October 2007 Volume 3 Issue 3

Trade Science Inc.

Macromolecules

An Indian Journal

Microreview

MMAIJ, 3(3), 2007 [128-137]

Moleculary Imprinted Polymers In Drug Delivery Systems

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Received: 9th September, 2007 ; Accepted: 14th September, 2007

ABSTRACT

Molecularly Imprinted Polymers (MIPs) which consist of sites of specific molecular arrangement into an otherwise uniform polymeric matrix are highly capable of Specific Molecular Recognition (SMR). SMR is a fundamental requirement of living systems on which some of the most diverse and important biological functions rely. Due to this capability these polymers have found extensive applications in various fields such as chemical separations, biosensing, analytical chemistry, drug discovery and drug delivery. Initially the brief historical landmarks in the development of these MIPs along with a few methods of their synthesis have been reviewed. Further, the characteristics of MIPs, which make them promising tools for drug delivery systems, have been discussed. Different approaches for the design of drug delivery systems along with examples of some established embodiments such as the delivery of Timolol through contact lenses made from MIP hydrogels have been cited. Finally exciting future prospects such as 'intelligent drug release' and 'magic bullet' drug targeting have been discussed along with a possibility of development of drug delivery systems to combat dreaded diseases like diabetes and cancer.

KEYWORDS

Molecularly imprinted polymers (MIPs);
Drug delivery systems (DDS);
Specific molecular recognition (SMR);
Soft contact lenses;
Intelligent drug release.

INTRODUCTION

Molecular imprinting is a means of introducing sites of specific molecular arrangement into an otherwise uniform polymeric matrix. The process of preparing a molecularly imprinted material involves three main steps namely, the mixing or binding of one or several (functional) monomers with the template molecule in a suitable solvent or dispersion liquid; the polymerization of monomers in the presence of a cross-linker to prepare a polymer network in which the functional monomers become fixed around the template and the removal of the template from the solid. (Figure 1)

This results in the production of a macroporous polymer capable of specific molecular recognition (SMR)[4]. SMR is a fundamental requirement of living

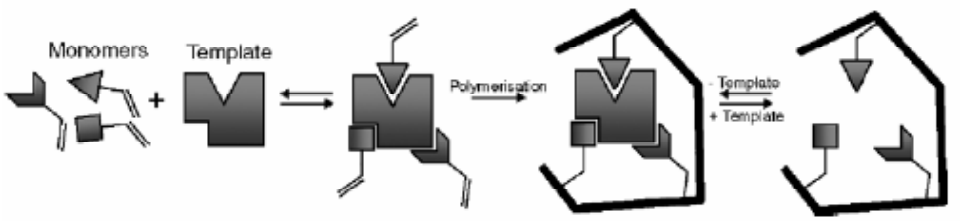

Figure 1 : Schematic generalization of the molecular imprinting process

systems on which processes as diverse as neural transmittance, respiration, immune defence, cellular differentiation and nutrition rely. Thus, molecular imprinting is one of the most promising methods of harnessing and mimicking biological functions[1]. Molecularly Imprinted Polymers (MIPs) , which contain binding sites complementary to that of the template molecule, can be programmed to recognize a large variety of target structures with antibody-like affinities and selectivities. These properties along with the ease of preparation and robustness of these artificial receptors have been harnessed in the areas of chemical separations[10,5], solid phase extraction[6,7], sensing[8], as screening tools in drug discovery[9] and in drug delivery systems.

A brief history of molecularly imprinted polymers

Molecular imprinting goes back to the early 1930s when a number of silica gels were prepared in presence of a solvent additive, the resulting silica demonstrated preferential binding capacity for that solvent. Later in 1949 when silica gels had been prepared in the presence of 'patterning' dyes[11], it was observed that after removal of the dyes the silica would rebind the same dye in preference to the others. The first MIP which was reported in 1972 was synthesized using what is now termed as the 'covalent approach' mainly to prepare an organic MIP capable of discriminating between the enantiomers of glyceric acid. The second major break through occurred in 1981[12] when an organic MIP was prepared using essentially non-covalent interactions, which was termed as the 'noncovalent approach' as opposed to the covalent approach. This approach is considered to have triggered the explosion in molecular imprinting that occurred in the 1990s. An intermediate approach was reported in 1995[13], which relied on covalent interactions during polymerization stage but noncovalent interactions during rebinding. The noncovalent approach has been more favoured in the recent years for the preparation of MIPs as molecular recognition materials, since MIPs made by this route have more favourable binding and release kinetics. The monomers, which are well established in the non-covalent approach, have been previously used in the synthesis of biomaterials and their physiological properties are already known[2].

Role of polymers in drug delivery systems

Drug delivery systems are required whenever an administered therapeutic agent needs to be protected against metabolic attack, or when there are absorption barriers or dosage limitations. The ideal delivery vehicle will ensure that the drug is released at the right site, in the right dose and for the required time. It will also be biocompatible or biodegradable such that the delivery system is transformed into non-toxic fragments that are eliminated harmlessly from the body. The importance of this field of research is growing as ever more complex drugs and biopharmaceuticals are being developed, many of which cannot be administered without a controlled dosage system.

Polymeric materials have been used for some time as drug delivery systems, most widely as implantable materials. In these systems the drug is dispersed within a polymer matrix designed to release the therapeutic agent over a prolonged period of time or under certain physiological conditions. Delayed release devices of this type have the advantage of increasing the residence time of a drug within a patient, ensuring better compliance with most dosage requirements, or in the case of those compounds that have a narrow therapeutic window, maintaining the concentration below levels where potential harmful side effects become prevalent. The simplest polymeric delivery systems are those where the drug is dispersed randomly within the polymer matrix and released as a consequence of erosion of the carrier in vivo. Although simple to prepare, these materials have the disadvantage that the drug can be released suddenly through breakdown of the matrix past a critical

threshold, leading to potentially serious consequences for the patient if the drug is harmful in high concentrations. To overcome this problem many drug delivery systems have been developed that are degraded in a more even manner when in contact with physiological fluids. This matrix breakdown can be accomplished by using a carrier polymer that erodes only at its surface and by ensuring that the drug is dispersed evenly throughout the matrix. In this way a slow steady release profile can be obtained keeping the drug at the right concentration in order to be effective. However, there are still a number of problems with many polymeric drug delivery systems that have limited their practical application. A particular issue is to effect feedback-controlled release, i.e. the maintenance of a therapeutic level of a drug within both, the drug reservoir and the target site. This requires a drug delivery system with molecular recognition properties, such that it is able to bind and release only very specific molecular species under conditions where equilibrium concentrations may be critical. Thus, Molecularly imprinted polymers (MIPs) have been a focus of research as a consequence of their molecular recognition properties combined with facile synthesis[2].

Rationale for imprinted polymer drug delivery systems

For applications of MIPs in drug delivery systems there are a number of specialized requirements relating to imprinted polymer preparation.

Generally MIPs rely upon a high degree of crosslinking in order to fix the spatial orientation of functional groups, which is generally thought to be required for the imprinted materials to retain its molecular recognition properties. However, imprinted polymer gels, which are not quite as densely crosslinked, are required for application in drug delivery systems. Many hydrogels, which are synthesized with water soluble monomers, may display a change in their swelling behaviour under the influence of an external stimulus which can be due to a change in temperature, pH, ionic strength, solvent quality, presence or absence of chemical species, electric fields and irradiation with UV or visible light.

Owing to their crosslinked polymeric nature they inherently act as drug reservoirs for low molecular weight species. Thus, they can potentially optimize drug release rates and residence times. A range of physical states of the MIPs with respect to swelling can be readily achieved. Both these parameters can be collectively optimized for specifically desired drug release profiles. For eg. An imprinted hydrogel can be designed which collapses to protect its therapeutic payload through the gastro-intestinal tract but expands to release the drug in the small intestine or the colon.

The modulation of drug release from an imprinted polymer by a feedback control mechanism can also be considered, such as insulin release when blood glucose level rises above a minimum threshold level, or release of a drug when the imprinted polymer encounters a specific target agent, such as a protein or cell surface receptor. One further potential advantage of imprinted polymers as drug delivery devices is that, in the case where a racemic mixture of a drug is used, they can selectively release the more effective enantiomer[10].

Approaches for the design of drug delivery systems based on MIPs

Efficient drug delivery systems(DDS) should provide a desired rate of delivery of the therapeutic dose, at the most appropriate place in the body, in order to prolong the duration of pharmacological action and reduce the adverse effects, minimize the dosing frequency and enhance patient compliance. To control the moment at which delivery should begin and the drug release rate, three following approaches have been reported[23] **(a)** rate-programmed drug delivery which involves drug diffusion from the system has to follow a specific rate profile; **(b)** activation-modulated drug delivery, where the release is activated by some physical, chemical or biochemical processes; and **(c)** feedback-regulated drug delivery in which the rate of drug release is regulated by the concentration of a triggering agent, such as a biochemical substance, concentration of which is itself dependent on the drug concentration in the body. When the triggering agent is above a certain level, the release is activated. This induces a decrease in the level of the triggering agent and, finally, the drug release is stopped. The sensor embedded in the DDS tries to imitate the recognition role of enzymes, membrane receptors and antibodies in living organisms for regulation of chemical reactions and for maintenance of the homeostatic equilibrium[24].

1. Rate-programmed drug delivery

Rate-programmed drug delivery encompasses a large amount of approaches such as the use of classical im-

printed particles as DDS excipients, imprinting polymers in water as DDS which further includes imprinting proteins, peptides and cyclodextrins and using weakly cross-linked MIPs prepared without solvents as drug delivery soft contact lenses, which have been discussed later. Classical imprinted particles can be used as DDS excipients by the two following means i.e. the use of MIPs prepared in organic solvents with a high cross-linker proportion, as base excipients for controlled release devices of drugs with a narrow therapeutic index and the use of MIPs as enantioselective release excipients.

Classical imprinted particles as DDS excipients

MIPs prepared in organic solvents with a high cross-linker proportion, as commonly designed for analytical purposes, have been proposed as base excipients for controlled release devices of drugs with a narrow therapeutic index. These drugs present a small difference between the minimum concentration to be active and the concentration at which the side-effects advise against their use. Therefore, they have to be administered in a device able to control their release precisely, as needed, for example for the antiasthmatic drug theophylline[29]. Norell et al.[30] prepared, in chloroform, non-covalent theophylline imprinted particles (65µm) with a view to oral administration, using the method proposed by Vlatakis et al.[31]. Theophylline-reloaded particles were able to sustain drug release in pH 7.0 phosphate buffer for several hours, especially those loaded with low amounts of theophylline (0.1-2.0mg/g) (Figure 3). The increase in release rate observed at greater loadings was attributed to a partial drug adsorption to non-specific binding points to which it was weakly attached. This hypothesis also explains that reference (non-imprinted) systems showed slightly faster release.

To avoid the decrease in interaction intensity between the MIPs and the ligands in water and to enhance their performance as sustaining release excipients of transdermal DDS, Allender et al.[32,33] proposed preventing water from associating with the imprinted binding site by embedding the MIP and the drug within a secondary polymer matrix made of a commercially available non-polar transdermal adhesive. The adhesive material-freely diffusible for drug molecules but relatively hydrophobic-was able to create an environment within which selective binding could occur. The transdermal devices were prepared dispersing propranolol (19.1mg) and imprinted or non-imprinted polymer(100, 300, and 500mg) in chloroform, and then mixing with the self-curing acrylic co-polymer adhesive. The viscous dispersions were left to cure overnight and then cut in 1cm diameter discs containing 0.5mg propranolol. Drug diffusion studies carried out in water: ethanol (50:50) mixture showed that the devices containing MIPs were able to substantially decrease the release rate, compared to the non-imprinted ones(Figure 4). The lower diffusion rate of propranolol from devices prepared with MIPs indicates that the specific binding characteristic of these systems can provide a useful means of sustaining the delivery profile.

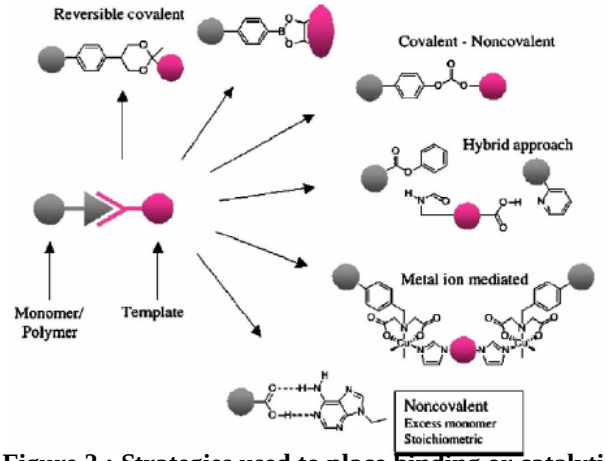

Figure 2 : Strategies used to place binding or catalytic functional groups at defined positions in imprinted sites of network polymers.

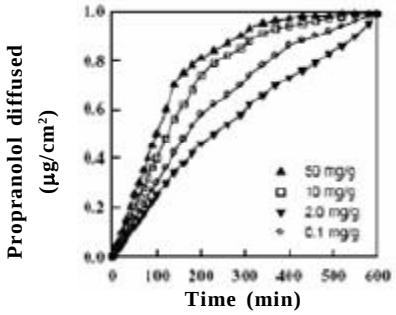

Figure 3 : Theophylline Release profiles in phosphate buffer pH 7 from imprinted polymers loaded with different amounts of drugs

Imprinting of peptides and proteins

Relatively low molecular weight compounds are generally used as templates in molecular imprinting. The synthesis of MIPs selective to macromolecules such as proteins is mainly hindered by steric and thermodynamic reasons. Bulky protein cannot easily move in and out

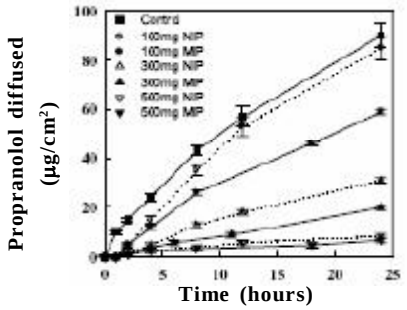

Figure 4 : Influence of polymer content and imprinting effect on propanolol release from 1cm diameter discs constituted by MIPs and Non-MPIs

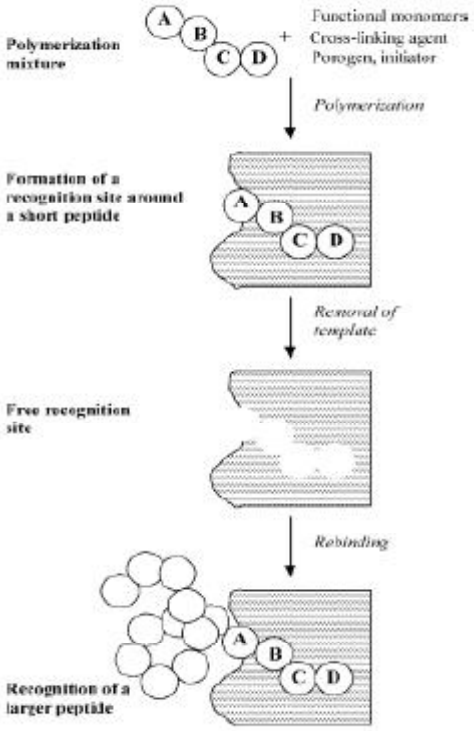

Figure 5 : Schematic drawing of the imprinting process of a peptide using the epitope approach

hrough the mesh of a polymer network[34] , although this may be overcome by synthesising macroporous MIPs[35] or creating surface imprinting using metal (Cu^{2+})–ligand monomers[36]. On the other hand, the use of large non-rigid templates, such as polypeptides and proteins, yields less well-defined recognition sites[37]. These considerations led Rachkov and Minoura[38] to create protein-imprinted polymers using a short peptide(epitope) that represents only a part of the large protein as a template. The MIPs are intended to recognise such a portion of amino acids in any protein, as the antibodies recognise specific sequences in macromolecular antigens. For example, a sequence of four amino acids(Tyr-Pro-Leu-Gly) can be chosen as the template of oxytocin(Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH2) using methacrylic acid as the functional monomer, EGDMA as the cross-linker(monomer to cross-linker ratios ranged from 1:30 to 1:7.5), and water acetonitrile mixture as the polymerisation medium. The imprinted macroporous polymer efficiently recognised both the template and the whole protein, even in pH 6.5 aqueous medium.

The high selectivity and affinity of these MIPs for peptides and proteins make them potentially useful for the development of DDS with a high loading capacity and able to control the release of these macromolecules in an adequate physiological environment molecular antigens. For example, a sequence of four amino acids (Tyr-Pro-Leu-Gly) can be chosen as the template of oxytocin (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-Gly-NH2) using methacrylic acid as the functional monomer, EGDMA as the cross-linker (monomer to cross-linker ratios ranged from 1:30 to 1:7.5), and water–acetonitrile mixture as the polymerisation medium (Figure 5). The imprinted macroporous polymer efficiently recognised both the template and the whole protein, even in pH 6.5 aqueous medium. The high selectivity and affinity of these MIPs for peptides and proteins make them potentially useful for the development of DDS with a high loading capacity and able to control the release of these macromolecules in an adequate physiological environment.

2. Activation modulated drug delivery

This approach basically leads to the development of DDS in which the release occurs as a response to a change in the conditions of the environment, which affects the binding of the drug directly(competitive binding or hydrolysis of the bounds) or through a change in the swelling state of the polymer(volume phase transition induced by a external stimulus).

Competitive binding

An activation-modulated delivery may be achieved with an imprinted gel that releases the drug because of the competitive binding to the polymer of another substance in the solution. The network includes a non-imprint drug and, when the imprint molecule appears in the surrounding medium, the network binds it and releases

the drug. If the concentration of the imprint substance decreases, the release stops. A system of these characteristics able to release testosterone at a rate depending on the concentration of hydrocortisone in the medium was described by Sreenivasan[39]. HEMA(1g) cross-linked with EGDMA(4g) and imprinted for hydrocortisone (100mg) in chloroform (6-8ml) absorbed, after removing the imprint, a considerable amount of testosterone (175ug/100 mg MIP versus 36ug/100mg control polymer). The release of the loaded drug to the aqueous medium was considerably enhanced in the presence of the template molecule(hydrocortisone) Other competitive binding experiments, in aqueous environment between bupivacaine and other local anaesthetic drugs[40], and between theophylline and other methylxantines (caffeine, theobromine) and 17-β-estradiol and very close structurally related sterols(17-α-estradiol, 17-α-ethyny lestradiol)[41] -have shown the ease with which a non-imprint specie bound to imprinted polymer particles may be replaced by the template molecule.

Hydrolytically-induced drug release

A particularly useful approach to modulate drug delivery consists of creating erodible systems from which the drug cannot be released unless the polymer degrades or polymer-drug bonds are broken. The external conditions that can induce these processes are, usually, extreme physiological pH or the catalytic activity of certain enzymes. For example, drugs that are unstable under the gastric conditions may be selectively released in the colon by preparing DDS with polymers that serve as substrates of the enzymes of this intestinal region or that degrade at slightly alkaline pH environments. In other cases, the rate of hydrolysis of the drug linkage to the polymer network controls the release rate. Ester bonds usually need alkaline pHs much stronger (pH 10-11) than those found in the physiological environment to be broken. Additionally, the presence of electron donating groups in the drug molecule (p-metoxy or p-amino) considerably suppresses the rate of hydrolysis[42]. To enhance the hydrolysis of polymer-drug ester or amide bonds under mild pH conditions, Karmalkar et al.[43] proposed incorporating imidazole groups (nucleophilic catalyst) near the drug linkage using a molecular imprinting technique. The hydrogels, designed for the release of p-amino benzoic acid, were prepared dissolving HEMA, N-vinylimidazole(NVIm) and ethacryloylethyl p-aminobenzoate(PAP) in methanol.Imprinted hydrogels were only obtained when PAP and NVIm were previously mixed together with Co^{2+} ions. The metallic ions bring together both monomers forming a co-ordination complex.Polymerisation of such a complex and subsequent removal of the metal ion would lead to polymers having the labile bond and imidazole located in contiguous positions on the same chain. In ethanol–phosphate buffer pH 8 medium, the release of p-amino benzoic acid from the imprinted system (PAP-1) was considerably easier (first order rate constant 39.8×10-3 per day) than from the other two gels (PAP-2: 8.1×10-3 per day; PAP-3: 6.1×10-3 per day) and even faster than from PAP-3 gels in 0.01N NaOH(pH 11). The cross-linking was essential for the catalytic activity of the hydrogel; the release rates from linear imprinted and non-imprinted polymers being similar.

3. Feedback regulated DDS

Frequently, the levels of some physiological substances are used as direct indicators of the degree of dysfunction of a certain organ. The availability of systems capable of selective recognition of these substances is an essential step to create feedback-regulated DDS able to modulate drug release as a function of the level of these substances in the body[25].

Most work carried out until now has been focused on glucose-regulated insulin delivery systems, using nonimprinted systems. However, since recently, the obtaining of glucose-imprinting has been tackling the issue from quite different approaches. The prevalence of diabetes in developed countries is quite considerable[44]. Therefore, from a practical point of view, simple methods of quantifying blood glucose concentration are required and, consequently, some MIPs have been designed as sensors in this field. Arnold et al.[45] developed a glucose sensing device based on methyl-d-glucoside imprinted polymer, applying metal co-ordination, that exhibits a change in pH proportional to the glucose concentration of its environment. This procedure was later improved by Striegler[46,47,48] for enhancing glucose binding at 5.5<pH<7.5. New functional monomers such as[4-(N-vinylbenzyl)diethylenetriamine) copper(II)] diformate or [(diethylenetriamine) copper(II)] dinitrate, which can form 1:1 complexes with carbohydrates in this range of pH, were synthesised. Although the ligand-Cu2+–glucose apparent binding constant is lower at physiological

conditions (pH 7.4) than at the pH used for polymerisation (12.4), the imprinted systems were still much more efficient than the control ones and showed a high selectivity over other 1,2-cis-diols, namely mannose and galactose[47]. Adequate imprinted networks even allowed selective discrimination of α-and β-glycosidic linkages of cellobiose and maltose[48]. Finally, to raise the overall loading amount of carbohydrates, cross-linkers and monomers that may establish hydrogenbonding interactions were also included. As the matrix polarity increased, the polymer preference for the large and polar disaccharide lactose also rose, in detriment of the less polar monosaccharide glucose[49]. Thus, depending on the specific carbohydrate to be recognised, it maybe practical to use polar or non-polar cross-linking monomers. In this way[49,50], demonstrated the feasibility of hydrogen bonding interactions between carbohydrates and methacrylic monomers, to produce high affinity binding polymer networks. These sensors may serve as a basis for the obtaining of glucose-responsive DDS.

Recognition and release mechanisms

The first reports of imprinted polymers that afforded a sustained release mechanism were by Norell et al.[14]. Polymers imprinted with theophylline, a methyl xanthine used in the treatment of asthma, were evaluated for controlled release in aqueous buffer. Theophylline has a narrow therapeutic window(30-100μg) and concentrations higher than 110μg are likely to be toxic. Theophylline imprinted polymers were prepared by the non-covalent technique using methacrylic acid(MAA) as the functional monomer and ethylene glycol dimethacrylate (EGDMA) as the cross-linker. These polymers were shown to be able to differentiate between the methyl xanthines theophylline and caffeine when the polymer was packed into an HPLC column. The release kinetics of theophylline were determined in phosphate buffer at pH 7 from polymers loaded with theophylline at concentrations varying from 0.1 to 50mg of theophylline/g dry polymer. Those polymers with the lowest theophylline loading (2.0 and 0.1mg /g) displayed the slowest release characteristics. The variation in the release profile can be attributed to the heterogeneity of the recognition sites.

The difference in the distribution of binding sites in the imprinted and nonimprinted polymers can influence how a bound drug is released from imprinted as opposed to nonimprinted polymer particles. Puoci[15] has used precipitation polymerization to generate polymers capable of controlled delivery of the pro-drug sulfasala zine used in treatment of diseases of the colon such as Crohn's disease, irritable bowel syndrome and ulcerative colitis. These polymers were designed to be used for oral administration of the drug, and to release sulfasala zine in the colon selectively. Therefore the pro-drug needed to remain bound tto the polymer under the highly acidic conditions found in the stomach but release its load under the more neutral/alkaline environment in the large intestine. The polymer matrix was made swellable by copolymerising MAA as the functional monomer in a 79:21 mole ratio with EGDMA as the cross-linker. This relatively high level of ionisable monomer allowed the polymer spheres to swell under changes in physiological conditions from acid to neutral, as the carboxyl groups were deprotonated. Under acidic conditions, both the non-imprinted and the imprinted polymers showed a small release of sulfasalazine, with the non-imprinted polymer releasing 20% of its load compared to the imprinted polymer which lost 5% of the bound drug. When the pH was raised to 6.8, the non-imprinted polymer released the rest of its drug load within 2h, whereas the imprinted polymer had only released 80% of the bound sulfasalazine in the remaining assay time. This behaviour demonstrates that the drug was either bound to carboxylic acid groups in the polymer matrix or that the matrix itself remained less swollen at a given pH than the non-imprinted polymer. At low pH the acid groups were protonated and bound to sulfasalazine, but as the pH was raised these acid groups dissociated and could no longer take part in template binding or in retaining carboxylic acid H-bond cross-links in the matrix. Thus, method of controlled release by imprinted polymers is promising and provides a useful alternative to other strategies for colonic administration of sulfasalazine and analogues.

The precipitation polymerization strategy described above is one way to avoid the introduction of potentially toxic organic solvents in imprinted drug delivery devices; another is not to use an organic solvent at all. This has been demonstrated with the synthesis of MIPs using the hydrophilic monomers (2-hydroxyethyl) methacrylate (HEMA), MAA and EGDMA. The use of these monomers was the first illustration that the interactions between monomers in the polymer backbone and template can have an influence over the release of a drug compound.

As these monomers are liquids and the template will dissolve directly in the monomer mixture, there is no need for a solvent, which is normally required in molecular imprinting, in order for template sized cavities to be formed in the imprinted polymer. In addition, as a low cross-linking density was used, the imprinted polymers obtained were soft and optically clear, making them ideal as a soft contact lens dosage form[16], which could be used directly as a drug delivery device on the surface of the eye. Imprinted polymer lenses overcome many of the problems associated with traditional ocular drug delivery such as the rapid clearance through tears and blinking and can of course be used for sight correction as well as the sustained delivery of a drug. Furthermore, the lens delivery device offers the possibility of extended use during the day followed by drug reloading at night. The first examples of these polymer lenses were materials imprinted with the β-blocker S-timolol, which can be used for the treatment of glaucoma. Several monomers used in the manufacture of soft contact lenses were evaluated in order to investigate the influence of microenvironment upon timolol uptake and release[17]. All the polymers followed the Langmuir isotherm for timolol adsorption from the solution.

$$A = \frac{SKC_{eq}}{1 + KC_{eq}}$$

where A is the amount of sorbed timolol, S is the maximum capacity, K is the affinity constant, K is the overall affinity and Ceq is the concentration of free timolol in solution.

Polymers based upon DEAA exhibited the lowest affinity for timolol while HEMA based lenses had the highest affinity. The polymers displaying the greatest imprinting effect were those composed of DEAA or MMA–DMAA copolymers. This can be explained in terms of greater capacity of HEMA to hydrogen bond with timolol. Together with MAA, HEMA-rich polymers can form a microenvironment to enhance the interactions of drug with matrix in the imprinted polymer. The backbone monomers also influenced the drug release profile of the imprinted contact lenses. The more hydrophilic lenses prepared with SiMA-DMAA and MMA-DMAA as the backbone monomer, released their entire drug load within 3h, while those prepared with HEMA maintained drug release over an 8-h period. This was probably due to the greater uptake of water by those polymers containing SiMA-DMAA and MMA-DMAA, which allowed the drug to diffuse out of the imprinted lenses more quickly. An in vivo study by Hiratani et al. [18]compared the release into and residence time in the tears of albino rabbits, from imprinted and non-imprinted soft contact lenses and topical application of timolol solution in the form of eye drops. The lenses were prepared from EGDMA, DEAA and MAA as this monomer combination displayed the greater imprinting effect. The imprinted lenses were able to maintain timolol release over a 3-h period, compared to the 90min sustained timolol delivery for the non-imprinted lenses. The greater duration of timolol release for the imprinted lenses was again due to the higher capacity of these compared to the non-imprinted lenses. Both displayed a maximum timolol release between 12 and 13min followed by mono exponential decay of timolol concentration. Timolol applied directly as drops was flushed out of the eye within 1h of application, irrespective of the initial concentration. Both the imprinted and non-imprinted lenses bestowed a greater bioavaila bility of timolol in the tear fluid compared to eye drops of similar total drug load. This was of course because the drug has to diffuse out of the lens matrix before encountering the tear film and flushed out of the eye. The greater duration of timolol release for the imprinted polymer over the non-imprinted lens was reported to be a consequence of the greater binding capacity for timolol by the imprinted lens. The imprinted soft contact lenses are an illustration of the potential utility of imprinted hydrogels as drug delivery devices. The high water content of hydrogels aids in biocompatibility and will not induce any immunogenic response[19,20]; however, as the crosslink density is generally much lower than usually encountered in molecular imprinting, the design of the polymer network needs to be carefully considered[21,22].

Future prospects

Significant future opportunities for the use of MIPs lie in the area of drug delivery, in particular 'intelligent drug release' and 'magic bullet' drug targeting, as to the potential of molecular imprinting.

Intelligent drug release refers to the release, in a predictable way, of a therapeutic agent in response to specific stimuli such as the presence of another molecule, whilst drug targeting is best exemplified by the 'magic bullet' approach where a drug conjugated to a targeting vector, such as an antibody or a peptide, interacts with specific sites of interactions. A good example of this might be a cell surface epitope. In both of these areas molecu-

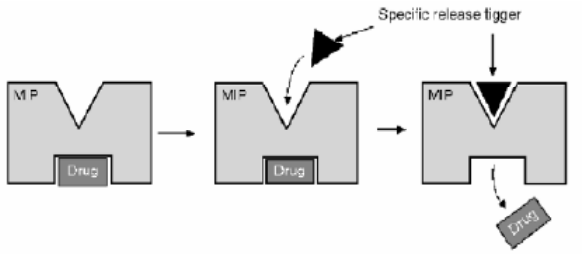

Figure 6 : Intelligent allosteric drug release from MIP carrier

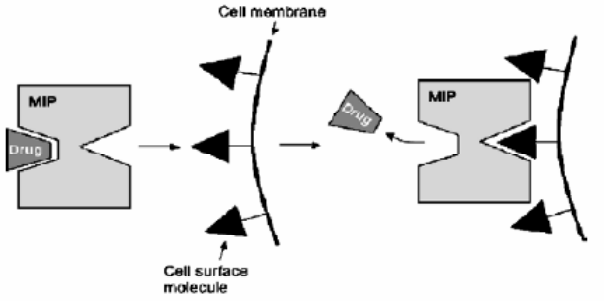

Figure 7: Targeted drug delivery using a molecularly imprinted carrier.

lar imprinting has very real potential. For instance, intelligent controlled release could be achieved by the competitive displacement of a drug by a structurally related crossreactant. This type of direct displacement is probably the simplest way of generating a release profile in response to a second analyte but other allosteric-like phenomena are also plausible(Figure 6).

Using MIPs to target drug delivery is also an exciting concept (Figure 7). The drug coupled either covalently or non-covalently to the MIP, would be released when the MIP binds to its target on the surface of a cell. This concept could be extended so that the binding of the MIP to the cell surface would bring about internalization of the MIP–drug complex and subsequent drug release.

To date, temperature- and pH-responsive imprinted polymers have generally relied upon strong ionic interactions between functional monomers and the template. The introduction of multiple hydrogen bonds or the use of hydrophobic interactions between the polymer backbone and the template would lead to imprinted polymers which might deliver a greater variety of therapeutic agents. The ability of an imprinted polymer to be able to recognize sugars, for example, would be highly advantageous in the treatment of diabetes. An increasing level of glucose in the blood could be used as a trigger for an imprinted polymer containing a reservoir of insulin.

Star-shaped and linear PEGs in combination with MIPs offer the potential of delivering a drug to a particular site through a further route[26]. Many cellular recognition process are mediated by polyvalent interactions at surfaces[27] and thus the complexation behaviour of PEG gels bearing pendant saccharide groups [28] might potentially provides a means by which an imprinted microgel particle modified with a multivalent polymer at its surface might be targeted to a target cell. The recognition capability of the hybrid imprinted microgel surface would then enable it adhere to a target such as a cancer cell, and subsequently release a high local concentration of the therapeutic agent.

CONCLUSION

The presence of drug reservoirs in a matrix that have a defined affinity as a result of the molecular imprinting process paves the way for fine control of therapeutic release, while the use of responsive co-monomers in the backbone matrix allows for external or biomimetic regulation of drug levels in a way not possible in conventional systems. The ability to engineer binding sites and material morphology in a relatively simple and controlled fashion is one of the most significant advantages of this technology which will in turn influence binding and release kinetics which is a crucial factor in drug delivery. Synthetic methods for the preparation of imprinted polymers are being refined to give much better control of macromolecular architecture leading to matrices with more predictable recognition and release properties. The advances in making MIPs in the form of spherical particles and films would be of crucial significance in wider use of MIPs in the area of drug delivery systems. The combination of these factors suggests that molecularly imprinted polymers will be both better defined and will have properties of real value in the biomedical field, leading to a promising future for these materials as drug delivery devices.

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