conjugation with the ligands of specific receptors expressed on target cells. Potential ligands include proteins, peptides, carbohydrates, nucleic acids and small molecules [75][76][77][78][79][80].

Nevertheless, actively targeted polymeric DDSs frequently face complex production processes, significantly high costs (e.g., the RGD peptide targeting sequence costs 145 USD per 10 mg) and/or poor drug release control [81][82][83][84].

In recent years, double-imprinted polymeric DDSs have been studied for active targeting drug delivery because of the unique features of MIPs as described in the introduction section.

For example, Jia et al. synthesized dual-template silicon MIP NPs used for theranostic applications towards pancreatic cancer BxPC-3 cells that overexpress human fibroblast growth-factor-inducible 14 (FN14) [85]. The 71–80 peptide of FN14 (FH) and bleomycin were used simultaneously as the template molecules to obtain the active targeting MIP NPs. Optical bioimaging technology makes it possible to use silicon NPs to diagnose cancer. The study showed that bleomycin adsorption to the MIP NPs (>4000 mg g^{-1}) was 4-fold higher than to the NIP NPs (1100 mg g^{-1}), suggesting that the loading capacity was markedly enhanced by the imprinting process. The FH adsorption capacity of the MIP NPs (450 mg g^{-1}) was also higher than that of the NIP NPs (130 mg g^{-1}), with 2.5-fold higher selectivity for the correct targeting peptide in comparison to a scrambled one. The in vitro release study performed at pH 5.3 (mimicking the tumor microenvironment) highlighted that the MIP NPs sustained the release of a total amount of 1900 mg g^{-1} of bleomycin over the course of 72 h, while NIP NPs released the drug more quickly and reached equilibrium (750 mg g^{-1}) after 10 h. At pH 7.4, NIP NPs and MIP NPs released 800 mg g^{-1} and 500 mg g^{-1}, respectively, after 70 h. The in vivo anti-tumor effect was evaluated in mice via a tail vein injection, and MIP NPs achieved the greatest effect. The tumor volumes of the groups treated with physiological saline, NIP NPs and free bleomycin were respectively 2.3-fold, 1.6-fold and 1.5-fold higher than the group treated with MIP NPs. These results demonstrate that MIP NPs have a superior potential for the treatment of pancreatic cancer relative to NIP NPs and free bleomycin thanks to the MIP system enhanced drug loading, specific recognition and sustained release.

Canfarotta et al. used the solid phase synthesis approach to prepare double-imprinted MIP NPs against the epidermal growth factor receptor (EGFR) that is overexpressed in many types of tumor cells (Figure 3) [86].

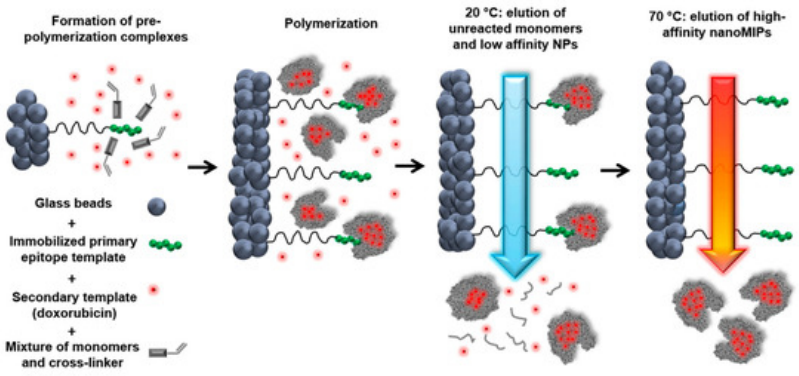

Figure 3. Scheme of the solid-phase synthesis process for double-imprinted nanoMIPs using a peptide epitope of EGFR as primary template attached to the solid phase and doxorubicin as secondary template in solution. Adapted with permission from Canfarotta et al. [86].

An epitope of the extracellular domain of EGFR and DOX were used as the template molecules. Flow cytometry was used to analyze the selective recognition capability for MIP NPs towards breast cancer cells overexpressing EGFR. Furthermore, DOX-loaded EGFR-MIP NPs decreased the cell viability of EGFR-overexpressing MDA-MB-468 cancer cells (lower than 75%) in comparison to free DOX (more than 90%) and control NPs (~100%). Moreover, the cell viability of non-EGFR-overexpressing cell-lines was virtually unaffected, highlighting the achievement of selective targeting and DOX delivery.

Similarly, Qin et al. studied active targeting MIP NPs for the treatment of breast cancer. The MIP NPs were prepared with an epitope of the CD59 cell membrane glycoprotein and DOX as templates such that the high concentration of GSH and weak acid environment created by the cancer cells would selectively trigger DOX release (Figure 4) [87].

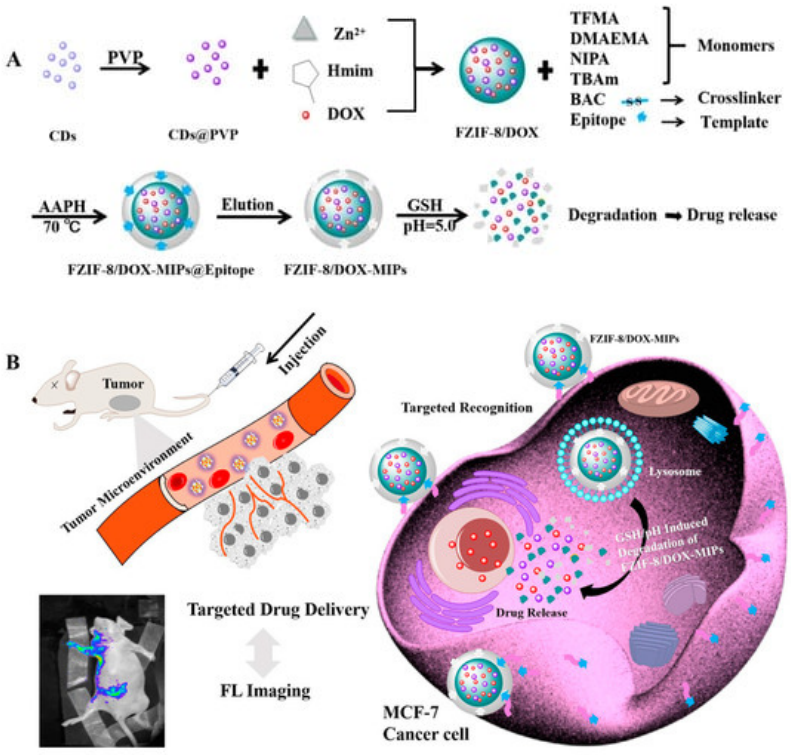

Figure 4. (**A**) Synthesis and GSH/pH dual stimulation degradation route of FZIF-8/DOX-MIPs; (**B**) Schematic illustration of targeted imaging and GSH/pH-responsive drug delivery of FZIF-8/DOX-MIPs. Reproduced with permission from Qin et al. [87].

Fluorescent zeolitic imidazolate framework-8 (FZIF-8) was employed as the framework of the MIP NPs because FZIF-8 is fully biodegradable in an acidic environment. The fluorescence intensity of the MIP NPs was ~4-fold higher than that of the NIP NPs with 0.1 mg mL^{-1} of the epitope, indicating the enhanced adsorption and strong specificity of the MIP NPs. After 15 days and in absence of GSH, about 50% of the drug leaked from pristine FZIF-8/DOX in PBS (pH 7.4), while

almost no DOX was released from FZIF-8/DOX MIP NPs in PBS (at pH 5.0 and 7.4). In the presence of GSH, the DOX release from the MIP NPs greatly increased (at pH 5.0 and 6.0) to more than 90% over 15 days. In addition, the viability of MCF-7 cells (CD59 positive) was significantly lower after treatment with the FZIF-8/DOX MIP NPs (20% cell survival after 72 h exposure to 40 μg mL^{-1}) than after control treatments: FZIF-8/DOX NIP NPs (50%), FZIF-8/DOX (60%) and free DOX (60%). Importantly, normal cells did not show significant apoptosis; the anti-tumor effects were limited to the MCF-7 cancer cells. Moreover, the tumor volume (10 mm) in mice treated with FZIF-8/DOX MIP NPs was more than 2-fold smaller than that in mice treated with the controls. These results indicate that FZIF-8 MIP NPs can selectively target MCF-7 cells and trigger an adequate drug release in the presence of GSH, thereby reducing systemic toxicity and improving the therapeutic index of DOX.

As can be seen, in comparison to the conventional active targeting polymeric DDSs, double-imprinted MIP NPs offer a benefit by significantly reducing aspecific drug release and improving therapeutic effects. In addition, while biological ligands might exhibit superior specificity in certain instances, the high costs and complex production processes associated with materials such as antibodies and peptides may be prohibitive [77][88][89].

Double-imprinted polymeric DDSs, on the other hand, are extremely affordable. Solid-phase synthesis technology, in particular, makes it possible to recycle the templates depending on the production conditions, which greatly optimizes the resources whilst containing the costs [50]. Furthermore, it is facile to prepare double-imprinted polymeric DDSs in comparison to analogous conjugates [50][57][86].

3. Current Challenges in MIP-Based DDS

In the last 5 years, a myriad of interesting studies has revealed great potential for the development of MIP-based DDSs. Many have focused on drug delivery for anti-tumor agents, which are important candidates for improved DDSs because the majority of these drugs possess a narrow therapeutic window. Methacrylic monomers and cross-linkers such as HEMA, MAA, MBA, EGDMA and EDMA have been widely used in the advancement of MIP-based DDSs [90][91]. These monomers are considered to have acceptable toxicity and excellent biocompatibility [92][93][94], though their long-term toxicity and metabolic pathways have not been evaluated in depth. Besides, additional materials such as POSS [45][95], β-CD [45], CS [96], silicon [97][85] and stimuli-sensitive materials [47][70][98] have been used to modify MIPs to improve performance parameters such as drug release behavior, biodegradability and biocompatibility [67].

Another major obstacle in the development of most MIP-based DDSs is the use of organic solvents (e.g., toluene, chloroform) [67]. These facilitate and maintain the non-covalent interactions between the template molecules and the functional monomers [99][100]. Nonetheless, in terms of medical translation and applications, the presence of residual organic solvents can damage healthy cells, leading to serious side effects [99][101]. Furthermore, the use of organic solvents during synthesis may result in a marked difference in drug-release behavior of MIPs in aqueous media, as well as potentially increasing the manufacturing costs [101][102]. Alternatives such as supercritical carbon dioxide (scCO2) technology exhibit great environmental and safety advantages because of the unique and beneficial features of the prepared polymers, such as a controlled morphology, non-toxicity, absence of solvent residues [60] and the ability to avoid purification and drying steps [103]. Furthermore, scCO2 can stabilize hydrogen bonds between the templates and functional monomers [104]. The technology, though, is still not widely used nor easily accessible (even at a laboratory scale), possibly due to the need for specialized expensive equipment as well as the extreme operational parameters (temperatures and pressures). Nonetheless, $scCO_2$ has a great potential for the development of highly pure, GMP-compliant MIP-based DDSs [103].

A further challenge that arises from the analysis of the above-discussed literature examples, is that only a limited number of studies reported in vivo data for the evaluation of MIP-based DDSs. In vivo research should be considered an indispensable step in the evaluation of any potential DDS. Since most studies evaluated toxicity and drug release only in vitro, further investigations and data are needed to ensure that the promising in vitro behavior of MIPs translates in in vivo models exhibiting safety and adequate release properties. Only through in vivo studies can we adequately evaluate the possible advantages of MIPs in clinical practice.

Another relevant concern in some cases is the inadequate drug loading of MIP-based DDSs (e.g., in contact lenses). This may result in sub-par, ineffective drug release. Importantly, though, even MIP-based DDSs with somewhat inadequate loading usually perform better than the corresponding NIP-based DDSs, indicating the potential advantages of molecular imprinting to enhance drug loading. The loading capacity may be increased by employing a smaller proportion of cross-linkers, but this strategy must also consider the trade-off between drug loading and the stability of imprinted cavities.

Furthermore, some MIPs may undergo a small initial burst release due to the adsorption of drug molecules onto their surface. For some drugs (e.g., anti-tumor agents), this may cause serious toxic effects. In other cases, however, burst release can be beneficial (e.g., at the beginning of antibiotic treatment) [42]. Perhaps better purification strategies can allow achieving an improved modulation of the burst effect. Although it is tremendously challenging to design a suitable release profile, MIPs offer ample opportunities for modifications that can implement a variety of release profiles to fit the requirements of the drug of interest.

4. Conclusions and Future Perspectives

Conventional drug delivery can be burdened by systemic toxicity and low bioavailability because of non-specific delivery and rapid clearance. Recently, in attempts to address these limitations, a variety of MIPs have been evaluated as novel DDSs. An analysis of the literature on MIP-based DDSs reveals a great potential for extensive research, particularly for the delivery of drugs with narrow therapeutic windows and/or low bioavailability. Although the process of designing and translating MIP-based DDSs into clinical practice is still in its infancy, ongoing development will most likely lead to the creation of innovative drug delivery vehicles with commercial value.

Imprinted polymers can not only significantly enhance the drug loading and the stability of drugs in harsh conditions but also attenuate the release behavior by engineering specific interactions between drug molecules and functional monomers. As an example of the advantages of rate-programmed drug delivery, MIPs as excipients can be used to develop sustained transdermal formulations, therapeutic contact lenses and oral formulations for protein delivery. In addition, MIP-based DDSs can be designed with stimuli-responsiveness, using properties of the imprinted cavities to achieve enhanced release profiles compared to conventional polymeric DDSs. Even more interestingly, active targeting drug delivery can be achieved via unique double-imprinting of targeting moieties and drugs.

However, much of the extant research does not go so far as to include clinical studies that address biomedical regulations regarding the novel drug delivery devices. Although some studies report the in vitro cell toxicity of MIP-based DDSs, the therapeutic effects and clinical safety cannot be determined without in vivo assessments. Therefore, additional ongoing efforts are needed to design, develop and evaluate MIP-based DDSs to evaluate their safety profiles and satisfy biomedical regulations.

With an eye on the horizon, a combination of MIP-based DDSs and implantable microchips has great potential for self-regulated drug delivery [5] as the novel DDS can detect changes in the level of a biochemical substance (e.g., glucose) and can prompt the rapid release of the drug (e.g., insulin) under the desired conditions [3]. Striegler proposed a MIP-based α-glucose-biosensor in which pH changes in response to changes in the glucose concentration in the environment [105]. In addition, several interesting studies have achieved controlled drug delivery based on implantable microchips [106] [107][108]. Therefore, the hybrid of the MIP and implantable microchips may prove to be a promising drug delivery avenue within reach of clinical applications in the coming years [5][109].

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