Review Article

Novel Strategic Innovations for Designing Drug Delivery System Using Molecularly Imprinted Micro/Nanobeads

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ABSTRACT

Molecular imprinting, the technique of providing a surface that can recognize and bind a specific drug or a therapeutic substance, has an enormous potential to revolutionize the development and performance of DDSs. A number of enabling technologies for the manufacture of molecularly imprinted polymers (MIPs) with target-specific cavities have been successfully developed. This has created opportunities for the designed structural polymers using knowledge of the chemistry of the template molecule that can provide other advantages, such as tailored predefined drug recognition systems with binding site functionality, allowing for precise control of drug release and delivery for an ever-growing number of pharmaceutical active agents. A strategic design can be served to meet the challenges of identifying recognition entities and specifically innovating in the required functionality, developing a diversity of different drug carriers and engineering delivery systems at the micro/nanometer scale. Combinatorial approaches have been developed, allowing optimization of potential combinations of materials with the specificity and efficacy of rationally designed molecular imprinted polymers. However there is still an urgent need to develop new ideas for creating the importance of the inherent properties of delivering drugs to desired sites and at appropriate speeds. Nevertheless advances in engineering nanoparticles, as well as advances in the mechanistic understanding of the molecular level of a synthetic recognitive-based network are creating opportunities for the development of artificial recognition nanoparticles for therapeutic applications. This review focuses on recent progress toward achieving the rational design of such polymeric materials, and discusses the challenges to realizing the potential of molecular imprinted microparticulate nanoparticles.

Keywords: Molecular imprinting, Controlled release, Cancer drug delivery, Self-assembly, Nanotechnology.

INTRODUCTION

The design of more effective drug delivery systems (DDSs) is one of the major challenges for pharmaceutical science. A special emphasis on developing a number of DDSs facilitates the delivery, ensuring therapeutic drugs at relevant concentrations, to sites of action, and at the appropriate time. Not only is an essential driving force for the recent spectacular developments in DDSs, but also have effectively contributed to the treatment and cure of diseases. As such, strategic innovations in DDSs have allowed the fabrication of new and more effective methods of delivery of the active ingredients that enable a therapeutic and nontoxic response, without any unpleasant side effects, for the safe and effective delivery of drugs. This is evident in the huge number of developing controlled delivery through recognition processes that hold promise for using biological receptors and macromolecules as carriers. In this sense, controlled release systems based on molecular imprinting involves the deposition of monomers around a template molecule, to form a mould stabilized by a highly cross-linked network with selective recognition to the template. This is followed by the subsequent removal of the imprint molecule, and resulting in an organic polymer with a predetermined arrangement of ligands tailored as binding pockets for the original imprint molecule or something closely related. Therefore, development of a DDS can be used to maximize a precise and effective release of an imprinted agent or targeted drug from polymer matrix or dosage formulation while maintaining a therapeutically useful concentration. Achieving a DDS based on molecular imprinting technique that provide a number of advantages, particularly with a greater potential for higher physical stability and non-toxicity and deliver drugs more effectively and safely. This review article deals with certain aspects of implementing the principles of the various approaches used in the imprinting process, and will explain how they can be furnished with biomimetic carrier and their applications. It includes known methods and describes the synthesis of the materials with physical recognition achieved by directly templating a polymer with the target compound, and also discusses of the impact of particle performances, as well as fabricating functionalized material into polymer particulates and intended function within these imprinting technologies. A novel approach here involves combining the emerging techniques for producing micro- and nanoparticles as controlled drug release systems that contain a template, and will selectively recognize a given drug and deliver them to target site for enhancing therapeutic effect. The ultimate goal is to provide a safe and effective delivery to the target site. When systemically applied, these systems will selectively deliver, e.g. anticancer drugs to target tumors without harming normal cells. Although a number of delivery methods, utilizing rational designs and approaches, allow for an increased level of the drug to

reach the tumor site[1]. In the following sections, a review of recent investigations and current trends in cancer drug delivery will hopefully highlight the immense potential and advances in this field.

CANCER DRUG DELIVERY

Cancer is one of the leading causes of human mortality throughout the world. It is also the most common to get side effects from the use of the cytotoxic drugs used in chemotherapy, such as nausea, hair loss, and pulmonary and cardiac toxicity. One challenge in using drug carriers to target cytotoxic agents or anticancer drugs is the rapid sequestration by mononuclear phagocytes of the reticuloendothelial system (RES)[2,3]. In addition, practical difficulties have been encountered by current carriers in extravasations from the drug carrier to a specific drug targets. There would be an immediate benefit if the drug could be localized directly or attracted to the tumor tissue, with the aid of a drug carrier to enhance the drug exposure to the target site. The biggest advantage of using a targeted and controlled-release polymer DDSs for anticancer therapies is that previously known severe negative side effects can be significantly reduced[4-8].

Recent developments of polymeric structures – including self-assembled monolayers, sol-gel polymers, dendrimers, poloxamers, lipoplexes and chitosans – have created a huge potential utility, as drug carriers, that can target the anticancer agent to a specific tumor. The diversity of these delivery formats can involve either the use of hydrogels, micelles[9,10] or polyplex or polymer conjugates[11], specifically developed to provide safe passage for therapeutic agents through inhospitable physiological regions. The most utilized synthetic biodegradable hydrogels have been hydroxypropyl methyl methacrylate (HPMA) and polyethylene glycol (PEG), but other systems used have been poly(glutamic acid), poly(L-lysine), polyethyleneimine (PEI), dextran, dextrin, and chitosan. These drug carriers can be developed with special features that can make them more multifunctional: for example, with affinity ligands capable of binding to cell surface receptors[12]. However, for a cancer-targeted polymer carrier to be both practical and effective, several features are desired. They should be nontoxic and nonimmunogenic, have long circulation times, allow renal elimination following drug release, and contain sufficient drug loading capacity regardless of the potency of the drug.

The delivery of anticancer drugs from the carrier component into the cancer tissues, so that the drug remains primarily localized with only a restricted amount entering the systemic circulation, is a means to control adverse side effects. Such an approach could employ the concept of biodegradability, this is now finding widespread use, where the active ingredient is slowly released by some type of barrier mechanism[6]. Factors that influence membrane interactions are part of the methodological advances that have greatly facilitated the design of anticancer targeted DDSs[12]. Further interesting observations and examples about this issue can be found, such as: exploiting liposomes or microcapsules[4], drug-targeted delivery[13,14] and the applicability of biomimetic carriers for therapeutic drug delivery[15].

Recent research devoted to cancer DDSs for intratumoral implantations envision the use of synthetic biodegradable polymers[16,17]. Carrier systems have been devised that deliver therapeutic agents into tightly sealed endothelial cells, where it can cross the blood-brain barrier (BBB) to a particular disease site, so that not distribute to other parts of the body as a means of targeted drug therapy. This challenge was met by using polyethylene glycol (PEG)-integrated polymer nanoparticles as a DDS for cancer chemotherapy[16-18]. The prime step for the use of these materials was the synthesis of co-polymers of polylactide and degradable polycaprolactone, which is by far at least optimal properties turned into drug release after an appropriate degradation time, as for a tri-component copolymer that served as a DDS for local delivery of anticancer drug into liver tumors in order to eliminate cancer cells[17].

Several strategies have evolved to utilize the unique extracellular environment of cancer cells to aid the release of drugs as a means of cancer-targeted delivery. Many of these techniques are based on the finding that areas around cancer cells normally have a lower pH (between pH 5–6) and a higher temperature (~ 42°C) because of their increased metabolic activity[19-21]. At present, the use of poloxamers and lipid micelles is one of the most important and widely used carrier systems for oncology applications, especially when they have been incorporated with a triggered release mechanism and a conjugated ligand that can facilitate active tumor targeting[19]. The design of certain cancer-targeted DDSs that can overcome the negative side effects of other anticancer agents may still be a flawed concept because of extravasations to adjacent normal tissues, causing adverse effects. One promising example of a tailored polymer designed to reach a target site is a micellar system combined with a pH-induced release of a conjugated ligand[20]. A functionalized folate-PEG-poly(β-benzyl-L-aspartate) block copolymer was combined with the anticancer agent Dox loaded into polymer micelles. By taking advantage of the folate tumor-targeting ligand conjugate, and offers the opportunity for preferential accumulation at the cancer expressing the targeted folate receptor. The presence of the hydrazone linkages is also important for this site-specific strategy, are cleaved under mild acidic conditions, another normal property of cancerous tissues. The above Dox micelle with a hydrophilic shell-forming PEG block allows for the intracellular pH-triggered release of the drug *via* a pH-cleavable hydrazone bond[19].

The unique advantage of biomaterials with responsive properties and smart polymer materials is their ability for a controlled delivery to the target site and ability to prolong the activity of the drug, thus exerting a greater therapeutic effect while reducing undesired side effects *in*

vivo. Other strategies used to enhance the molecular interactions between the carriers and tumor cells can assist carriers to identify tumor tissues and facilitate their uptake of a drug[22]. Dendrimers are well known as a material suitable for the delivery of drugs and other bioactive molecules, allowing for a selective intracellular distribution and even become localized in the nucleus. This will lead to an increased drug level in the tumor, improve circulation half-life, and limit signs of severe systemic toxicity, such as loading a doxorubicin (Dox)-bound oligonucleotide into a dendrimer resulted in a much slower clearance and fewer side effects than the use of the drug alone[23].

Targeted delivery using chitosan and derivatized chitosan has received a great deal of attention on account of their promising attractive properties, such as low toxicity, biodegradability and biocompatibility[24]. Chitosan nanoparticles may also be formed *via* an ionic gelation method using tripolyphosphate (TPP) as a precipitating agent. Chitosan can promote macromolecule permeation through well-organized epithelia; and make it an eminently acceptable vehicle for the transport of drugs, genes, proteins or peptides upon systemic delivery. A recent example of exploiting chitosan nanoparticle DDSs containing Dox, involved the release of Dox by a temperature-responsive chitosan, grafted with polyethylene glycol (PEG-*g*-chitosan) nanoparticles[25]. Employing chitosan carbohydrate conjugates is an additional rationale, as a matrix for encapsulation, is the capability of cellular internalization them, as it makes dependent on interaction of the carbohydrate backbone of chitosan with the cell membrane e.g. galactosylated chitosan-graft-dextran-DNA complex with encapsulated hydroxycamptothecin (HCPT), this is the tactic of producing a nuclear entity, in which case an active delivery of HCPT is the most advantageous, to provide better anticancer cytotoxicity[26].

Despite such innovative designs for drug carriers to deliver various antineoplastic agents the strategy as it presently exists is not without limitations. However, the design of new drug carriers has allowed for specificity, increased circulation life-time and kidney clearance. This has also been possible to provide highly specific interactions of selective, ligands with associated cell surface receptors for enhanced distribution and accumulation of the active ingredient and carrier. Tumor-targeting strategies rely on the properties of the targeting ligands such as transferrin and folate receptors[28]; that are expressed only on tumor cells to improve the efficacy of the binding to the tumor and the drug to enter tumor cells. Coupling of the polymer backbone chains with appropriate molecules can lead to active targeting to specific tissues and mediate endocytosis by the receptor cells. A conjugate of cisplatin-heparin-folic acid nanoparticles considerably contributed to an increased antitumor activity of cisplatin and specifically targets folate receptor (FR)-expressing tumors[29]. Folate conjugation had a minimal effect on the pharmacokinetic profile compared to the systems without the targeting ligand. Nevertheless, the drug carriers also reduced the non-specific toxicity of cisplatin, and give rise to improved therapeutic efficacy. Additionally, this targeting strategy, involves utilizing several other targeting ligands, such as antibodies or small fragments of RNA or DNA and active peptides, biotin and aptamers, can facilitate intracellular uptake and intracellular retention.

Drug delivery technologies can be brought just about devised strategies for the attachment of multiple drugs to the same polymer and are useful for giving a more robust, effective therapy for cancer treatment. For example, tetrapeptide GFLG (Gly-Phe-Leu-Gly) are now commonly used in polymer therapeutics, led to the delivery of a mixture of gemcitabine (Gem) and Dox conjugated to HPMA, achieving a slow release of drugs and a longer duration of action after systemic delivery[30].

STRATEGIC DESIGNS OF MIP DDSs

Classical techniques have been used for many years in the pharmaceutical manufacture to incorporate therapeutic drugs into synthetic and semi-synthetic polymers. This approach has to date produced only a prolonged-release dosage form, without any control either on the rate of release or its site of action. More recently, advanced DDSs have been developed that can enhance the driving force of a drug: *via* diffusion processes, chemical control or by externally triggered systems. These approaches have emphasized the need for precise fabrication in order to achieve useful synthesis or amalgamations of the components for drug delivery. There has also been a concerted effort to search for new therapeutic vehicles for precise drug delivery purposes. Scientific interest is an obvious and essential driving force for the recent spectacular developments of DDSs and other beneficial improvements, especially in the fields of synthetic processes and material sciences. In the past two decades, DDSs based on molecular imprinting – has proven to be an efficient method that enables the introduction of specific recognition sites into a polymer matrix, allowing delivery of several promising bioactive compounds. These polymer systems harness the opportunities enhancement a more precise drug transport process that will, help to prolong its half-life, and improve therapeutic efficacy. Compared to conventional synthetic polymer these new synthetic polymers with precise recognition ability have not only proved capable of providing a stimulus to the design of new delivery devices. Indeed, such properties have made MIPs a tool of great interest in many different scientific fields, including analytical chemistry, separation sciences, sensor construction and drug design[31]. The biomedical and drug delivery fields now appreciate their highly desirable ability to mimic biological delivery and recognition systems, consequent designing of various controlled drug release systems towards molecular imprinting technologies.

Molecular imprinting is a process that enables the formation of tailor-made recognition materials by

copolymerizing appropriate monomers in the presence of a desired template or target compound, and subsequent removal of the template leaves a cavity that retains affinity and selectivity for the respective template. The technique allows the direct production of recognition matrices that are suitable for use as a system for delivery of a given drug molecule. This is due to the advantage of man-made mimics gives to the DDS, both in terms of stability obtained from the MIP and the ease of operation and storage of imprinted material. In 1949, F.H. Dickey described the imprinting of a molecular memory with pigments (alkyl orange dyes) on silica gels[32]. But it is an established practical tool only in the last decade. The imprint is like a lock that is only compatible with the correct key, similar to biological systems, such as enzymes and substrates, antibodies and antigens, and hormones and receptors. The use of MIPs, as recognition sites, has been a focus of research because of their highly specific recognition properties combined with carefully worked out synthetic processes and designing DDSs[33]. Emerging techniques over recent years have thus made MIPs become more affordable, with easier operation and processability. Something is much different is a particularly attractive tool – in an ease to shape these recognition materials into a diversity of delivery formats such as fabricated systems can be decorated with recognition properties of efficient drug delivery – depends on the chemical properties of the delivered drug and an appropriate delivery device. Table 1 illustrates a MIP micro/nanoparticle with their characteristic particle size for different types of controlled release DDSs. The molecular imprinted polymers (MIPs) have been well established for transferring specific chemicals usually produces with high biologically molecular recognition within a well-defined phenomenon of cavity. However, not only how to design a novel DDS or systems, with binding sites capable of regulating the release of the template molecule, but the introduction of high recognition ability induces conformation change or fitting into the active site mimicking to specific recognition by a natural antibody or a biological receptor and devote for the efficient recognition systems for the target location at specific biological environment when using MIP to target drug delivery.

Table 1: Types of MIP micro/nanoparticles for controlled release DDSs with their characteristic particle size

Type of MIP delivery system	Particle size
Stimuli-responsive drug delivery	5-50 nm
Controlled release-long circulating	100-300 nm
Controlled release-targeted drug delivery	50 nm-1 µm
Poorly water soluble drugs	100 nm-1 µm
Ocular/bioadhesive	400 nm-3 µm
Pulmonary	1 -5 µm
Nasal	10-30 µm
Controlled release-depot	10-100 µm
Controlled release-oral/supplement	25-100 µm

1. Processes for molecular imprinting of polymers:

Molecular recognition aligned within a polymer network is one of the means to control the rate of therapeutic diffusion of the drug from the carrier to its site of action. The basic fundamental insights into the physical factors governing the formation of the template-monomer interactions and ligand-polymer binding can lead to rationally designed systems with greater control over their three-dimensional order and recognition specificity. If you think of constructing the non-covalent MIP cavities in the polymer, what you should choose the imprinting for 'target recognition' require for drug delivery, materials for the formed a target-specific binding site and what structures, if any, the chemically synthesized binding sites would be produced with a large interfacial contact of both the binding counterparts. When complies many ideas and a broad range of materials, these will clarify and visualize which component is important and which one may need. Considering the methods themselves and the materials can use, define the building polymer with specific recognition for drug delivery. Some strategies for producing systems of drug delivery by means of molecular imprinting techniques that are remarkable because they reflect precise selectively enhance the release of the drug.

a) Types of imprinting processes

The key element of success in creating an engineered MIP now in use for delivery of the pharmaceutical or therapeutic active molecules is a link with nature and of course pharmaceutical aspects. This is all part of recognizing that the synthetic selective material itself is dominant and their combining delivery components are just a small part of something much bigger. A design for MIPs should therefore pay to this bigger picture, draw in polymer components need, the functions they perform and how they relate to each other and incorporate the best of what's already there to highlight it. The first generation of MIPs used for drug delivery applications were primarily based on a single functional monomer unit using mainly the so-called non-covalent approach[34]. This non-covalent approach was first introduced in 1972 by Günter Wulff, whose research group published extensively on this subject. It requires a highly cross-linked system that becomes self-organizing sites in the

presence of a structure-directing agent[35]. In 1981, Arshady and Mosbach reported that they had prepared an organic MIP using non-covalent interactions of the corresponding template with the functional monomers, also called "host-guest polymerization," an approach that, the most flexible for the selection of functional monomers and template molecules[36]. For this reason, the non-covalent approach has now become the most widely adopted procedure in use[37].

In the non-covalent imprinting process selective polymer recognition sites can be achieved by equilibrating the template molecules with an excess of functional monomers, achieving the most favorable template-monomer complexation, in the presence of suitable cross-linking agents, and turn out to lead to interactive functional group randomly situated outside the imprints. Nevertheless the covalent bond production and cleavage that achieves these tailored interaction sites require fine-tuning for the desired features of the DDS. In any cases, the tailored selectivity and precise control over the release for rapid, inexpensive, and robust system of the delivery with the variety of functional monomers and cross-linking agents can be accessed. All these factors provide the major reasons for the present greater emphasis on the use of non-covalent imprinting for drug delivery being preferred over covalent bond imprinting since it requires the cleavable covalent bond within the cavities, yet limited to the template-functional group can be solely converted in a quite harsh condition.

Any design techniques used generating polymers capable of molecular recognition and releasable drug loading will require the following characteristics[38]: first, selectivity is introduced during the preparation of the MIP by dissolving targets or a selected delivery system as a template molecule or a molecule for imprinting in a porogenic solvent, together with one or more functional monomers at the start of reaction. Second, a template-monomer complex occurs or is induced, and the strength of this will depend on such factors enabled the complementary intermolecular interactions with those in the template functionalities, and the underlying chemical and physical properties (e.g. dielectric constant, dipole, polarizability, and hydrogen bonding capability) of the solvent in which they are dissolved. Third, after the addition of cross-linking monomers (whose hydrophilic or hydrophobic characteristics can also be appropriately adjusted) is followed by the polymerization process by which the solvent acts as a porogen and plays a pore-forming role with the non-interfering features of the template with the polymer matrix. The required degree of polymerization is achieved by carefully controlling the reaction conditions. Fourth, the removal of the template molecule is carried out by extraction with the selected regenerating solvent that will dissolve out the templates without modifications to the cavities. The resulting MIP will contain molecular imprints that are sterically, conformationally and chemically complementary to the template molecule and perhaps even to structurally closely related compounds, if the designed system was created appropriately.

Innovative concepts based on the chemical synthesis of MIPs – be it part of the advances in techniques or methodologies of engineering principles – helps to fulfill the great expectations in producing effective DDSs. The self-organization processes are obviously essential of oriented artificial system and frequently make a physical feature between the growing polymer backbone and the reacted monomers lead to a geometrically and sterically defined cavity. Any disturbance to the bulk polymerization and tie-points and energization of the microcrystalline regions of the recognitive chain network can affect microscopic events that reflect the mesh chain level into macroscopic phenomena, determining mechanical properties of the material and important evaluating the material, so make sure that approach extends the ability, to regulate the diffusion behavior of molecules in or through them. Also, energization of the cross-linked polymer structures in the presence of the templating polymerization has resulted in blends lacking homogeneity, it has affected the inherent property and physical stability of the MIP matrix and it can affect the stabilization of the interactive sites[39]. The impact of delivery efficiency for imprint molecules partly relies on the inherently poor mass transfer kinetics of the imprinted polymer matrix. The macroscopic level on the polymeric performances is the influence of the polymeric structure formation. The delivery systems that allow for a regular release of the incorporated active agents will be dictated by the entire network structure of the material containing the interaction sites, important for molecular recognition events. During the course of the development and optimization of MIP-based DDSs, a series of parameters must be identified that favor template-MIP interactions and simultaneously maximize imprint distribution into the polymeric matrix, and with a preferably controlled mass transfer kinetic. These include the contents and type of a preferably selected monomer, cross-linker, porogen and initiator as well as the methodology such as the initiation process, temperature and viscosity. The chemical properties and inherent nature of the template of interest affect enormously and determine what selection of a particular imprinting method. An inherent characteristic of selected template such as physical property and stability and molecular structure, is a decisive factor of formation of a pore structure with pre-defined interaction sites for the target delivery within the polymer networks. Better recognition sites are also expected using a template with more noncovalent interacting groups. As a result of the high amounts of the cross-linking monomers, the structure does not collapse upon the removal of the imprinting molecule, but remember that an assembly of weak interactions can yield a highly efficient binding between the templating polymer material and the selected drug, and as such is the best suited to its efficient transport and delivery to a specific target where it can be efficiently removed from the imprinted cavity[40]. However, potential

pitfall is the difficulty in the ability of the regeneration solvent to extract the template from within the polymer matrix, in which it is without any effect on the imprinting areas and significantly renders non-specific binding of the template/analyte, thus all of these issues have to be seriously considered.

b) Types of polymerization

Whenever create the molecular recognition properties, remember that themed imprinting process can be influenced by an appropriate selection of elements – polymerization process, and polymerizing compositions – will give arise to chemical parameters influencing the synthesized MIP products through its patterning structure. Imprinted polymer is one way to implement this into material designs in which a number of different formats as well as composite drug carriers of various sizes, morphologies and structures with the potential to be used in drug delivery devices have been established. Not only polymerized mixture affect the success of an imprinting scheme, but also relates to the comfort of imprint polymerization reactions that produce polymeric networks; they can be chosen by a variety of polyreactions such as radical polymerizations, the most preferred technique, otherwise polyadditions, or polycondensations, depending on the polymerizing component.

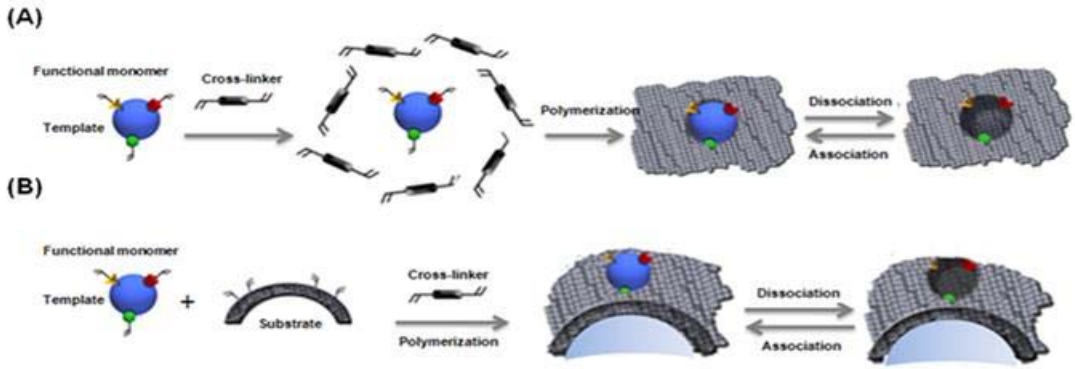


Figure 1: Schematic illustration of preparation of MIP drug delivery system by: (A) bulk imprinting: the structural feature of the print molecule is imprinted, and the three-dimensional orientation remains in the whole matrix; and (B) surface imprinting creates the obtained template surface.

Many of the most common methods of molecular imprinted materials can fabricate the confines of system into a different format, capable of delivering drugs and selectively release to a target area of actions. This is normally achieved by creating MIP-based DDSs inspired by other biomimetic recognition systems. The effect can be very real: with biological system and resources of ingredients, it may only take a simple, robust method, to make a particularly biofunction setting in engineering device. Design techniques can be broadly divided into two main categories defined as either a bulk or surface imprinting process. Fig. 1A illustrates the generation of molecularly imprinted bulk polymers with irregularly shaped particles obtained after crushing/sieving in which different imprinted sites which are distributed entirely the polymeric matrix. The easily-obtained product obtained from a traditional bulk polymerization process involves a macroporous matrix of undefined size. The structural feature of the print molecule is imprinted, into whatever the polymer system, this is a genre of the three-dimensional orientation network design that is highly effective in creating a memory of entire molecule remains in the whole matrix. Since bulk imprinting procedures involve crushing the matrix after polymerization, to produce irregularly shaped materials and polydispersed particles which are time-consuming and labor intensive and there has to be a potential to destroy binding sites. On choose to replicate the analogue of a bioactive molecule, but synthetic products that encapsulate specific entities are especially worthy. Some multiple-template approaches, or those of intended well-transport, or targeted towards different areas, may even be devised into a same polymer matrix each delivering a different location. How far we can create such a novel delivery system depends on whether or not the researchers apply them to the specific purpose, or totally devise into different format as particles or thin films making them the best system – ideal for coupling multifunction for advanced delivery systems, as such a detail on emerging techniques related to this polymerization process is given later. Nevertheless, before a successful MIP system can be developed, it has to be recognized that the template cannot be completely removed from the network, and the number of possible binding sites in the rebinding experiments may decrease[41]. Typical MIP bulk polymers have an amount of cross-linking monomer which provides the opportunities for balanced improvement in polymer properties that falls above 80 mol% (moles cross-linker, total moles of monomer and cross-linker), to even retain the recognition capabilities for the imprinted materials in the DDSs. Fig. 1B sketches of a surface imprinting polymerization underlying the synthesis: an interaction between the template and functional groups of the monomer(s) on the surface of the matrix materials, as illustrated in following sections. While, surface imprinting provides for the generation of MIP systems that allows for

the readily accessible interaction for rebinding of template together with fast and cost effectiveness since no grinding process of the polymers is required.

In more recent years numerous approaches have been successfully utilized for the fabrication of reproducible and uniformly sized spherical MIP particles e.g. multi-step swelling polymerization technology[42,43], precipitation polymerization technique[44-48], suspension and emulsion or mini-emulsion polymerization [49], and core-shell polymerization process[53,54], and thus offer an interesting alternative formats for purpose in drug delivery. So many technologies have occurred as a result of advances in chemical engineering and material sciences together with an improvement in methods that it is almost as if they have often focused to investigation and characterizations in the physical properties and chemical surface functionalization of the MIP beads[54]. Providing beads of tunable size and porosity during polymerization process allows different formats in micro- and nanosized MIP particles, furthermore tunable surface characteristics are allowed by the judicious selecting of substrate or monomers for the pre-polymer complex and protocols for polymerization process. Make sure there is minimal density fluctuation of different polymer networks, substantial difference of screening particle size, on the other hand polymer assortment of different generations. Wet decantation was then employed to remove fines of particulate MIP beads, and proper sedimentation and filtration leading to adequate screening particle size resulting from a decrease in the particle fractions. Some success was achieved by choice of porogen solvents used to adjust performance of the spherical MIP materials dominated a rendered effect that include a particle size and nature of the synthesized polymer products, then the solvent has to be strictly used to enhance template solubility. The solvents also involve partly imprint site formation that they will allocate dense ordering of macromolecular chains rendering network stiffness in the stabilized recognition site. This is because solvent has also the impact on crosslinking polymerization causes substantial different physical entanglements and heterogeneity within the polymer network, apart from it supportive to intermolecular interactions to form template-monomer complexes. Generally, a spherically MIP hydrogel particle is generated to produce a controlled release of therapeutic agents that is significantly advantageous for the selective rebinding properties, with easy access for the target molecules and rebinding for inherent recognition and implication of synthesized products. Keeping match polymerization and rebinding solvents is crucial importance, at least polar, dielectric constant, or for a right choice, is the original solvent during rebinding step this will help reduce differences in Gibbs free energies related with elasticity of the network architecture and the energy of combination.

The polymerization producing uniformly shaped spherical MIP bead can also be performed by the traditional suspension polymerization techniques, in basic solvent systems, using an aqueous phase for suspending the monomeric species. The imprinted material is typically prepared using a suspension polymerization process to create a uniformly spherical particle after the imprint material are added at the beginning and dispersed or emulsified in a porogen solvent. By increasing the solvent amount the number of imprint molecules to polymer chains within a given polymer matrix affords the possibility to optimize the molecular imprinted polymer performances whereas a high dilution allows for the final polymer to be in the form of nanoparticles. The use of suspension polymerization, as a technique appears to be an efficient alternative for obtaining improved reproducibility and uniformity of molecular imprinted microparticles. A striking advantage of suspension polymerization techniques is their ready scalability. By using multilayers of particles, the strategy can be extended to the preparation of three-dimensional structures with monomodal size distribution, reduced low-affinity sites. Generally, synthesizing polymerization protocols developed for long-term stability of imprinted microspheres, and can conveniently be transformed into preparative procedures, providing for manufacture of the synthesized polymer in industrial scale. Particles in a size range of about 5 to 10 µm are traditionally produced by multi-step swelling polymerization in the presence of spherical polystyrene with the imprint enantiomer, and monomers acting as a polymeric cross-linking agent that result from both hydrogen bonding and hydrophobic interactions[42].

Core-shell polymerization is one of the most alternative technical advances that have led to the creation of a spherical MIP nanoparticle by imprinting a shell layer with a core-shell emulsion polymer[53,54]. Core shell approaches create high-performance MIPs with potentially a combined property for a well-defined functionalized interface for a controlled drug delivery to a target site, in conjunction with other functions. Applications would require large amounts of material on the industrial scale, a controlled suspension polymerization process in to a spiral shaped micro-reactor appear very promising to provide an easy handling when dealing with MIP microparticles and will add not only to your pleasure in the simple and contemporary system and provide synthesizing from handy monomeric ingredients, it will also lend to real-world DDSs in a large scale process[55]. This imprinting approach involves the formation of MIP microparticles employing a two-phase flow reaction with or without perfluorocarbon as the continuous phase in mineral oil as the porogen solvent. Changing the flow conditions, the continuous phase, and the technique by which the particles are formed affects the droplet/particle size and capacity for template in the produced MIP spherical beads.

Precipitation polymerization is one of the most common technique building imprint materials which evolves to the formation of imprinted particles in a solvent in which the

growing polymer chains capture monomers from a reaction mixture and continuously grow to enough size so they become relatively insoluble material and rapidly precipitate out from the reaction medium, facilitating entirely removal of solvent. The precipitation polymerization techniques have been found to provide a simple and efficient preparation of molecular imprinted polymer micro- and nanoparticles[56-58]. A strategy for the precise control over the particle size of the imprinted polymers is specialized for the growing polymer matrix redirected an alternative to the conventional procedures for engineering imprinted uniform beads. Most of alternative imprinting approaches to the conventional emulsion or suspension polymerization methods in fact, that usually employ surfactants or a stabilizer to create MIPs in the form of microparticles or nanoparticles, within the precipitation procedure are also a good choice. As no surfactant is used during polymer synthesis by the precipitation polymerization method, which this is a benign process in comparison to other methods. Molecularly imprinted micro- and nano-spherical beads by precipitation polymerization have been shown to have the potential to produce controlled release devices, since they can be particularly used for the sustained release of a variety of different active pharmaceutical agents[59,60]. The technique is particularly helpful when producing surface imprint matrix that offers distinct advantages which the drugs are able to bind with stronger binding characteristics to accessible sites. Because of the use of a "conventional" rather than an "alternative" precipitation polymerization process for preparing the MIP micro/nanoparticles, it was possible to adjust and control the final particle sizes without reducing the imprinting effect. This was achieved by varying the ratio of diverse cross-links in the synthesized MIP products. Although the driving force behind the development of these MIP particles was not for improving drug delivery but to a desire to facilitate memorizing the therapeutic drug shapes, nevertheless the imprinted micro/nanobeads turned out to be much more useful which have strong potential for delivery of clinically used therapeutics.

c) Types of MIPs

In recent years, imprinted polymers in different MIP formats have emerged with the potential for use for the delivery of drugs that provides the resultant required clinical responses. The drug delivery process associated with different MIPs is based on the release of drugs from a number of imprinted micro/nanoparticles as the recognition system that now acts as delivery devices. The functionality of these MIP systems is commonly dictated by the process of their formation and the structure of the imprinted polymeric networks[38]. Thus, the MIP protocols employing to synthesize materials involve a number of different factors that can affect the final polymeric performance. A porogen solvent is known to help facilitate the formation of a continuous pore structure. The properties of a porogen solvent required to achieve the pore structures with sufficient permeability dictates the microenvironments that the porogen solvents supportive to the intermolecular interaction between monomer(s) and template molecule complexes and present as a pore-forming by dissolving template and monomers to provide diffusion pathways during imprinting process. Thus, the propensity to create the site-specific cavities in a network of polymer chains can be dictated by a dedicated porogen solvent. Different solvents or different amounts of one solvent can create effective binding sites with different properties. Varying the pore size by altering the type and ratio of the porogenic solvent has led to differences in tortuosity of the structure of the polymer matrix, which cause alteration in conductive property in the polymer structure. However the use of binary solvent system can provide addressing the solubility of template and providing the resultant polymer system more porous enable the increase of one-dimensional transport of the encapsulated drug molecule. It is difficult to achieve a site with a strong affinity for the template for binding yet with the flexibility with respect to successful drug delivery. It is conceivable that the presence of water or a strong polar solvent does not facilitate the non-covalent techniques since its polar protic nature readily disrupts crucial interactions between the template and monomer, hence formulating MIPs in these systems often proves to be a challenge.

With regard to the aspects of binding site homogeneity in the resultant imprinted polymer, investigations have been carried out to try to avoid one of several challenges related to a specific format of the MIP for solid particles[57]. Once, formulating delivery device with optimum incorporation of MIPs on a material surface must include: stable, efficient immobilization; a procedure that does not disrupt the molecular recognition of artificial recognition materials; selection of imprint component that do not affect the properties of the polymer; and enabling of direct interaction of substrates or polymer system containing the active functional monomers can also be effective in a self-trigger release. However, they represent serious limitations in choosing the chemical nature of polymeric systems, the dissolving solvents, and the environmental conditions for the efficient molecular recognition capacity so the imprint sites will maintain their inherent feature and give the greatest capabilities for biologically active molecules.

Designing the tailored recognition sites can confine the chain propagation on the vicinity of the support surfaces of the material or pores require not only a predefined strategy, but also considering the possible problems (related to the issues of low binding kinetic and mass transfer of template in delivery device) is usually difficult. So far, the usefulness of DDSs needs to use the MIP surfaces as well as to combine the pre-eminent features of their traditional delivery complement where the enrichment of selective binding sites on the surface of the forming materials come to an enhanced transport rate that surpasses with a conventional imprinted polymer[40].

For such an approach to be the most effective, it is essential that an imprinted material which can obviate producing of the homogeneity of biomimetic interaction sites, and thus offering the possibility of a desirable drug delivery, although the more favorable the functional group, the more non-specific binding can be.

Given due to the enhanced necessity in the surface-attached monomers, polymer growth tends to occur preferentially for unconstrained monomers in polymerizing solution, leading to low attachment, heterogeneous distribution of binding sites in MIPs, polymer coverage and even to pore destruction effects, results in compromising mass transfer kinetics and thus poor delivery efficiency of chiral drug molecules. The development of a novel polymerizable functional monomer derived from small molecule host-guest chemistry is the most promising alternative and applicable so far. In addition, the use of interactive functional monomers capable of producing strong interactions with an induced-template complementary should be highly benefit leading to the tailored target-specific site with high specificity and affinity so that the technique in stoichiometric template-monomer complexes is also possible to be employed during imprinting process, and may have added advantage of implications for shaping of MIPs into more practical formats.

Up to now, several controlled polymerization processes serve to facilitate production of different polymer layers that allows for enhanced permeation of drug molecules into the MIP binding sites and improved selective release. On the upside, design method of a MIP system as thin-film on a support or small particle is easy to imprint the template molecules on the prepolymerized surface by, a stamping or grafting method. The surface modification provides the opportunities to obtain multi-functionalized layers differently imprinted via several successive polymerization processes, allowing the targeted optimization of polymerization. Thus the patterned polymer surface even generates the molecular imprint, and the target molecule can be exclusively extracted from the polymeric matrix. The imprinted matrix should be made from a biocompatible material that can withstand the harsh condition and be effective in a complex arena in physiological in vivo. So far, the development of adsorption phase based on these surface molecular imprinted polymers that combine the pre-eminent features of their traditional delivery counterparts as a means of improving low mass transfer conditions, but yet their form offer new flexibility to overcome some of the key biological barriers is gaining momentum. Synthesis of the imprinted polymers might include the use of a degenerative chain transfer *via* the reversible addition-fragmentation chain transfer (RAFT) agent and the addition of an iniferter in the reaction mixture to favor the inherently high activity of the surface-anchored azo-initiator [38,57]. A surface imprinted matrix has been made through materials from either a self-assembled monolayer or a sol-gel process of a TiO_2 nanofilm or an ultra-thin film polymerization – stay true an approach can provide wander opportunities to tailor the surface chemistry into the well-defined nanosized environments. The final materials were shown to produce a behavior that had a thermodynamically homogeneous association with a single binding constant and also exhibited a substantial enhancement in substrate specificity relative to those prepared conventional bulk polymerization techniques[9]. Another area that can benefit greatly from future advances in this field of polymer technology is that of real world drug delivery systems for biological molecules (e.g. nucleotides, enzymes, peptides and proteins). The details of understanding biomimetic imprinting for proteins are important because they will determine the characteristics of the delivery systems required to synthesize materials that will sustain, enhance the loading capacity, and tailor the type and amount of cross-linking, for the intelligent release of the biotherapeutics, after responding to an internal or external stimulus targeted to the required sites of action. In this sense, development of an imprinted polymer gel with a composition, allowing for effective recognition sites in the polymer macromolecules that will specifically bind such large template molecule in aqueous environments will be highly appreciated. More selective interactions could be achieved by weaker, but multidentate interactions. This strategy will also lead to minimizing the irreversible binding of proteins to polymer architecture surfaces. The use of polar, aprotic solvents with biological molecules and soluble crosslinking and functional monomers is leading to new solutions to imprint structures designed for biological relevant network molecules, apart from small organic molecules. Also, molecular imprinting of polymers is to mimic the chemical structure of the template enantiomer at molecular range by self-organizing the polymeric chains around it, which on polymerization then become integrated into the macromolecular network. Consequently, the solution mixture is sufficiently flexible to mold the chemical properties and surface features of the macromolecular template while not subsequently altering it in such a way that the template–monomer assemblies become distorted. In one example, when lysozyme-imprinted polymer networks were produced in an acrylating system, this enabled the appreciable absorption of the imprinted hydrogels in comparison to the nonimprinted gel with an imprinting factor of 1.83-3.38[47]. Of course many techniques including the manufacturing process of thin-films, surface graft MIPs have led to studies that have involved the fabrication of nanocarriers capable of the transport and controlled release of the drug[51].

2. Delivery strategies:

There are many ways in which a polymeric-based system can reflect its own performance for drug delivery application, and one of most promising ways in recent years has been to replicate concepts that interest the

pharmaceutical scientists – like a molecular-specific polymer release system. This comes as no surprise, considering that global synthesis of novel synthetic specifically recognitive-based networks of advance materials and imprinting technologies have made their development and application more and more accessible. Although a designed delivery system based on molecular imprinting polymers has led to a heightened interest in the pharmaceutical applications and drug delivery, they are, in fact, carefully design with a well-established strategy for modifying the delivery and absorption of therapeutically active molecules. Several approaches can be used to produce MIP-based controlled release DDSs and it is likely that will result from dedicated efforts in this field. In some of the greatest designed MIPs are purpose built to the need to the approaches of the generating of carrier systems or devices more selectively deliver and much more efficiently of the therapeutic substance. Whilst most traditional polymeric DDSs used for the sustained delivery or extended delivery, continue to be used today or the rationale design of MIPs using computational approaches and systemic methods to formulate processes that incorporate recognition materials have been achieved over recent years. Most research in this area has focused almost exclusively in the past 5-10 years on the behavior of MIP by the production of DDSs which is devised in different formats ranging as beads, membranes and microdevices. Table 2 illustrates molecular imprinted polymer of engineered particles with varying structures and drug release characteristics could be potentially used in various DDS of many promising therapeutic substances. The highly cross-linked polymer with recognition for a specific molecule can drastically improve the delivery performance of a drug of interest the time for diffusion of the template molecules into the cross-linked matrix. Proof-of-this concept can be found in the recent work exploiting enhanced recognition ability of the imprinted polymer allows separation process and selective release of a biologically active compound within delivery devices – will all work well. There are several excellent review articles that have documented the progress of molecular imprinting polymers for delivery of various drugs[40,46]. What follows, provides an overview on some of the currently used molecular-imprinted polymer systems that can demonstrate the strategies, being adopted for addressing the drug release problems related to the mass transport and binding parameters of the imprinted polymers for enhanced drug delivery and selectivity.

Table 2: Molecular imprinted polymer particles as system used in drug delivery

Formats	Material	Biological molecule(s)	References
Nanoparticles	MAA-EGDMA-NIPPAAm	4-aminopyridine, L-pyroglutamic	[52]
	AA-MAA-MBAA	sulfasalazine	[44]
	MAA-EGDMA	α-tocopherol	[45]
	MAA-EGDMA	5-fluorouracil	[62]
	MMA-MAA-TRIM	caffeine, theophylline	[34, 102]
Microparticles /Microspheres	MAA-EGDMA	(*S*)-propranolol	[78]
	MAA-EGDMA	nicotinamide	[68]
	MAA-EGDMA	5-fluorouracil	[48]
	MAA-EGDMA; VPD-EGDMA	17β-estradiol	[57]
	MAA-EGDMA	caffeine	[46,47,48]
	MAA-EGDMA	propranolol	[59]
	MAA-EGDMA	dipyridamole	[73]
	MAA-HEMA-EGDMA-DMAEMA	glycyrrhizic acid	[61]
	MAA-EGDMA	salicylic acid, acetyl salicylic	[109]
Imprinted polymer surfaces on nanoparticles	MAA-EGDMA	(*S*)-propranolol	[78]
	MQN-EGDMA	(*S*)-omeprazole	[77]
	MQD-EGDMA		
Liquid crystals	4-pentyl-4-biphenylcarbonitrile /N-(4-methoxybenzylidene)-4-butylaniline/Chlolesteryl oleyl carbonate	paracetamol, ascorbic, catechol	[31,85,86]
Particles of therapeutic proteins, peptides stabilized with excipients	acrylate	lyzozyme	[47]
Porous membranes	MAA-EGDMA	(*S*)-propranolol	[73,74]
Nanostructured nanoparticulates	MAA-EGDMA	(*S*)-propranolol	[78,100]
Nanocapsules	vinyl-styrene	estrone	[103]
Dendrimers	polyglycerol	(*D*)-fructose	[104]
Finally granules or spherical agglomerates	MAA-EGDMA	(*S*)-propranolol,	[76]
	MAA-EGDMA	(*S*)-ibuprofen, (*S*)-ketoprofen	[76]
	MAA-EGDMA	theophylline	[34]
	MAA-EGDMA	citalopram	[66]
	MAA-EGDMA	bromhexine	[67]
	MAA-EGDMA	tramadol	[65]
Nanogels	diphenyl phosphate	carboxypeptidase A	[105]

There are varieties of MIPs used for controlled-release DDSs. Fig. 2A shows category of engineered principles with recognition by the MIP that is physically entrapped in or absorbed onto a solid or a material or a gel through non-covalent reversible interactions by hydrophobic or ionic forces that regulate drug release. A multitude of approaches focus the delivery of drugs based on molecular imprinted polymers. This is essential for utilization of strategic design, as it were, and providing simplicity, robustness and practical system, although a

chosen imprinting technology should allow one to enjoy enhance the release performance of delivery devices. This has been achieved using these three predominant strategies.

i) The first form relies on the permeation of a target drug in a highly cross-linked network and then diffusion from the imprint sites usually consists of a single functional monomer that can move from the imprint site to the delivery site that may have a higher affinity for the drug[46]. Designing molecular recognition materials into the network chain creates a bulked polymer and versatile formats for modified drug delivery or even application in advanced drug delivery; MIP micro or nanosphere or membrane with a localized higher cross-linking chains, to proper rigidity to produce sufficient specificity. Functional monomer and a crosslinker are the two limiting factors when creating a self-supporting, macroporous bulk polymers for being use as stationary phase in chromatography or in incorporation of sensitive materials for intended application recognition of a wide variety of template. For polymer formulations, the large excess of crosslinker needed to achieve appreciable of network rigidity to help to preserve the binding integrity in polymeric environments and ensure the formation of shape and geometrical fit for specific binding template to the binding site. As a useful chromatography study and spectroscopy such as FT-IR, fluorescence spectroscopy, ^{1}H-NMR, can be used to determined binding capabilities, incorporation in molecularly imprinted polymers and the recognition properties of the resulting polymers, as well as chances will be able to produce a specific pore with functional groups in their interior. This delayed release occurs due to transport, non-selective cross-linking polymer networks, especially beside physical features, where the highly cross-linked networks can be reflected in template molecules of interest of a certain size range in the pre-polymerization complexes to be trapped in substrate-specific cavity in the polymer matrix. By using non-covalent imprinting method, the chemical properties and important counterparts in template's structure are transferred into the chemically synthesized cavities, thus lead to tailor the pre-defined selectivity, and is a really straightforward way of producing recognition materials. This recognition polymer produces a delay in the release of the therapeutic agent when the drug diffuses through polymeric barrier and interacting differentially between selective and non-selective components and then forms multiple binding on the target sites. The initial degree of porosity and the tortuosity of the polymeric chain network is a crucial importance in controlling the diffusional transport rate of the drug molecule. A certain amount of flexibility in the reversible polymer chains is also essential to facilitate mass transfer and allow for both the template removal and its re-binding. An increase in the loading capacity of the delivery molecule will enhance the time of providing a therapeutic dose.

ii) The second, advanced method is relevant to ocular applications and other drug therapy, and a molecule imprinted polymeric network that has been investigated for their enhanced diffusional template transport and the controlled release relies on exploiting a mixed functional monomer approach for drug selectivity. Imprint polymerization reactions with one type of functional monomer perhaps does not provide optimal interactions between the polymer chains and the template (i.e. depending on the chemistry of the template molecule). The imprint generated by multi-crosslink systems is favorable as each functional monomer will have a preferred functionality and more energetically favorable interactions with certain chemical groups on the template molecule. The potential use of a mixture of two or more entities of the functionalities available for rebinding a given template almost for any structural feature will eventually allow for a controlled therapeutic delivery and an increased drug loading to therapeutically useful levels. A certain fraction of the randomly oriented functional group within the polymeric phase requires stronger interaction to the functionality of template. The alternative strategies that use of interactive functional monomers, by varying the amount of functional monomers and template ratio and to adjust the degree of cross-linking of the synthesized material, can lead to an increase in association strength and the number of interactions between the monomers and template molecule, resulting in obtaining a delivery device suitable for application in an aqueous solvent. The exploitation of a multiple monomer formulation has led to forming non-covalent associations that can produce a specific binding sites involving a direct tuning interaction and cooperatives of function between the template and functional groups positioning in the surrounding polymeric network after crosslinking polymerization, thus providing the predominant parameters that determine the imprinting effect and control a constant release of the incorporated therapeutic substance[40]. Although it is rather important aspect of the macromolecular structure increase in size within the growing polymeric chain networks that the entanglement of individual monomer will also increase and thus influence the transport of the therapeutic agents toward the imprinting effect. The imaged structure of the binding moieties of template of interest are readily molded into the polymer surfaces of the additional polymeric macromolecules or any macromers during the *in situ* polymerization, and it was this approach, with its simple, that induced the functionalized monomers can capture a template molecule dissolving in a methanol used as porogen solvent to promote the macroporous polymer with specific recognition sites. Molecular imprinting technology also gives rise to the advantages of combined the multifunctions to the binding moieties was applied for developing molecular-specific delivery system utilizing their ability of the shape recognition properties and the functionalities of a chosen functional monomer leading to specific recognition ability towards the biologically active molecule. This approach offers unique opportunity to tailor target-specific site combining with sensing system

or forming optically or photochemically coupled hybrid architecture building blocks of drug carriers.

iii) Recently, the third form has made substantial progress. This is achieved by dictating the composition of the recognitive forming polymer to possess a higher selectivity and substrate-specific polymers which have found for both ocular applications and other therapeutic areas. The method used to design a potential molecular imprinting delivery system relies on the drug carrier being imprinted in the aqueous condition by exploiting multiple diverse functional groups for extensive non-covalent interactions between the MIPs and the drugs. As a result, intensive efforts are currently underway to use the wealth of chemically diverse functional monomers on such imprinted polymers[59-63]. From a diverse functional monomer viewpoint recognition and selective delivery may have two objectives, both of which involve the polymerization conditions and the chemical precursors for preparing MIP during imprinting process. Use this strategy as a direct mean for tuning the maximum diversity in chemical functionalities to manipulate the macromolecular structure within the imprinted cavity provide for tailored interaction centers built around the non-covalently embedded template. The underlying association and distribution processes are governed by complex equilibria between the interacting components under the exposed conditions. The factors governing these multiple interactions are poorly understood, rendering the optimization of MIP-based controlled release protocols a difficult task. For such cases, the degree of success relies on the exploitation of the appropriate cross-linked portion of the polymer chain to ensure molecular recognition events. Alternatively, strong template-MIP interactions are desirable for surface coverage and charge compensation, and this exclusively influence not only on the binding affinity and capacity of MIP, but also on the heterogeneity in respective cross-linked structure.

Some of systematic research studies have opened light on how to influence polymer composition, the degree of cross-linking and the polymerization method lead to most importantly the preparation of controlled release formulations. Overall, the approaches of generating molecular-imprinted polymers for recognition to and drug delivery purpose are given in more detail below.

a) Biomimetic receptor

Appreciable technologies have occurred as result of the development of MIP compositions for reversible rebinding biologically active molecules to be embedded inside a polymer matrix and released over an extended period of time as it slowly diffuses out. The use of more traditional and well-established imprinting methods has gained in importance due to the insight in the transfer of molecular structures of MIPs. As well, parallel developments in the design of materials are able to provide reproducible interactions at the imprint site of the formed matrix in an aqueous system[35,37]. One of the most promising alternative approaches involves the building polymeric structures and architectural features mimic to the specific recognition event in natural antibodies that allow shape the original molecule and the chemical properties transferred into the imprint sites. This idea can be realized using a buildup of reversibly self-organized materials similar as natural antibodies applied for selecting specific antibodies having a high recognition area to respective antigens; since the molecule achieving pre-arrangement for target antibody is amplified and then ready for immune responses. Numerous biological structures themselves have evolved from this spontaneous self-reorganization process. This specificity for target binding in many cases arises from a combination of non-covalent interactions, such as hydrogen bonds, hydrophobic interactions, dipole interactions or π/π-interactions. But keep in mind that hydrogen bonding formation is especially exceeded a certain threshold, the bond between the binding partners become irreversible. The most impressive example of this kind of supramolecular structure is the self-formation of specific DNA sites through recognition of nucleotides, indeed it is the fact that DNA double strand is strongly held together on the basis of non-covalent interactions[64]. This principle was also applied to the choice of methacrylic acid (MAA) as the recognition center which has been shown to interact through hydrogen bond with amines, amides, carbamates and carboxylic groups and *via* ionic interactions with a given template. Much of these strategic designs rely on the properties of the methacrylate system, the precursor of a delivery vehicle for use in therapeutics. The diverse methodology of the utility of MIPs for drug delivery applications has emerged over the years with a considerably simplified construction for the structure of the drug and bioactive molecule in the polymer networks by polymerization through initiation by radicals in the presence of light or heat. However, some of several systems in nature have diverse dynamic binding functions due to side chain flexibility and/or domain flexibility cause spatially variations in structural arrangement. The imprinting process consists of a print molecule bound covalently to functional monomers then crosslinked with an excess of crosslinking monomer in porogen that have exclusively helped to achieve much of the seminal knowledge on the creation of physicochemical properties of an active therapeutic or other biomolecule of interest within the imprinting polymer. For example, the macromolecular memory of a template polymer can affect the release of the templating species as in the case of the amount of α-tocopherol used to formulate imprinted poly(MAA) cross-linked ethylene glycol dimethacrylate (EGDMA) nanoparticles (size range 100-500 nm)[45]. A variation of the hydrogen bond strength led to a shift in the threshold behavior for a drug template which provided a better tuning for hydrogen bond interactions and resulted in a structure-breaking effect at lower template incorporation in both organic (acetonitrile) and aqueous (ethanol/water 6/4 v/v mixture) solvents. The integration of the

thermodynamically unfavorable solvent molecules disturbed the hydrogen bond interactions between the methacrylic acid units and this affected the rebinding and template release. The imprinted nanoparticles formed under photopolymerization conditions at a low temperature in acetonitrile as a porogen solvent did induce shifts in the relative populations and association energies of the MIP binding sites. They showed that the best enhancement of the template binding affinity for the imprinted preparation over the control had a value compared to the control range of from 2.25 to 3 times, higher after incorporating acetonitrile. The imprinted nanoparticles produced an extended release period of α-tocopherol in a simulated gastro-intestinal fluid, with 50% release in 4 h and 100% release in 40 h, compared to the non-imprinted nanoparticles (100% release in 4 h).

b) Functionalities

The most common strategy for optimizing functionality permits a specific location within the receptor binding sites to provide type of substrate or functional monomer for the pre-polymer complex. A fine-tuning of the template/functional monomer ratio into the bulked polymer matrix should also be a priority when synthesis with suitably cross-linker followed by crushing, ground and sieving of the bulked polymer products. Increasing mass density of polymer crosslinking network, the length of functional monomer and monomers needs to increase appropriately and extend to robust, rigid structures of the imprints and overcome loss of binding regimes while compromising polymer swelling or shrinking effects. This mainly focus with polymerization kinetics and the intrinsic feature of the macromolecular chains formed during polymerization, reflecting their network morphology at a molecular level. The concept of the fine-tuning in functionalities has been mostly used in delivering for hydrophobic active agents such as tramadol[65], citalopram[66] and bromhexine [67]. It must be acknowledged that structural properties of the matrix, its micro morphology and pore size play significant roles on the mass transport (of water) at the area of the recognition cavities into and (of drug) out of the polymeric network. Although it is the imprinted polymer that is responsible for the adsorption process and subsequent release of the drug, the physical properties of the polymeric recognition material also contribute to the controlled release characteristics of the required pharmaceutical carriers. Rather than relying on the preparation method itself, a ground bulked particle, imprinted with tramadol, an opioid analgesic, used for moderate to severe pains, was generated that allowed for a controlled release of the template. This MIP system exploited rather simple poly(MAA-*co*-EGDMA) imprinting formulations for the template molecule with chloroform as the porogen solvent[65]. All the MIPs showed affinities of ~1.1-5.4 for recognition compared to the non-imprinted control polymer, with a loading capacity (81 mg template/g polymer) existing for the template/monomer ratios of 1:6. The drug loading and release efficiencies of this system were tremendously dependent on the pH of the solution, with an optimum at pH 7.4. As was the case with the recognition studies, the systems prepared from the template/MAA molar ratios of 1:6 had an ability to enhance, extend or delay the template release profiles by twofold over that of the control network. A nonpolar solvent is usually necessary to allow for access of the template to the functional group of the monomer. Regardless of the template removal strategy, this regulates the rebinding efficiency for the resulting MIP particles. Some of the non-ionized form of an incorporated, weakly basic drug, within the polymeric phases might diffuse freely across the matrix upon reaching a specific binding site and lead to a substantial difference in the drug release profile; the imprinted polymers showed a twofold increase in the template release time compared with the control (recognitive polymeric network released 100% of template over 24 h compared with only 10 h for the control)[65]. This work also established that the imprinted sites had a high cross-selectivity towards diphenhydramine and dextromethorphan (which distinguish from tramadol by as little as one lost OH group) a behavior frequently observed for conventional imprinted polymers.

But it is possible to produce the target-specific cavities for a broad range of delivery compounds by carefully selecting chiral selector with polymerizable functional groups with enhance chiral recognition capacity by incorporating into porous functionalized bulk polymers by imprinting technique. Creating this sort of approach will require careful skill and integrating, particularly around the margins where it interfaces with the 'real' world.

c) Steric or size constraints

The polymer imprinting for large molecular weight templates can be overcome by making an imprint using a multiple monomer approach in comparison to the use of the single functional monomer process. This method derives from the polymerization of a highly cross-linked macromolecular matrix that can house species with large structures. This strategy has been developed with features and transport characteristics for producing imprinted polymers with large molecular sized templates[59]. This strategy has been attacked using a diversity of functional monomers that can match the template molecule, for example hyaluronic acid (M.W.~1.2 million) that needs to be released at the therapeutic level of 6 μg h^{-1} for 24 h. This is even higher than the capacity of the system prepared with the single functional monomers. Large template imprinting polymers consisting of ACM, NVP and DEAEMA offer possibilities for both proton donors (NH) and acceptors (CO) moieties and readily undergo hydrogen bonding with the template as functional monomers and nelfilcon A combined with a copolymerized DEAEMA, exhibit a rate of release of the total amount of a therapeutic level of hyaluronic acid at 6 μg/h over 24 hours. The ACM-*co*-NVP is available for a high possibility of multiple H-bond interaction centers within the material and thus allows

for an efficient delay in the release of the template molecule. This can also provide the necessary delay for template release in an aqueous solvent. The enhancement of therapeutic loading and delay of transport via molecular imprinting has been reported and has opened the door for a sustained release dosage form for molecules with large structures.

These three research studies as abovementioned are promising for use delivery of ocular therapeutics at a constant rate over an extended period of time. The binding kinetics and mass transfer kinetic of this MIP system can be enhanced, which causes by mass transfer is slow and adsorption capacities is low as templates inherently are trapped within the crosslinked polymer matrix. Even if the macromolecular architecture suit well with such a template species, one may need to crosslinking polymerization results higher cross-link containing an effective imprint and some sort of adding proper rigidity of the polymer network to adjust adequate specificity. Revert focus on the design of crosslinking monomers for molecular imprinting, can, however, lead to a novel strategy relies on crosslinked polymers to optimize performance of MIPs, using crosslinking monomer derived from amino acids, that simultaneously serves as the functional monomers that provides the feasibility in an enhanced improve polymer property.

d) Epitope or moiety imprinting

Tools for creating recognition for an entire drug molecule by forming a template in a synthetic polymer network have been widely developed. Strategies that aim to use a controlled dosage system by its release after recognizing just a small part of the drug, such as a simple epitope, can have many advantages over the need to recognize the structure of the whole drug such as the speed of delivery is significantly enhanced. Recognising the whole drug will involve many interactions of surface chemistry between the template and the binding polymer and this will increase the time and costs for recognition of the whole molecule for either proper binding or release. Proof-of-this principle was given for the imprint of a D-glucose for the subsequent recognition of a large molecule *i.e.* 2-(*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino)-2-deoxy-glucose (or 2-NBDG) that does contain a glucose moiety[60]. The nonimprinted hydrogel control exhibited a longer release time for 2-NBDG compared to the imprinted polymers which is often in contrast with what is seen with MIPs. The feasibility for using this approach is dictated by polymer surface chemistry, and the interaction between the template and functional groups of the monomer or binding polymer chain. This site reactivity can also be modified by using tighter networks, increasing the amount of polymer used or using shorter cross-linkers all able to increase the affinity, capacity, and release times.

e) LCP method

Strategic designs for specific-molecular imprint systems have been developed that rely on living control polymerization (LCP)[38,57]. The first report of a living polymerization in the field appeared in 2006. This promised to facilitate greatly classical chemical engineering procedures. Exploiting LCP methods with reversible termination that can exert their influence by increasing the potential for the growing polymer network and by resulting in the template binding complexes ability to reach a global energy minimum. The unique advantage of this system is that the growing polymer chains would have more time during the reaction to move to the lowest energy conformation. The result provides for a remarkable success for enhanced loading and for a delay of a drug template within polymeric networks. In one example, used systems that minimized reaction energy within cross-linked networks of poly(DEAEM-*co*-HEMA-*co*-PEG200DMA) gels imprinted with diclofenac sodium and a poly(MAA-*co*-EGDMA) gel imprinted with ethyl adenine-9-acetate[79]. These recognitive gels displayed a twofold extended template release profile over that of an imprinted gel prepared with conventional free-radical polymerization, to indicate their promise for the development of molecularly imprinted hydrogels which had low heterogeneous binding sites compare to the conventional method.

3. Sustained-release MIP drug delivery systems:

Much of the research to date has directed mainly toward the delayed release *via* interactions between the MIP-type affinity materials and the drug template bearing a wide variety of functionalities. Most of this research has made use of *in vitro* measurements for the formulation of delivery characteristics. The vast majority of results have been found that the ability to control the rate of template release from the imprinted microspheres was mainly due to the appropriate quantitative recognition sites of the synthetic polymer, and to manipulation of the cross-linking polymeric network. Recently, it was found that the delivery of a pharmaceutically active substance using the molecularly imprinted microspheres as base excipients occurred in a sustained, controlled manner. MAA cross-linked poly(EGDMA) matrices are the most common building materials in a MIP-mediated recognition phenomena have attracted strong interest from the scientific researchers. A versatile monomer MAA is fabulous, of course, to serve as the recognition elements, although individual interactions of such monomers with a given template are generally weak. It makes use of monomers not by keeping a myriad of dependent functionalities positioned properly, but rather by using a large excess of functional monomer to favor template and functional complex and enriching pre-polymerized conditions to feature status. Sole and colleagues synthesized MIP microspheres in the presence of a nicotinamide template under polymerization condition of an MAA-co-EGDMA-crosslink polymer. However the rebinding characteristics of the template to the resultant MIP microspheres, determined by the solvent in which they were prepared, showed marked differences in their release profiles; a sustained delivery depended on the template-to-monomer ratio, using a pH 7.2 solution[68].

However, these imprinted microspheres prepared with the higher ratio of template to monomer (1:6), from 2.58 mmol MAA and 7.74 mmol EGDMA, exhibited the greatest ability to control the release as it was sustained for 8 h longer from the imprinted compared to the control polymer[68].

Template binding onto MIP swelling, could be detected even macroscopically e.g. a strong shrinking due to binding of template to imprinted material. Furthermore, template binding in integration of microporous MIP membrane within thin-layer coating results specific adsorption of the template and subsequent release and can lead to molecular recognition of the selective site on MIP membrane by sieving process. Studies with different coating barriers of MIP beads via a high-swelling formulation have also shown the change in template diffusive permeability, and selectivity to the template during course of the application, which is probably, this effect was induced by the change in the polymer morphology due to specific binding with their templates. During imprinting process, channels can be generated by template molecules increasing the fraction of micropores in the polymer while also producing structures, complementary to that of the template, and the interconnected pores should be observed, as one of evidences was seen in the finding in the molecularly imprinted poly(MAA-co-EGDMA)[69]. A most remarkable template specificity could be observed with thin-film composite membranes (or matrixes) an effect of template binding onto substance transport was detected directly. Imprint in general represents cavities that can bind template molecules with a high recognition ability regardless to the number and nature of the functional groups, located in these cavities. Imprinted channels can recognize template also, but they have an additional function. They can act as template-specific binding sites on the large pore surfaces. Cascades build up from such selective pores in sequence could serve as means for improving selectivity. Permeants with different structure will possess different diffusion paths and this phenomenon can be responsible for molecular recognition.

Furthermore diverse fabrication techniques have created MIPs where the affinity was typically involved with specific chemical structures designed to interact with the template molecule by non-covalent chemistry could render them suitable as a tailored molecular-specific delivery system for the sustained release and selective targeted delivery of drug of interest.

The study of the pharmacodynamics of a pharmaceutically active substance in relation to its pharmacokinetics can be used to achieve improvements of medicinal therapy. An ideal drug would rapidly bind to their sites of action in an adequate quantity, be eradicated from other systemic sites, and be eliminated from the target site after a proper exposure; however, the ability to address the potential optimization of the affinity from imprinting molecule in the polymer allows utilization of pre-polymerized materials to enhance release performance with high selectivity that would provide transport of therapeutic concentration of the drug over an extended time period, and at concentrations within the therapeutic range. Imprinted polymeric hydrogels might also reduce the need for repetitive dosing and there are a number of other benefits including time and cost savings. As example of ocular therapy required a highly efficient delayed drug release and therapeutic payload from the imprinted contact lenses, because only by enhancing the bioavailability of the drug by increasing the retention time on the cornea would limit the loss and minimize the need for repeated administration. Imprinted hydrogel contact lenses were prepared from a polyMAA-co-*N,N*-diethylacrylamide and EGDMA as cross-linker with a model drug, and the anti-glaucoma timolol as the template molecule(at 1:4 template/monomer ratio)[70]. The imprinted hydrogel film displayed a three-fold increase of up to 180 min, in the sustained release time for timolol in the tear fluid in the rabbit with an ocular bioavailability with the AUC (area under concentration-time curves) being considerably higher compared to the controls[70].

One of the easiest ways to replicate the above strategy is to vary the ratios of the functional monomers and template, the loading and release of a target drug in the therapeutic range was achieved. This renders feasible to use it in pH-adjusting system, as the optimal formulation of the imprinted hydrogels. Such MIP system displayed a threefold increase in the sustained release of timolol in rabbit tear fluid for up to 3 h[71]. The imprinted gels produced an area under the timolol concentration-time curve (AUC) that was 3.3- and 8.7-fold greater for the imprinted contact lenses compared to the non-imprinted systems. This was far better than previously achieved using conventional contact lenses and eyedrops The imprinted gels consisted of the copolymer from *N*,*N*-dimethacrylamide and *tris*(trimethylsiloxy)silylpropyl methacrylate as the backbone monomer and functional monomer MAA (100-400 mmol) and EGDMA (150-600 mmol) as the cross-linker, and timolol as the template with various ratios of template to monomer (1:4 to 1:32). The authors demonstrated a significant improvement over those previously reported, and suggested that the monomer-template interaction and cross-linker content were the predominant important parameters that determined the imprinting effect and controlled a constant release of the incorporated timolol[70-72]. In another study, an MIP hydrogel consisting of *N*,*N*-diethylacrylamide (DEAA) and MAA to serve as the agent that readily bound the anti-histamine ketotifen fumarate, normally used for treating patients with seasonal allergic rhinoconjunctivitis, as the print molecule, and EGDMA as a cross-linker to reduce the diffusion of the drug from within the gel. If this imprinted hydrogel networks acted as a sustained-release delivery system, it should be possible to prolong the duration of delivery while maintaining an efficacious drug concentration. The delivery vectors were based on 2-

hydroxyethylmethacrylate (HEMA) as the cross-linker and PEG(200) dimethacrylate as the polymer backbone and acrylic acid (AA) or acrylamide (Aam) or *N*-vinyl-2-pyrrolidone (NVP) either as a single or a mixture of functional monomers. The optimized imprinted gels were shown to bind selectively to the antihistamine ketotifen fumarate with a higher affinity and an extension of the retention time within the synthesized gels. The best affinity towards ketotifen fumarate was more than 5-fold higher than that obtained by the non-imprinted polymer and a threefold enhancement of loading capacity compared to the imprinted gels that contained two or three functional monomers. A selective gel synthesized from the HEMA copolymers demonstrated a tailored binding site, whereby a study of the binding site parameters indicated that it was suitable for the controlled delivery of the template from within the resultant synthesized polymer [61,62]. The delivery system consisting of a 2-hydroxyethylmethacrylate (HEMA) cross-link network composed of PEG(200) dimethacrylate as the polymer backbone and acrylic acid (AA), acrylamide (Aam) and *N*-vinyl-2-pyrrolidone (NVP) as functional monomers. Proof of these principles have also been demonstrated in designing a microfluidic device that simulates ocular conditions so as to evaluate the release characteristics of the same systems as described above and for an experimental evaluation that demonstrated a release with zero-order kinetics (or concentration independent release) from these hydrogels[59]. Despite preliminary proof-of-estimation results from their studies, the authors still report considerable improvements in which the capacity of the recognitive hydrogel increased by about 2-8 times when compared to the control gel. The imprinted contact lenses can be readily given a therapeutically relevant concentration of the antihistamine, or provide at a constant rate for an extended period of five days. Overall, the drug distribution thus rely on the drug release from the imprinted cross-linked gels, which has an ability to retain drugs at the site of action and minimize their content to fall into the trap of emphasizing materials.

4. Stimuli-responsive MIP drug delivery systems:

Current research has recently made progress in the design of stimuli-responsive imprinted polymers can be achieved through the incorporation of a stimulus-responsive material that changes state on exposure to the targeted environment[46,52]. Stimuli sensitive MIPs have been shown to induce a rapid and simultaneous response or be triggered by one or more of a number of physiological parameters (such as pH, temperature, ionic strength, or an applied magnetic field or exposure to a specific wavelength of light). Many potential applications of stimuli-responsive MIPs have provided much interest where physiological triggers can be explored for induction of a change that will provide a selective delivery. This could be a major stimulant for producing a responsive DDS or smart delivery devices that as a result of a pronounced volume change results in a transition of the drug into an aqueous solution. Stimuli-responsive MIP-based DDSs are comprised of a responsive-imprinted component, in particular, those with an ability to release the template after responding to the external environmental stimulus. This can in turn be used to achieve a controlled drug release appropriate for the local and system pharmacokinetics to produce the desired therapeutic level at a specific site. This method has greatly increased attention for targeted drug delivery using imprinting technology, but is particularly useful, for in addition to the chemical modifications and other delivery strategies, it provides the regulated control or closed-loop delivery of drugs the greatest challenge for MIP-based DDSs in future. An established MIP can be combined, however, to use with the sensitive components provide innovations for ensuring the system responds more rapidly to an external temperature change. An energetic advantage of this approach is to comply the entire items, consider giving them all a uniform treatment and synchronized monomeric network as well as with the added advantage of additive to tie the counterparts together, for example, the adding of a functional monomer (e.g. MAA, acrylic acid) in to pre-polymerization mixture or a self-assembly polymerization shape secondary binding sites around the template-monomer complexes as well as the use of long distance of molecular spacer linking to the functional group on individual imprint, due to an increase of large surface contact between both species. Formulating the polymeric composition of temperature responsive MIP hydrogels that the constructed materials can be used to recognizes and releases the template, when exposed to a temperature trigger such as an adjusted local hyperthermia or thermal ablation. With temperature changes, equal to that of a naturally high fever that advantageous for the targeted delivery of the anti-cancer, as such stimulating by natural immunological attacks against the tumor to release the ligand in vivo. Also in the near future, intelligently designed stimuli-activated MIP drug delivery devices will hold a great promise as an efficient alternative means for a targeted therapeutic and advanced drug delivery. This type of augment should encourage the development of dedicated a stimuli sensitive monomer or polymer system and this engineered device could effect both the function of the recognitive polymer or the rate at which valuable therapeutic is released from the synthesized materials using an aqueous solvent system. Several approaches can be utilized to generate the externally activated DDSs and the rate of drug release from thermally stimulated MIP drug delivery devices may be critical as this will determine the duration of the activity. For a given dose and a minimum effective therapeutic level, there is an optimum release rate with a maximum duration of action. A temperature dependent MIP procedure that the polymerization has often employed basically responsive-derived adding most acrylamides and additional monomers (e.g. methacrylic acid) is a vital key in a temperature-controllable mediated transition from a

binding to non-binding template, especially with one of the cross-linked *N*-substituted polyacrylamides. For example, thermo responsive dopamine-imprinted polymers containing *N*,*N'*-methylene-*bis*-acrylamide as a component in a temperature sensitive hydrogel can undergo a temperature-controlled volume phase transition near to physiological temperatures (called a lower critical solution temperature or LCST). This is an account for the thermoresponsive hydrophilic surface property usually generates thermally responsive MIP carriers. Using Scatchard equation an assessment of the binding parameters, then the adsorption data of the template on the *N*,*N'*-methylene-*bis*-acrylamide MIP, followed with the bi-Langmuir isotherm model, which in turn allowed for the determination of the non-selective and selective sites in the resultant synthetic polymer. The selective temperature dependence of the template was explained based on an assessment of the number of binding sites and the capacities of nonselective and selective sites in combination with the binding constant for the template. The main advantage of the thermoresponsive MIP within the structurally flexible material can, thus, allow for a self adaptment process to the structural features of the target analytes.

All the three main factors (the capacity of the MIP to incorporate a drug, the material used and the degree of cross-linking of the polymeric backbone chains) that have been shown to affect the drug release of thermally stimulated MIP DDSs are each dependent effects. Reliability imprinting polymer materials may experience douse to withstand external stimulus while increasing slightly higher degree of cross-linking may ensure the ability to recognize the template due to a slight reduction in the close proximity of the drug to the imprint sites. For example, polymerization of *N*-isopropylacrylamide (NIPAAm) and MAA acting as functional monomers together with EGDMA as a cross-linker in the presence of the template molecules, subsequent template removal, has been demonstrated to generate a molecular memory for molecularly imprinted poly(NIPAAm) hydrogels exhibited the facilitate uptake of a 4-aminopyridine template at an elevated temperature above its LCST at 32 °C[52]. At the higher temperature the gel was in its collapsed state for retaining the binding sites and this had an influence on the affinity and diffusion rate for 4-aminopyridine with a selective release of factor of about two. It is important to consider that as the macromolecular chains increase in size, the flexibility of the imprinted materials will also increase. Therefore, the potential role of the intermolecular interactions between the template and the individual functional monomers that arise from a few low energy conformations should be altered to consider a more realistic situation, however, are where the energy-allowed conformations come into play – the molecular recognition events. With a change of temperature the nature of the carrier surface changed the interaction of the drug with the imprinted cavities within the MIP materials. These features are due to the rapid changes in the polymer conformation that are attributed to the mobility of a cross-linked polymer having a NIPAAm-modified surface. Used thermoresponsive MIP, the structurally flexible material patterned chemical features of the drugs that may be viewed as the trigger to "turn on" and "turn off" the release of a drug as a function of the temperature.

5. Combinatorial strategies:

The need to overcome the important biological barriers limiting drug delivery has driven scientists to further expand their studies for rate-controlled drug release applications. Moreover, the design of an intelligent MIP system or smart materials with feedback controlled drug release mechanism from engineered materials may be generated to include potential synergistic outcomes to systems that might provide a more robust, intelligent characteristics including: layer assemblies; physical/chemical coatings; the potential use of thermal- or photo-induced in situ polymerization fabricate composite MIP microparticulates that provides new and innovative polymer structure for applications in novel drug delivery. Fig. 2B illustrates several categories of a DDS or carrier based on MIP immobilization techniques for targeted drug delivery application. These MIP-based targeted DDSs can also be designed to have the selectivity of the delivered drug and multifunctions by a variety of attachments onto the surface of preferably pre-functionalized carrier materials, physical fixation employing coating techniques, and direct combination into polymeric network structure via copolymerization, or combination of these procedures in a support that method associated with the engineering of suitable delivery formats, for example bead or thin-layer or membrane.

Extending the functionality of the surface onto the device by including targeting ligand, coating of a biomaterial with the biodegradability and swellable properties of the synthesized MIP products and selective release of drug in response to environmental stimuli may also be a sensible option. The various surface modifications can be designed that could be, such as: (a) covalently linking the molecular imprinted polymer to a particle or material (b) on coated membrane barrier for molecular imprinted polymer that are physically entrapped, the carrier degrades on entry into a predefined environment, thereby releasing its drug by individual MIP microparticle. (c) in situ polymerization or a facile synthesis of one step achieving via self-assembly polymerization of imprinted polymer bead matrices into a resultant synthetic membrane. Such an approach offer opportunities in improvement for the shell permeability response to various stimuli and enhanced cellular accumulation. In fabricating, the formation of a self-assembly layer should allow for adjustable controlled permeability of template and tunable accessibility to their sites[78]. Investigations on the nature and inherent structures for an imprinted polymer network within these approaches have used a diverse range of technologies based upon the MIPs

available for targeted-drug delivery purposes that depend on their versatility and handling characteristics being highly appreciable.

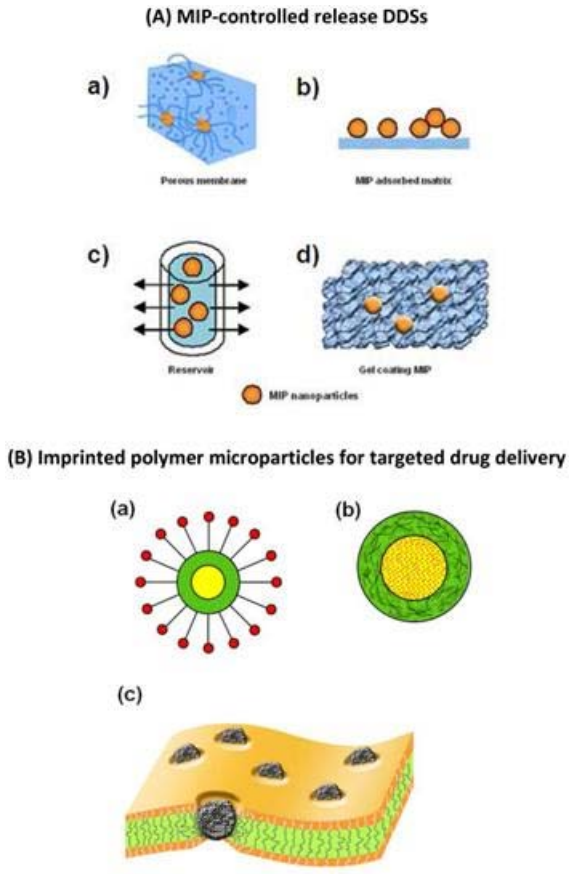
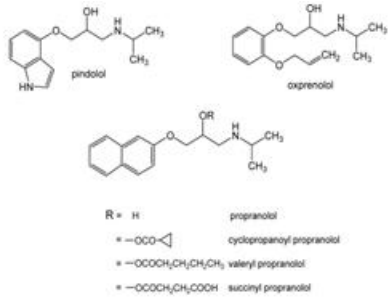


Figure 2: (A) Type of MIP controlled release DDS. (B) Schematic representation of an imprinted polymer microparticle for targeted delivery of a drug, by physically entrapping the cargo in the carrier.

A hybrid approach of in situ polymerization and imprinted polymer bead matrices is prominent in the development of MIP for controlled release system of the drug. With established imprinting technology, this strategy utilizes pre-formed MIP beads, which serve simultaneously as functional recognition elements for the templates and as supporting matrices for the binding to be formed.

The predominant method of generating polymeric recognition with a three-dimension ordered pore structure is MIP particles that were directly incorporated by a polymer or into a dosage formulation unit. In this process, the template enantiomer from the loaded racemic compounds is allowed to attach to the existing MIP bead; thereafter the void spaces and the pore system and to within these polymer layers were filled with a cast solvent of a given polymer. When the MIP is embedded in the membrane – it is important to preserve its intrinsic feature of the imprinted cavities, and engineering chemistry – can be carried off the diffusion of the solvent into the designed polymeric membrane to the location of the selective sites. The increased hydrophobicity in principle can have an effect on the solubility that is dependent on whichever one of the solvents favors the solubility product, such that the cohesive energy densities of the solvents are driven towards the cohesive energy densities of the liquid form of the respective solutes. In one example, the dipyridamole-molecularly imprinted microspheres were produced by the traditional precipitation method using a copolymerization reaction of MAA as the functional monomer and a rather high concentration of cross-linker (EGDMA - 87 mol%) and the dipyridamol template with a (1:2-1:10 template and monomer ratio) in chloroform[73]. This compound offers four OH groups, which makes it an interesting element for a selective recognition event in the polymeric networks *via* hydrogen bonding. Such a system was an effective tool for delaying the release of the basic drug, dipyridamole by modulating the electrostatic and hydrophobic interactions at a slightly acidic pH value. The MIP beads with a high template to monomer ratio (1:6) led to the largest template rebinding (9-45%) with considerable selectivity (~2.5) compared to the controls, when exposed to the same solvent that they were synthesized in at pH 6.8. The results indicated that the imprinted microspheres adsorbed and released a therapeutic agent at a slower release rate and a longer duration that was superior to a non-imprinted controlled release profile.



Compound	#C atom	#O atom	#N atom	J_{ss} (μgcm^{-2}h^{-1})		ΔJ_{ss} (μgcm^{-2}h^{-1})	
				R-form	*S*-form	*R*-form	*S*-form
Pindolol	14	2	2	3.83	4.48	-1.21	-0.43
Oxprenolol	15	3	1	16.77	19.48	6.92	9.04
Propranolol	18	2	1	0.43	0.57	0.1	0.26
Cyclopropanoyl propranolol	22	3	1	8.72	11.79	6.55	9.83
Valeryl propranolol	23	3	1	4.62	5.87	-0.24	0.70

Figure 3: Chemical structure of propranolol compounds and structure activity relationship of permeation rates of the enantiomers[78]

The well-designed fashioned pre-determined selectivity provides a possible recognition mechanism by which drugs can be undertaken their three-dimensional structures that fit into the imprinted cavities. Supported polymeric membrane or device based on MIPs could be generated by introducing them either the stand-alone MIP microstructures or linking MIP on the pore surface of a membrane support which have an affinity of the drug of interest. Fig. 3(top) shows the chemical structures of propranolol and analogs. A MAA-co-EGDMA polymer templating with (*S*)-propranolol enantiomer as a selective carrier, on a membrane[74,75] (or matrix tablet[69]) with three-dimensional pore structures was produced *via*

molecular imprinting polymerization that (*S*)-enantiomer of propranolol which is an adrenoblocking agent was used as the printed molecule. Uses and limitations of MIPs depend on their materials in the presence of charged, swollen, polymer matrix surrounding conditions that binding parameters would influence profoundly the access of substances and ions to the membranes present on the imprinted sites. Propranolol enantiomers contain a naphthyl ring and a hydroxyl group at a particular chiral center on the aminoalcohol side chain and one chiral amine nitrogen close to chiral center can be imprinted in the polymeric material and provide molecular recognition of binding to the enantiomeric drug molecule. For instance, the (*S*)-propranolol was chosen as a template, a functional group on a chiral center could interact with the functionality area on the imprint in the polymeric networks containing a COOH functional monomer. In this case the pre-polymer consisted of template-methacrylic acid-EGDMA 1:6:25 molar ratio. The methacrylic acid (MAA) functionality offers hydrogen bond interaction. The hydrogen bonding is formed while imprinting with a chiral template, followed by copolymerization with EGDMA as a crosslinker in order to maintain the alignment of the functional group. Despite the physicochemical properties of the composite MIP membranes within thin-layer: solubility, hydrophobicity, and localized charge along the polymer chains. While the thickness of the transdermal patch consisted of the porous membrane containing a MIP thin-layer onto the pore surface will not profoundly affect diffusion properties, it will however greatly increase the extent to which access of the drug molecule, to the underlying cells, or the skin, is retarded. Adsorptive losses to the matrix might occur for highly charged drug molecules as such agents would become strongly bound to the predominant reactive sites, and would have to saturate each and every available binding site by diffusion through the patch and thus act in an analogous means to an ion-exchange chromatography. In real-life conditions, however, the volume and reactive capacity of a composite membrane would be inadequate to deplete the bioavailability of the therapeutically active agent, and interfacial interactive sites within the matrix polymers would be saturated with the adsorbed drug. Given the exposure to the targeted molecule, or that the given enantiomer molecule was not in an infinite excess of requirements, then the reaction-diffusion limitation properties of the polymer matrix could allow, especially for the high-affinity enantiomer, binding at the membrane base which would then flourish. The retardation might plausibly be to such an extent that, where courses of delivery are periodic and short-lived, the deeper-lying membrane might escape exposure. A quantitative assessment and molecular understanding of the specific attributes arising from the imprinting process can be obtained comparing the diffusion coefficient of the template to the template delivery through MIPs, which results in a linear relationship. This chemical reactivity based on the imprint cavities enable to distinguish specific and non-specific binding events. As shown in Fig. 4, the filled circle along the straight lines is the permeability of the template delivery through a MIP thin-layer integrated in membrane, with open circles of the delivery through NIP control polymer membrane[75]. As in this case the overlapped open circle on the lines indicates the effect of barriers in the membrane base during the mass transport. Clearly, the polymer matrix is relevant as the macromolecular architecture constitutes a physical barrier to the drugs penetration that depends greatly upon the nature of the pharmaceutical agent, the binding capacity of the MIP towards it, the levels of the active agent required for effective therapy, together with the distribution of mass and local hydrodynamics.

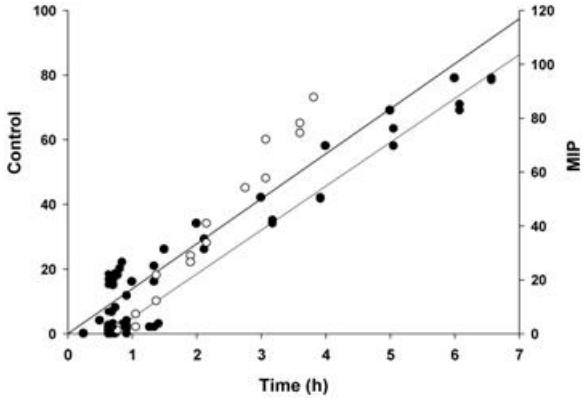


Figure 4: The effect of membrane base on the permeability of the template delivery through; close circle: a MIP thin-layer integrated in membrane, and open circle: NIP control polymer membrane[74]

If, however, the bulk concentration of the stereoisomers of the chiral pharmaceutically active agents were not reduced to low levels by adsorptive loss within the chiral membrane, then neither of these processes could account for the observation of a long-term controlled release towards one enantiomer print molecule. Either mathematical model has claimed that the diffusion of stoichiometrically reacting enantiomers through the porous membranes containing thin-layer MIP is not significantly retarded. The rate of diffusion of drug enantiomer from the donor phase across the membrane can be described by Fick's first law of diffusion:

$$\frac{dM}{dt} = -\frac{DA}{h}(c_s - c)$$

where *D* is the diffusion coefficient of the enantiomers, *dM*/*dt* is the rate of diffusion, *k* is the rate constant of dissolution, c_s is the saturation solubility of the drug in the dissolution media, *c* is the concentration of the drug at time *t*, *A* is the surface area of the drug undergoing dissolution, and *h* is the thickness of the diffusion layer. Hence the diffusion rate is dependent on the drug diffusion through the diffusion layer of thickness *h*. If the aqueous diffusion coefficient of propranolol optical isomers in water at 37 °C is 7.0×10^{-3} cm h^{-1}, then for a 5 μ-membrane thick, the time needed solely for a single (*S*)-isomer diffusion through the membrane to the excised rat

skin is around 43 min, or 140 min for (*R*)-isomer ($D = 2.1 \times 10^{-3}$ cm h^{-1}) for 300 µg/mL of racemic propranolol solution in donor phase[75]. This distinctly difference in diffusion coefficients between the two propranolol enantiomers through the MIP membrane is related to the size and lipid solubility of the drug and the viscosity of the diffusion medium as well as the cavities capable of incorporating the (*S*)-enantiomer printed molecule. As lipid solubility increases or molecular size decreases then *D* increases and thus *dM*/*dt* also increases. For surface area, if this parameter increases, the rate of diffusion also increases: the smaller the membrane thickness, the quicker the diffusion process. $C_s - C$ is the concentration difference; it is this concentration gradient which allows the rapid complete absorption of drug substance[75].

The (*S*)-propranolol imprinted polymer layers exhibit a substantially differential release of the propranolol enantiomers of the racemic template molecules within matrix across the membrane into an aqueous medium, is seen to be marked that the polarity of the environment extremely affects the chiral (molecular) recognition of the MIP. Generally speaking the adsorption of the isomers on a MIP within a polymeric matrix occurs via the imprinted site and the non-specific adsorbent, but additionally chemical surface are great of importance. Since the highly directional hydrogen bond between the carboxyl moiety of MAA and an hydroxyl and amino group of propranolol enhanced and the electrostatic interactions from ionized carboxylic group of MAA is likely driving force that seems the chiral recognition can be achieved in a pH-adjusting condition. The difference in the enantiomeric ratio for the ester prodrugs of propranolol indicates the existence of imprinted enantioselective sites with some cross-selectivity that can provide a diversity of conformational structure and stereochemical properties relative to the template isomer, rising from the maximized intermolecular physical forces at the asymmetric carbon within the polymer matrix. Consequently, the highly selective recognition of the integration of MIP system in thin-layer into the porous membrane can be attributed to the result of adjusting the side chains on the ester group to alter structure around the β-carbon, that optimal geometrical functionality of the binding sites governs chiral recognition capabilities of the imprinted cavities[75].

Changing the film barrier that consists of a lipophilic coat caused a relatively modest change in the deposition profiles of enantiomeric forms from within the matrix compared to that of a thin-film hydration. This particular formulation showed an enantiomer-specific drug delivery that can be specifically tailored for the additional control on the rate of diffusion of the specific isomeric compounds out of the polymer[76,77]. This lower level of hydration would also reduce the diffusion coefficient (by decreasing the porosity of the polymer matrix). On the other hand, the selectivity of the sites within the polymer or material could be the actual factor to control the release characteristics of an enantiomorph. In that case other formulations for excipients, vehicles and surface characteristics would be less important.

Controlled drug delivery of MIP microspheres can occur through specific interactions of synthetic MIP receptors with template molecules interacting with the binding groups on the imprinted cavities in the polymers, polymer matrices or drug formulations, and the total mass transfer characteristics of the MIP-based DDSs were dominated by surface diffusion. Overall, simultaneous template binding and thermodynamic mass transfer occurred at the same time with heterogeneous binding kinetic at the binding sites on the MIP surface. It was evident that the observed concentration dependence of the surface diffusion and inversely selectivity for binding template in polymeric matrix[74]. Furthermore, the combining a high yield of MIP sites with a pore structure needed to be well suit for efficient membrane separation. A certain amount of redistribution of drug between different binding sites occurs as whatever method of drug incorporation and components in the presence of other excipients or a polymer or material. Fig. 5 summarizes the formulations with coated barrier or incorporation of excipients with MIP microspheres, formulations containing drug loaded MIP microspheres and other excipients produce greater diffusion coefficients than those non-MIP microspheres with coated barrier. The carrier threshold concentration that can affect the transport rate, to a molecular recognition interaction created inside the polymer matrix, and the phenomenon of the solvent movement inside the polymer chains towards the carrier molecules by rebinding the template to adjacent imprint sites. On the other hand, the rate of release of the stereoisomer drugs through this MIP beads within the casted membrane can be conveniently tuned by changing the amount of the particles in the resultant polymer membrane, with an increasing polymer content giving rise to the facilitated release and enhanced diffusional permeation when the template molecule binds to the memory site.

The concept for the production of systems with stereoselective release derives from the ability for interaction of the MIP with chiral binding groups of the templates. Most of the investigations of such MIPs have been shown to enhance binding and achieve selective delivery of the specific molecule in any carrier system dependent on the effective means of chemical surface properties since pre-organized processes occur between the assembled template and functional group of the imprints. In essence, the recognition cavities in a cross-linked matrix will become critical to their performance as it dictates that preferential complexation and release of bound can occur. A possible extension of the system would be to design a surface that supports a cascade reaction mediated by immobilized molecular imprinting polymer used as self-regulated DDS. In such cases, they could be used to determine the site of delivery of the incorporated drug-MIP matrix before a regulated release effect is obtained. In contrast to MIP microspheres the thin-film composites grafting or incorporation of

polymeric structure in a controlled manner, may be anticipated to provide a greater penetration of the template into the monomeric phase and show a greater benefit by accessibility of larger target molecules or particularly is required for specific surface recognition onto the cell membrane as would be the case when targeting of drug-carrying MIP microparticles. Nevertheless, an inherent problem associated with graft-polymerization onto pre-functionalized pore surfaces is the difficulty in generating a homogeneous polymer growth from the surface in the confining pores, which needs to be addressed.

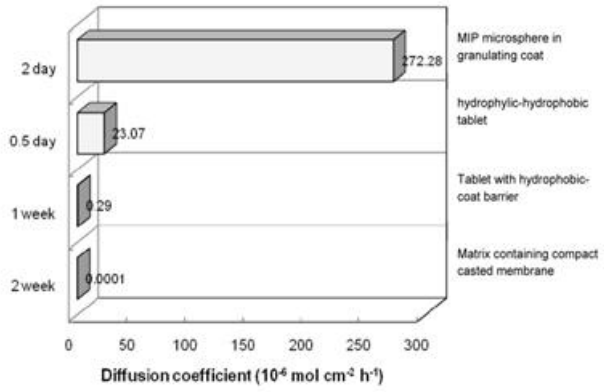


Figure 5: The effect of (*S*)-propranolol MIP microparticles in various polymeric matrices on release rate of the template enantiomer: the improved template diffusion coefficients between the MIP systems due to the inherent and different features of the surface and could provide a means of imprinting surfaces to create stereospecific binding cavities upon templating[67,74,77].

Chiral recognition by molecular imprinted polymers using multiple and complementary interactions including the use of stronger hydrogen bond donors and acceptors, or the use of stereoselective or non-stereoselective ionic interactions directed recognition sites with hydrophobic domains, and that in so doing provide the necessary three-point stereospecific interactions required to effect separation. The negatively charged anionic analytes and this kind of positively charged chiral functional monomer, at this point, non-stereoselective ionic interaction is significantly accompanied by additional template-monomer intermolecular interactions like the aromatic entities of the template. The steric effects of two chiral centers could be used to adjust the streochemical recognition by imprinted polymers has been shown[76]. In addition to steric considerations, the distance of a molecule's discriminating features from the binding group interaction with the polymer becomes an important factor. The conformational entropy of both the substrate and the polymeric receptor is important consideration, that for MIPs there are, however, different sources of conformational entropy, which is primarily determined by the amount of cross-linking; a second source of conformational entropy is from the functional monomer and; the conformation of the substrate molecule on rebinding to the polymer.

A great deal is known about the structure of enantioselectively MIP binding site obtained from a polymerizable functional monomer containing a chiral center around a chiral template, then copolymerize with crosslinker to form cross-linked network polymer, but the precise method by which two enantiomeric forms of a chiral drug are resolved and the controlled release of only one is already proven. For example, imprinting using methacryloyl cinchona alkaloid-type functional monomers, that requires the preassembly arrangement of the isomeric print molecule with methacryloyl quinine (MQN) or the methacryloyl quinidine (MQD) congeners involved in chiral recognition[77]. Forming such imprinted cavities possess a chiral molecular memory of the (*S*)-omeprazole-imprinted methacryloyl quinine-EGDMA polymer that provide an enantioselective resolution towards the isomeric print molecule of a racemic drug, taking advantage of multiple point interactions of the template and the anchored monomer (e.g. hydrogen bond, hydrophobic and *pi-pi* interactions). The enantiomeric recognition of this system lies in the fact that a stereochemically imprinted polymer with isomer specificity is generated by constraints imposed from the networks to polymerize around the drug and the monomer complex and was supported by additional sites generated by the surrounding polymeric matrix, and thereby providing discrimination of enantiomers of pharmaceutical compounds.

Control of the stability and permeability in biological membranes is essential to allow for the proper functioning of biomolecules. The selective and controlled permeability of a cell membrane, which connects the inside of a cell to the outside, represents a key factor in the proper operation of a sensing and signaling pathway. The introduction of different biomolecules during assembly polymerization generates very sensitive biological receptors having tunable selectivity. The use of chiral imprinted polymers that could facilitate the transport process through membranes has demonstrated the potential to control the molecular diffusion in trans-membrane transfer with an enhanced selectivity and stereospecificity. It is interesting to note that the enantioselective binding sites on the imprinted cavity in the polymeric matrix are activated in the presence of the self-assembly component from the synthetic polymers, which proves that the copolymer is a helpful building block for the mass transfer of the delivered molecule[78]. Porous MIP membranes have been tested as a target-specific release system to ensure that the imprints will fulfill for recognition aspects and be the most favorable for delivery of the target molecule. Fig. 6 illustrates the manipulation of investigating of drug delivery using a composite membrane and MIP nanostructures prepared with recognition for (*S*)-enantiomer selectivity for enantiomer transport experiments. It is possible to be shown that selective materials demonstrates selectivity and stereoselective transport of chiral drug of interest, showing the increased permeation of (*S*)-enantiomer printed molecule rather than the non-printed (*R*)-

enantiomer when change the concentrations of loaded racemate in the presence or absence of dispersed MIP particles in the donor solution, compared to reference material and the blank membrane.

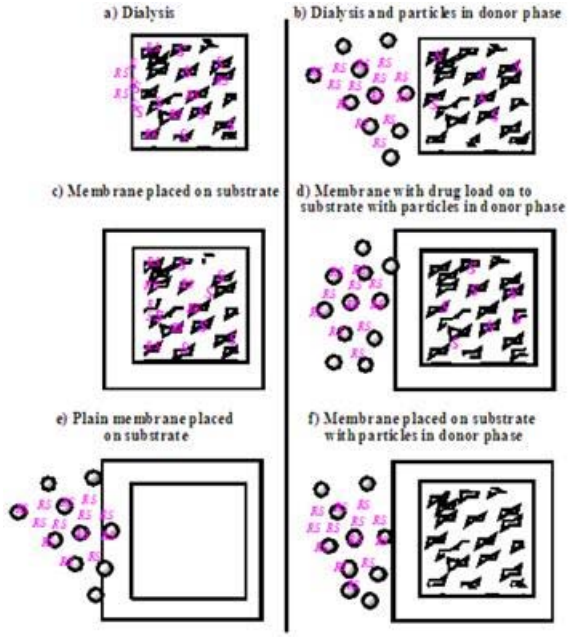


Figure 6: Illustration of the investigations of drug enantiomer transport and delivery by dialysis method using a composite membrane consisted of MIPs that demonstrates selectivity and stereoselective transport of chiral drug of interest, showing the increased permeation of (*S*)-enantiomer printed molecule rather than the non-printed (*R*)-enantiomer.

A special format produced surface rearrangement and the hierarchically nanostructured polymer entirely attached on ensemble spherical polymer microparticles with porous structures in which the copolymer is placed mainly at the cavity interface[77]. Such MIP system possessed microphase separation nanometer-sized cavities entirely covered with nanostructured polymer beads during polymerization process and the phase inversion between MIP and a polymer solution dose not only yields deposition of MIP particles onto the membrane surface but also takes place inside the casted membrane. The latter process can be considered as a filling step resulting in an inter-penetration network, i.e. the formed functional MIP is entrapped and entangled in the precoated polymer membrane to produce a high surface area adsorbent. Fig. 7a depicts the effect of drug:polymer ratio on and the template permeabilities of the imprinted surfaces were observed of the (*S*)-propranolol-MIP for the nanoparticles surfaces onto the surrounded microsphere-containing a cast membrane, indeed in this case almost constant, with a drug to polymer ratio of 1:5. In the same drug:polymer ratio range, *S/R* enantiomer ratio binding of propranolol enantiomers showed also an almost plateau. As shown in Fig. 7b, increasing the amount of mesoporous MIP bead with nanostructures in the membrane base, permeability and binding capacity are almost not affected during the filling stage of the functionalization until the capacity of initial deposition is exceeded (note that the observed chiral selectivity is a function of transmembrane flux.

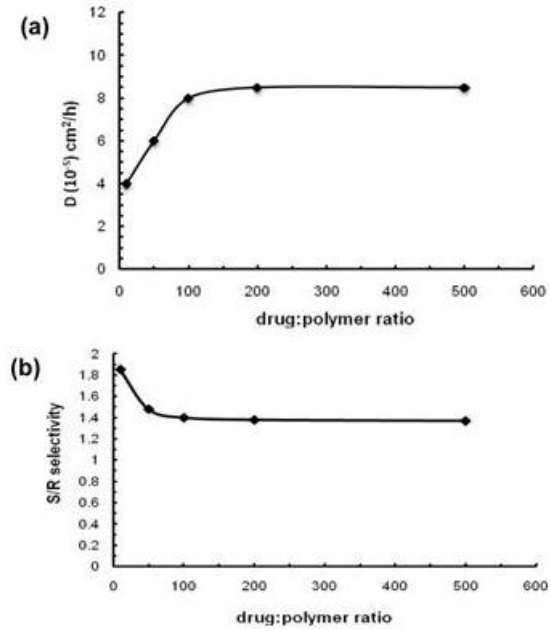


Figure 7: The effect of polymer amount of MIP microbeads containing surface binding site upon in situ polymerization on: (a) the diffusion coefficient of drug enantiomer, and (b) selectivity[77].

Like surface confined binding site in silica chemistry, mesoporous MIP beads containing surface confined binding site mold, polymerization mold the chemical transformation from the bound chiral template in the well-defined nanosized environment of the target-specific imprinted cavities can be used to create their image in the pore wall providing a functionalized MIP into composite membrane. The supported membranes have been produced by the use of target-specific cavities for the chiral-selective gate effect that provide selective membranes with self-controlled permeability when the target analyte is bound[77,78]. In the particular case of enantioselectively molecularly imprinted sites immobilized on a hydrophilic-hydrophobic polymer layer formed by self-assembled polymerization together with loaded racemic drug, the molecular recognition efficiency of the imprinted polymers was maintained under aqueous conditions. The increased selectivity of this synthetic polymer membrane was achieved by the enforcement of the polymers to form multipoint interactions in the matrix, that serves to keep the complex in a stable conformation and protects it from attack by a harsh condition. Because the strongly charged or highly reactive therapeutic agents are, then their diffusion will be restricted either by adsorption to matrix-associated charged iterations or by direct neutralization reactions, the selectivity and their diffusion of enantiomer templates are usually rather low[77]. This phenomenon turns out, however, the feasibility of transmembrane pores offer opportunities to the study membrane organization, dynamics and functioning membrane-

spanning channels. The advantages of nanopores based on surface-imprinting approach which is the fact that, they are easier to manipulate, while retaining the ability to transport small molecules. Using MIPs as recognition materials offer a simple model for studying formation of molecular recognition with respect to their interactions and stabilization of the pore in a synthetic environment, such as polymer membrane.

For the application of the MIP for efficient separations *via* "smart membranes" that the use of presynthesized MIP immobilization surface for composite membranes, either *via* creating filter beds from nanoparticles or *via* entrapment or other immobilization of nanoparticles or microgels in filter structures can be achieved[69,78]. In such purposes, biomolecules can combine with a membrane-forming polymer to form biomolecule–polymer hybrid materials. Immobilization of biomolecules can be achieved by attachment at the surface of the polymer, by insertion within the membrane, or by a combination of attachment and insertion procedures, allowing for the wide applications. In order to achieve the performance goals, further improvements of the preparation of composite MIP membrane, or thin layer will be most effective approach. Owing to the higher spatial order of functional groups in the imprinted sites on the accessible surface, MIP membrane – will per se have high capacities. The attractive feature of molecular imprinting is that it is a straightforward method with sufficient ruggedness to generate robust and highly selective systems possessing synergistic effects. Progress in this field should provide the more suitable polymer systems or available materials have created an increase in the significant number of existing highly target-specific cavities or producing an imprinted material for recognition sites. Thus the development of MIP nanoparticles assists other synergistic combinations with separation membranes that offer the feasibility for effective separations can be achieved and also render for use as materials for a broad range of chiral recognition applications. This approach has interesting implications for targeted drug delivery, as it is a possible way to shape a flexible functionality in a minor abundant conformation adaptability at which has the direct product of enantioselective receptors through native interactions of chiral print molecules that are complementary to the imprinting mixture. Consequently, the active domains on the protein template are conformationally oriented outward. Also, the Coulombic interactions between the template molecule and surface critically distort the imprinted surface structure, so that it is possible to make them maximally effective in triggering a biospecific bioreaction. These aspects represent the challenges and opportunities of targeted delivery systems. The development of smart material, in a polymeric membrane has still not been investigated – although it has been shown, for example, that a pH-stimuli-responsive DDS may be implemented in an imprinted polymer-based DDS[77]. This possibility of pH-stimuli-responsive enantioselective-controlled release based on MIPs leads to the assumption that by using an engineered polymer, the applicability of such a system can be expanded to therapeutics.

Numerous examples of MIPs used for the selective delivery of a particular enantiomeric molecule have demonstrated the benefits for newer formulations of chiral drugs. This attempt includes the approaches of formulating controlled-release drug delivery devices by dispersing a spherical MIP bead in an underlying carrier membrane, or by producing a hydrogel support with spherical MIP beads as the sacrificial template, or the use of support nanoparticles (usually derivatized with a polymerizable group on the surface). The inherent stereoselectivity of a controlled delivery system can be influenced by the features of the formulations and types of devices for the purpose of specifically synthesizing to coverage on the template molecule in a reciprocal form, which ideally should be an appropriate polymer or material in terms of its compatibility and the components of the synthesized MIP product do not disturb the essential non-covalent template-monomer interaction that are crucial for the imprinting effect. Given the mechanisms that govern the transport in relation to the membrane structure the polymer will not only bind the matrix, but will also form compartments of diffusion hydrophobicity and diffusivity throughout. Such interactions must be considered in terms of partitioning and restriction of the diffusion of the drug species.

Starting from a single-template approach then changing to a polymeric structure with high recognition selectivity is decorated by a multiple-template approach. There are a number of processes have developed for imprinting the polymer with two or more templates[40]. A number of investigations over recent years have been performed with mixed templates to create molecular imprinting in synthesized polymers. The MIP materials with 2 or more templates offer opportunities for their potential role in controlled drug-release devices and some have succeeded in producing a multiple drug delivery system that also offers distinct advantages for agents which are required for their sequential release. A modify the ionic interactions or to change the pH for each of the templates on their imprinted sites this results in a selective transport of the multiple drugs in aqueous solution, dependent on the composition of the dissolution medium[48]. It was plausible to utilize the saturation capacities of the selective sites to create a multi-drug delivery formulation. Furthermore, the different templates used could complicate polymer morphologies by inducing changes in the porosity and swelling characteristics of imprinted recognitive networks and restricting the template diffusion that occurred from the multiple-recognition MIP to the external environment. However, this approach inevitably led to customized polymeric devices with multiple recognition profiles that may offer interesting opportunities for the multiple simultaneous release of multi-drug formulations.

Equally important to the development of modern pharmaceutics has been the ability of pharmaceutical

scientists to optimize controlled dosage system. Rationally tailored designs for MIPs have enabled the generating of promising drug-carrying vehicles as such they have a timing of the release of a therapeutic agent. Although, the imprinted cavities of the polymer material employed in intelligently controlled DDSs should have eminent advantages of producing shape specific cavities for templates. This is made-up by applicable rational approach of MIP selections, which evokes the formation of target-specific distinct recognition sites due to multiple stabilizing, concerted, well-defined interactions of supramolecular chemistry in the highly cross-linked networks. Also, the imprinted cavities of a MIP system, has greater possibilities for tuning cross-linker systems when applied to a multi monomer system and that give rise to an increased number of active sites, while retaining selectivity[78]. The methacrylic acid polymers together with the weak interactions of monomers are expected to produce an increased number of interactions for a stable binding. One example investigated, was glycyrrhizic acid-imprinted polymers. These have demonstrated good recognition and selectivity of release of the template due to an increase of the potential of forming non-covalent sites in the polymeric networks[61]. It is worthwhile to take into account to that the functionality of methacrylic acid (MAA) combined with 2-(dimethylamino)ethyl methacrylate (DMAEMA) and 2-hydroxyethylmethacrylate (HEMA) functional monomers with polymeric cross-linked EGDMA can ensure the formation of the hydrogen bond interactions with the glycyrrhizic acid template and render to a tailored release of the drug in a microenvironment that mimics physiological conditions. The resultant imprinted particles exhibited good recognition and selectivity for template release in both ethanol and ethanol-water solutions.

METHODS OF RELEASE

Achieving releases for conventional controlled delivery systems that usually rely on a passive release can be influenced by a change in temperature or pressure resulting in either a rupture or eventual triggered release. Strategies to optimize the three-dimensional network chains in order to recognize a drug molecule using molecular imprinting approach and then substantially effect release of the drug would also be very attractive. The rate at which a recognitive network swells and releases its payload is dependent upon two coupled parameters, the rates of polymeric chain relaxation and solvent penetration into the network. This has to include a radically changed release rate profile of preferred enantiomer and the other that will also depend on the method of synthesis for a given MIP. Especially if the ratio of the number of binding sites to the molecular mass is highly favorable. Interactions with the particles and the non-selective sites at the macromolecular chains can result in the release of a drug template. Eventually, the result is a carefully balanced polymer feature yielding respective release patterns towards favorable chemical functionalities on the chiral cavities within the imprinted polymers. Second, very slight changes in solvent fronts to the polymer material have influenced the selectivity of MIPs. Thus the favorable binding affinity parameter and excellent selectivity of recognition the details of the mode of release within the carriers are important because the partitioning of active ingredient is dependent of non-specific interactions in the bulk materials. Imprinted DDSs have not reached clinical application yet, but this technology has an enormous potential for creating satisfactory device and efficient DDSs. Despite control of the established approaches for the manufactures of MIP materials having achieved high levels, some technical problems and challenges to make them more efficient remain.

Providing approach has been predominant to fabricate the imprinted gel particles containing a hydrophilic biodegradable polymer such as PEG and the attachment of the imprinted particles with thin coatings of imprinted films (*via* adsorb or graft a hydrophilic polymeric coating)[79-82]. An example of exploiting this approach involves the incorporation of a hydrophilic biodegradable polymer such as PEG to a self-assembled framework with the arrangement of functionality within the polymeric networks that help stabilize the binding cavity on the PEG-based recognition material leading site-specific compartments with an improved biocompatibility and lower immunogenicity. In general, the mechanical strength of the cross-linked polymeric networks is important to PEG-based MIP hydrogels have been developed in which *in vitro* release studies have shown success for imprinting biogenic species such as glucose in a multifunctional cross-linked system that consisted of MAA and poly(HEMA) containing PEG(600)DMA and tetraethylene glycol dimethacrylate (50%, TEGDMA) as a cross-linking agent[83].

In addition, drug diffusion in an imprinted recognition release system can be regulated by swelling controlled systems or stimuli sensitive MIPs. The molecular recognition environment could play a key role in the tailored release of a drug from an imprinted network structure leading to possible differences between intelligent vehicles for drug delivery. Sensitive MIP gel systems have been shown to induce a rapid and simultaneous response or be triggered by one or more of a number of physiological parameters that provides the potential for targeting and a controlled release of a drug or bioactive molecules including peptides, proteins and oligonucleotides in either reservoir-based, controlled release-systems or carriers[74,84]. This can apply many external triggers including temperature, pH, light, electric field, biological binding and unbinding events (e.g. antigen-antibody) to mainly an induced change of a volume change and release of the drug, or will be released in competitive binding response to free of the drug.

The applicability of strategies/designs of MIP based DDSs is contributed greatly by an enhanced understanding of the underlying basic principles relevant to the field. The

preferred enantiomer preferentially bind to the areas on surface of MIP particles the strongest binding increase surface the drug liberated from MIP microparticles, increasing the incorporation of drug available onto the epithelial cell layers. The rationale for designing the binding agents in a dosage formulation which enable stereoselective and selective transport of racemic β-blocking agents, such as propranolol in this way depends on two considerations:

(i) The therapeutic effect of its administration arises from an increase in the plasma concentration in body compartments and

(ii) Such increase is fostered by the (*S*)-enantiomer found in plasma that can diffuse into fluid from racemic propranolol in vehicle through MIPs in polymeric matrix.

On the basis of *in vitro* strict isomorphous replacement, thermodynamically and kinetically differences of species which appear to be feasible excludes from binding in endogenous receptors or metabolic enzymes. The whole process of imbibing an element, or energy-rich compound, of it traversing composite membranes, of its concentration being buffered at each stage and of it being excreted involves in many complexing reactions. On the other hand, dermal route of administration has the advantage. Such a strategy represents an alternative means of transdermal drug delivery for analogues and prodrugs of the β-blocker propranolol when a highly metabolized drug such as propranolol is protected from first-pass elimination. Thus if the eutomer of β-blocker agents and prodrugs are to be selectively transported across the skin a better therapeutic response might be expected relative to that obtained using a racemic mixture of the drug.

A passive approach to using of MIPs that combines a membrane-forming polymer to bio-polymer hybrid-materials integrates biomaterials that are prime candidate for the creation of different DDSs. The design process comprises engineering the architectural design of the use of a composite membrane. Some of the different techniques are the utilization of an immobilization of an imprinted polymer with the addition of the optimized carrier content and polymer that can be used as a means for tuning of different polymer properties including membrane thickness, polarity, toxicity and functions. While the development of delivery device by the utilization of biomaterial to increase drug partitioning is an overriding requirement to delivery of drugs in vitro and in vivo. Such alternative approaches, that will allow for a favorable diffusion rate of specific drug with a much better enhanced active imprint sites but it also provides a certain level of predictability concerning the chiral resolution with a significant difference in permeation rates by varying the structures[78]. In chiral membrane-diffusion experiments performed with chiral drugs an enhanced diffusion through the composite MIP membrane consisted of microparticles with MIP nanostructure surface. The MIP beads containing of (*S*)-propranolol recognition site into a membrane, as previously mentioned, in Fig. 3, illustrates the representation of functionalized-MIP membrane and structure activity of permeation rates of an enantiomeric pair of a series of chiral β-blockers. By varying in the chemical and molecular properties encompassing low to moderately polar (propranolol), highly polar (pindolol) or highly apolar (oxprenolol, propranolol prodrugs) compounds – exhibit enantioselective separation characteristics of rationally production, extend and ratio of the partition coefficients of the structurally closely related analogs under exposed physiological solutions. Furthermore, the functional polymer exhibited selective recognition properties, but sterically more demanding analogs of propranolol (e.g. oxprenolol, pindolol). On the other hand, the prodrugs that have a 10-20 fold greater uptake of both enantiomers than the parent compounds with the stereoselectively facilitated permeation from the MIP into biological barriers [78].

The imprinting approach, coupled with prodrug designs of the target delivery, provides a much better enhanced mass transport after their penetration through the skin membrane. The increase in permeability is attributed to the prodrugs that have a higher uptake from the MIP and their diffusion throughout entirely composite matrix and transit across the epithelial layers. The subsequent metabolism of the prodrugs over a prolonged period of time would release active drugs after their penetration through the epidermal membrane. These MIP systems have been used for the recognition and subsequent rebinding of a therapeutically active enantiomer – for example, one that exerts anti-hypertensive activity, i.e. β-blockers possessing an aminoalcohol structure. Even with pro and con that approach allows the feasibility of the formation of specific nanosized cavities in situ polymerization, but it relates to a vast variety of support materials chosen suitably for particular application. Perhaps the polymer-template self-assembly is a highly useful as an alternative attractive means for strategies of exploiting especially an oriented surface immobilization[84], that further they highlight the insightful 'site-directed synthesis' experiments and bring out the condition of facilitated template release that is rather rapid release in an aqueous system. In phosphate buffered solutions, as a mimic biological condition, the exposed MIP surfaces onto thin-film in polymeric matrix carrying-synthetic or bio membrane was found to induce swelling of the physically adsorbed hydrophilic polymer, to trigger structural and conformational changes in the membrane itself as well as repulsion or neutralization of charged drug on the charged support surface. This is according to a base issue of chemical interactions between components of the MIP composite membrane, to preclude undesired conditions becoming manifest in capability of separation of enantiomers and enhanced selectivity. On the other hand, the added benefit of attachment of sensing technology, of which the presence

of the fluorescent monomer-bound MIPs in the imprinted cavities make them amenable to mechanistic scrutiny by fluorescence spectroscopic techniques with sample surfaces exposing molecular-imprinted polymer. The derived mechanistic rationales helped to establish method optimization parameters by a genuine pattern of discrete fluorescence and evaluation of the binding kinetics. Also, it is possible to exploit such approaches integrating the MIP systems thus giving implications for their synthesized sensor products to *in vivo* diagnostics and self-regulated medical therapy.

MOLECULAR IMPRINTED MICROPARTICULATE NANOPARTICLES-BASED CONTROLLED DRUG RELEASE SYSTEMS: CHALLENGE

The use of nanosized materials would allow us to place man-made nanoscale things inside living cells. Fabrication of a nanocarrier-based DDS, where have at least one dimension in the nanometer size range is less than 100 nm, and therefore is of a comparable size to naturally occurring proteins and biomolecules in the cell. The engineered design of nanocarriers has the potential to revolutionize the more precise delivery of therapeutic compounds and provides for an enhanced targeted-drug delivery in accordance to its physicochemical and biochemical properties. The challenge associated with the directed tuning of the important features and supramolecular chemistry of imprinted nanoparticles, which determine modifications of their chemical and physical properties, is creating new opportunities for drug-targeted delivery and therapeutic applications. At the same time, the development methodologies suitable to modify at an atomic level the structure of condensed matter have offered horizon in which devising materials whose property was thought in connection with new functionality. Recent research progress in molecular imprinting technology, has confirmed that the materials have a huge potential as carrier systems. The elaboration of platforms for nanotechnology along with the propensities of the inherent characteristics of materials made of templating polymer is needed for the field of targeted drug delivery. Factors other than the recognition fidelity and intrinsic feature of the MIPs governing to the drug delivered, by the carrier-based MIP nanoparticles are given below.

a) Type of delivery device

The diversity of nanocarrier platforms used for imprinting has encouraged the research community to develop DDSs based on nanotechnology in order to implement bioanalogous recognition abilities into a nanosized material, thus surmounting the limitation of biological barriers. Utilizing platforms of MIP nanocarriers provides a wide variety of drug carrier system to entry in systemic circulation and targeted drug delivery, and allows novel ones to be designed in improvements to drug encapsulation. Polymerization in self-assembly of building blocks of nanocarrier including micelles, vesicles, colloidal materials and nanogels, with template assembled to the functional group have led to – a three-dimensional organized nanostructures in crosslinked polymers – because of extremely high surface area and their controlled geometrically conditions – making them are desirable platforms for MIPs. Of particular interest is the encapsulating of drugs into an association of imprinted polymer such as – nanovesicles or liposome carriers – that make use of the remarkable physical properties of carriers for example access into tissues or to their target site. An optimized design of imprinted polymer vesicles with respect either to the membrane protein being reconstituted or to the enzyme for the encapsulation in the polymeric vesicle, all can be accomplished by molecular imprinting. Some, as imprinted polymer-based liquid crystals they make innovative systems for controlled drug delivery, which is an excellent mean using either the imprinting approaches to imprint liquid crystals[85], or the integration of the MIP material and a liquid crystalline material. The products provide for enhanced supramolecular chemistry of active binding sites and improved recognition by the MIP combined the sensing elements or other analytical detection, in the interface, that act as an intelligent system in advanced drug delivery.

b) Design of delivery system

New trends and strategies for drug discovery with the advent of highly potent drugs or biopharmaceutical products some of which require location to a targeted site at a proper time, have attempted to address the extent of a drug release and delivery. Approaches to formulate the designed MIP are being developed, one of which incorporates the imprinted polymer as a recognition system in terms of an enhanced drug delivery and/or an improved controlled drug release. The concept of optimizing particle products by MIP nanoparticles in terms of surface properties, size distribution and density all which offer a means of fine tuning the device either high efficiency (analytical) or high capacity (preparative) applications; it is also related to the particle's efficiency in prolonging transit time in the GIT making them the best – ideal the circulating nanoparticle in the systemic circulation. Additionally, the well-defined particle size, shape and pore systems for the carrier systems can be precisely tuned when using interfacial imprinting approach in nanotechnology and feasibility of the potential submicron-sized particles by the optimal polymerizing reaction that MIP nanoparticles can be administered parenterally. As the choice of materials, the drug substance and the biological environment of delivery govern the delivery characteristics of MIP carriers that can deliver drugs more efficiently and safely.

A better understanding of the biological and cellular barriers is the fundamental to the success for the produced dosage forms and DDSs. On the other hand, the polymer mimicking for protein recognition provide a significant impact in targeted delivery of biological compounds or biopharmaceutical therapeutics[80]. Reported delivery approaches with MIP magnetic

nanoparticles entail both the simultaneous formation of MIP sites and the formation of magnetic cores with an appropriate morphology – for example in the case of aspirin recognition and selectively release by generating of the MIP magnetic particle[88]. This synthesis has included the use of covalently-grafted silica with template-linked silica, a core-shell process of polymerization[89]. Further, the use of living controlled polymerization methods, *via* atomic transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) are being developed[38,57]. A helpful delivery technology has also provided benefits by incorporating active agents that can mediate intracellular delivery. These include: the cell-penetrating properties of peptides or proteins[90,91]; calcium phosphate nanocomposite particles favorably coupled with a carrier that provides information regarding the anatomical location (e.g. amines, polyethylene glycol, anti-CD71, and penta- and decagastrin)[92-94]. Surfaces have also been modified with fluorescence bioimaging molecules[95]; nanoparticles loaded with biomarkers (monocytes and endothelial cells); and the use of gold nanoparticles attached to a polymer (Newkome-type dendrons) or proteins (bovine serum albumin). Beyond these designs, considering when the biomolecule is embedded in the imprinted polymer matrix, it is important to preserve its initial characteristics and to allow the diffusion of specific molecules. The incorporation of MIP systems into these developments needs to be systematically explored, and will undoubtedly lead to applications in advanced drug delivery in future.

c) Incorporation of required formulation

The imprinted recognitive systems continue to grow, as does the novelty of alternative approaches for intelligent drug release and drug targeting. Drug carrier system-based molecular imprinted nanoparticles offer opportunity for site accessibility to templating species and higher surface area – can be realized in many different ways in order to optimize drug delivery. This yet also requires scientific knowledge of formation of the matrix material within a nanotechnology. Furthermore, the type of carrier materials used for imprinting technologies, the therapeutic substances incorporated and the biological environment (e.g. pH, temperature, ionic strength, enzymes) for drug delivery, all influence and ultimately control the release of the drug. Recent developments have further extended opportunities with an improved performance through enhanced resolution in diagnostic imaging together with the added benefit of the target being readily accessible to circulating nanoparticles. In a non-MIP approach, it may be possible to produce and prolong the activity of the incorporated valuable biotherapeutic molecules using liposome-encapsulated calcitonin nanocarriers that have strong potential they can be coated with biodegradable/biopolymers (e.g. pectin, chitosans)[96-98]. Most recently, drug delivery to specific biological tissues or sites has led to the development of magnetic nanoparticles composed of a coated dopamine-PEG monolayer. This represents an attractive alternative approach as they can provide advantages for magnetic hyperthermia and biocompatibility and also for the possibility of co-delivery of drugs and/or use for photodynamic therapy[99]. With an MIP approach, the components of a pre-formed MIP magnetic nanoparticle coated with a dopamine-PEG monolayer and a protein-templated MIP attachment has been tested and is one of the first examples of a superparamagnetic nanoparticle capable of binding to a template protein (human hemoglobin) with a relatively high selectivity[82].

In pharmaceutical development of dosage form, optimization process often requires alteration in formulation composition, pharmaceutical manufacturer, batch size, etc., that changes are therefore applied to a formulation and studies in human volunteers may be required in during the formulation development, increasing the cost of optimization processes. The correlation between quantitative or qualitative data of drug release rate and amount of drug absorbed and can serve as surrogate for *in vivo* bioavailability, which have been main focus of pharmaceutical industry, this can assist in quality control for certain scale-up process. The ability for establishing correlation of plasma drug concentration profiles for oral extended release products of MIP nanotube-based controlled-release systems can be predicted by the *in vivo* dissolution rates for 12-h pharmacokinetic profiles of propranolol enantiomers in Wistar rats[100]. A change in manufacturing process, minor formulation modification, and even product strength using the same formulation can be justified for additional *in vivo* studies. Indeed, the materials obtained natural source or generated from natural or synthetic building block using nanotechnology can be introduced within molecular imprinting approach, unless they can be applied, and their suitability involves similar issues. The naturally occurring materials sometimes have found applications required for a favorable DDS and can be used as the in situ implants of biomaterial-derived materials and their microencapsulation of therapeutic agents or other biological objects, but with demanding identification and experimental practice[101]. Some of the carrier biodegradable materials incorporated into the formulation or devices with potentially distinct pharmacological and toxicological properties can affect partly to different pertaining to the fundamental of delivery or the complexity of the drug absorption. They perhaps have a large number of parameters affecting drug release *in vivo* so giving the difficulties in establishing the correlation between *in vivo* parameters and *in vitro* drug release profiles.

DESIGN AND PERSPECTIVE OF MIP NANOPARTICLES / NANOSTRUCTURES

In the past few years, molecular imprinting has developed tremendously and has resulted in innovative designs for modern engineered nanoparticles with more advanced selective recognition abilities that have considerably broadened the possible applications for conventional

nanoparticles. When talking about utilizing natural antibodies as recognition elements we recognize that nature provides us with a wide variety of highly specific or even multispecific antibodies. While we attempt to mimic these natural situations to yield say promiscuous antibodies, the latter generally requires a preferred system for systemic administration or for targeted drug delivery. Advances in polymer science and chemical synthesis have led to more advanced recognition abilities using polymerizable materials for templating that are close to or can better mimic those of natural biological recognition systems and cell receptors. The strategy of well-defined molecular imprints in a microparticulate nanostructure has also enjoyed increasing attention, while they can potentially ensure an ability to circumvent the template diffusion problems in bulk layers in addition to its predefined selectivity. The development of synthesized MIP nanoparticles for drug delivery, however, is not yet fully controlled nor is the amount and period of the drug release within an *in vivo* system of drug delivery. Therefore, chemical strategies have been employed to enhance efficient imprint-binding properties.

Several techniques have been applied for the introduction of important features to nanoparticles that will enable an accelerated facility of development in MIP nanoparticles for different approaches. Those therapeutic substances are capable of coupling together following an imaging process to form more stable, multifunctional units in the imprinted polymers and devise in the final size to the polymeric nanoparticles. The core-shell technique has also been applied to provide binding sites preferentially on the core-shell surface imprinted particles, and technique is simple and robust to precise control the monodisperse particles, is a viable, will also realize the potential of component delivering transmucosal macromolecular, combined with images and sensing application. The ability to imprint molecular recognition sites on nanoparticles has been shown for a theophylline-controlled release that is generated by direct surface polymerization using a mini-emulsion polymerization method[102]. In addition, the production of nanocapsules that are molecularly imprinted on their surfaces represents an alternative promising means that provides an opportunity to study physical performance and the recognition for drug therapeutics[103].

Many improvement of drug delivery as result of imprinting theme is actual spot of an enhanced controlled release of the drug, and affinity and capacity for template binding with an increased number of existing specific cavities, furthermore render preferable controlled-release devices for drugs either in gastrointestinal or in plasma simulating fluids. In a study of the recognition performance of the caffeine, and theophylline imprinted nanoparticles in aqueous conditions, it was reported that nanoparticles prepared from a polymerizing mixture of methyl methacrylate and acrylic acid functional monomers and trimethylolpropane trimethacrylate (TRIM) and loaded into a supporting membrane of the same polymer composition as MIP beads intended for clinical applications. These days a highly cross-linked network associated with template molecule have improved so much increasing the efficiency of template rebinding[102].

Imprinting polymer is an emerging technique of building recognition materials because of the simplicity and straightforward way of synthesizing with strength of materials transferring important motifs from a templating species to the polymer matrix. Technique also obviates the need for creating sophisticated receptor sites. Owing to advances in polymer chemistry, there is the possibility of finding a hybrid with the promise of a 'monomolecular' imprinted material and produce dendrimer macromolecules through binding to defined molecular targets with a more accurately controlled structure with a single molecular weight material. If an imprinted dendrimer is furnished with a polyfunctional core linked to a layer of several repeating units (or so-called generations) to create a highly branched three-dimensional structure in which growth emanates from a central core molecule; this will produce good recognition and selectivity for a truly nanoscale molecule[104]. Recent applications of sophisticated, yet challenging, chemical synthesis are leading to the creation of nano-copies of nano-objects formed by a classical suspension or emulsion polymerization method with nanometer dimension precision (5-10 nm) using a binding site functional monomer, for example for the enzyme carboxypeptidase A as a catalytically active imprinted polymer with approximately one active site per molecule[105]. The uniqueness of the imprinted nanogels is to recognize a specific ligand, and allows the mimicking of the active site of antibodies, or even an enzyme activity with the properties of a soluble artificial receptor, the sizes of a small protein approach enzyme dimensions may enable them to traverse the blood stream with endocytotic activity.

Next, substantial progress has been made in the manufacturing processes that lead to the development of spherical shaped MIP nanoparticles for industrial applications based on supercritical fluid techniques. A supercritical solution containing a dissolved solute is rapidly expanded across-orifices into a vessel for forming particles held at constant temperature and supercritical pressure conditions. The process usually involves instantaneous dispersion, by mixing followed by extraction of the solute from the solvent (typically carbon dioxide), leading to very high supersaturation ratios[106-108]. In imprinting, supercritical polymerization provide MIP particles imprinted with two templates such as salicylic acid and acetylsalicylic acid in supercritical carbon dioxide by varying the working conditions with the use of a carboxylic acid end-capped perfluoropolyether oil as stabilizer. After template removal the resultant MIP particles displayed a good binding capability dependent on the template:monomer ratio, but that it did not permit for an extended release of the drug[109]. Using supercritical

fluids will provide the most impact, may be the production for imprinted nanoparticles in 'clean' solvent in which provides opportunities for enhancement in the precise manipulation of critically important properties of drug and carrier particles, and featuring coupled to consistency within and between batches.

1. MIP nanoparticulate nanostructures for controlled drug delivery:

Major recent efforts have been invested that MIP nanoparticles have evolved the potential to a vast opportunity for drug delivery and targeted systems for example allowing a drug and drug carrier to the internal cellular. Some aspects of implementing are so elaborate that helpful fabricating of MIPs with molecular recognition is really mimicry of nature using an artificial system as a mean of creating nanoparticles DDSs. Therefore, the concept of using nanoparticulate MIP for therapeutic applications can be achieved by using the normal polymer imprinting procedure, then devising a variety of methods to obtain a suitable carrier system or device. Modifications to polymeric nanocarriers with integrated MIPs can improve those that used nanotechnology can provide particularly enticing opportunities.

Many future applications of imprinted polymers are envisioned in the fields of microfabricated and nanofrabicated devices that involves small amount of materials. Therefore, considerations of the imprinting materials with the best performance possible are the target of micro/nanofabrications is of which issue is to design an MIP nanostructure with good compatibility to the matrix components so as to effectively to the target sites *in vivo* drug deposition. So far, traditional methods for the preparation of the imprinted nanoparticles are not fully specific for producing a modulated and targeted drug delivery yet. On the other hand, diverse approaches for addressing the long-circulating nanoparticles to the release of the drug to its site of action for MIPs are helpful which may represent an attractive platform. In addition, the use of imaging techniques can be coupled and provide detailed information and in-depth understanding on imprinted particle adhesion as well as epithelial barrier permeability of the particles. Combining the strategies of proteomics with nanotechnology would be helpful to develop nanomaterials with an imprint polymeric delivery system that has an increased circulation residence time (e.g. derivatized gold nanoparticles)[110]. Alternatively, the development of a targeted MIP-coated metal nanocarrier system would allow for feedback regulation from their active coatings, provide access for the carrier to the desired target sites with enhanced cellular accumulation such as gold and magnetic nanoparticles. The drug delivery technologies using gold nanoparticles provide the possibility of the addition of an optical element for the long-term visualization and tracing of intracellular functions upon reaching the functional site[111]. The extrapolation of this biomimetic polymer using imprinting technology has further provide possible development of polymer carriers by which creates approaches by means of molecular functionality able to provide the imprinted polymers capable of emulating membrane-lytic abilities of toxins and viruses bearing fusogenic peptide revolutionize the diagnostic and treatment of many diseases. A number of challenges to date have been proposed to these methods of incorporation that include the generation of peptide-coated metal nanoparticles[112] and the production of biocompatible gold nanoparticles using laser-based bioconjugation[113] as well as the core-shell reversible nanoparticle of an ionic liquid block, precipitated from aqueous di-stimuli-responsive *N*-isopropyl acrylamide with excess bromide[114], all these offer ample opportunities for future developments. A microstructural design unit combines with the chemical composition can also be used to adapt the structural property relationships, and therefore produces nanoparticles with an improved integrity for recognition. Great emphasis is placed on development of materials and synthesis by either cutting-edge polymerization, supramolecular self-assembly or living polymerization methods which ensure the availability of imprinted nanoparticle.

There have been a variety of approaches to tailor chiral nanoparticles coupled with an added benefit of high substrate specificity and enantioselective functionality interlinked with readily detectable substances to serve as versatile sensing elements for an enantioselective sensor system within this imprinting technology. These have been reviewed recently by Maier and Lindner[115]. As a result, these methods explain a mimicking the active site of natural antibodies or biological enzymes in fact that underpin much of the current thinking in generating recognition of different biomimesis enantioselective receptor on MIP nanoparticles that will lead to the eventual goals of delivering drug enantiomers; ideally one that is amenable to automation, allowing for fast, real-time and in-situ determination.

2. Prospects of developing MIP nanoparticles for targeted delivery:

Significant improvements in carrier-based MIP nanoparticles have been impressive and may pose a considerable challenge for efficient drug delivery and targeting, but that there is still some way to go to fully achieve for these purposes. The theoretical and practical problems of exploiting imprinting approaches to deliver the drugs and drug carriers are usually dependent upon the application of materials, which in turn is highly dependent upon the routes of administration and suitable dosage forms or carriers. In recent years, scientists have designed imprinted nanocarriers that can be functionalized: for example, with ligands to receptors on the cell surface that can promote targeted delivery. In another important application, imprinting technologies have been exclusively interested by biomedical scientists, especially their application for remarkable therapies and biomedicine[116-119]. The recognition efficiency generated by mimicking biological counterparts is a highly promising

role of MIP nanoparticles in the targeted delivery of drugs or to act as antigen-antibodies or antidotes for toxin, achieving life-saving for patients, and conditions that potentially could be treated with imprinted polymer medicine. This can be achieved, as pointed out earlier, by a strong inventory of different experimental and theoretical techniques. Despite the challenges inherent in the limited availability of the biological templates from their natural sources, one strategy of producing analogues could be to allow for the potential use of a nonbiological approach for molecular imprinting, while the established techniques for MIPs warrant more studies for modulated and targeted drug delivery.

Many studies have so far been focused in this direction, and often they rely on the established enhanced features and architecture of existing drug delivery materials. One area where severe systemic toxicity can limit treatment is cancer chemotherapy due to the inherent toxicity of the drugs used, so the release of the cytotoxic agents or anticancer compounds in the body has to be controlled to reduce tissue damage and the systemic toxicity. Another useful application of MIP nanoparticles concerns the sustained release *in vitro* of 5-fluorouracil, as well as cross-reactivity for a template analogue with the potential for controlled release of the drug[48,62]. The production of 5-fluorouracil-imprinted nanoparticles *via* a precipitation method differs from the optimal MIP polymerization process, in that the obtained nanoparticles are about 300 nm in diameter, with a rather uniform particle size[48]. These efficiently provided a delayed release of the drug *in vitro*, although the delivery system still remains to be examined *in vivo*.

While the role of the form of the dosage or carrier is important in a rationale drug therapy, it still represents the real DDS which is the living organism that receives the drug in the body of human. The challenge to pharmaceutical scientists is one of learning the language of scientists whose research contributes to understanding of the biology and immunological aspects of the delivery of drugs. Apart from this desirable potential, the use of bio-imprinted nanoparticles as artificial antibodies has the benefit, providing for a response to a specific molecule in their environment, or could be used *in vivo* for the release of therapeutic biomolecules, so helping to provide for an enhanced bioavailability and get to where it needs to be in the body quickly and in greater amounts[120]. Nevertheless, the impact of biomimetic recognition for a peptide biomolecule or cell species using this technique, that relies on the influence of antigen-antibody interactions is well recognized and is producing valuable consequence, for instance the artificial antibodies made of the particles loaded with a specific biospecies, represents a very sensitive approach allowing for the development of responsive, activated surfaces with a very specific response that mimics natural responsiveness[121,122].

The creative and collaborative combination of physicochemical, biological, chemical, as well as clinical approaches to understanding to such problems, the scientific design of carriers for administering the drug complexes into a complex milieu in the body. As for example, producing an imprint with specific binding sites for biomacromolecules on protein-sized nanoparticles administered into the systemic circulation[117,123]. The delivery of melittin-imprinted nanoparticles of 30 mg/kg as artificial antibodies to capture toxin in the body *via* intravenous infusion have been proven to be a marked treatment that they could be successfully used to detoxify the melittin bee-toxin in the bloodstream of mice treated with the toxin at a dose of 4.5 mg/kg, and produced a reduced mortality of the mice after 4.5 mg/kg of melittin[117]. Further developments of this intriguing methodology could provide a tailored delivery of a discrete nanoscale therapeutic system and the targeting system represents the next frontier in pharmaceutical sciences.

A strategy of methodologies is desirable for fabricating the nanoparticle/nanocarrier hybrids of biocompatible polymers with recognition integrity to produce properties for the release of drugs from the circulating MIP nanoparticles. For this purpose, a combined theoretical and experimental exploration has synergistically yielded insights into the nature of nanomaterials and nanodevice DDSs, in more detail than what can be achieved by the use of either approach alone. Perhaps the most significant recent advances in imprinting recognitive polymer delivery system have come in the area of molecular nanotechnology and the further applications of its effects on cellular internalization and circulation times.

CONCLUSION AND OUTLOOK

Strategic approaches for developing novel DDS have been made in MIP micro- and nanoparticles for drug delivery applications. Development of strategic designs and engineering solutions for these platform technologies as well as the concept of drug delivery formats from a recognition polymer such as described within this review still find it difficult to compete with the properties of biological antibody or immune systems. Ongoing research aims to identify and overcome these difficulties. An understanding of each of the components and standardization of each component will lead to enhancing the applications for design of MIPs creates an effective delivery for any given drug. It is feasible to give molecular imprints a helping hand to target deliver to cancerous cells and to increase their nuclear and cancer killing abilities. Perhaps is encouraging to know that this could be achieved *via* localization of a synthesized MIP on the surface of an immune system. Because cancer cells are remarkably like our own normal cells, so the mechanisms available to detect cancer cells must be sophisticated and able to differentiate self from non-self, exactly. This is what an MIP system must be designed to do.

However, some of the methods described here will be optimized to yield recognition polymers in the form of MIPs at the micro/nanosize scale. Developing the

requisite tools to dictate events to achieve success in molecular imprinting and for achieving a controlled release and delivery of a given drug at the bio and non-bio interface requires a highly interdisciplinary approach that has benefited tremendously from the increasing collaboration between scientists from the physical and life sciences. The ability to guide therapeutic agents to particular sites in the body to achieve precisely defined therapeutic effects is still in its infancy. As this trend continues, the potential of MIP nanoparticles with increasing complexity and efficacy will be achieved. Future advances in molecular imprinted nanocarriers would be a proposed strategic innovation with biomimetic recognition for future applications. This will then provide a recognitive imprint network design in combination with intelligent complexation mechanism leading to a new generation of micro/nanodevices that will have a huge effect on targeted drug delivery. Finally, an enhancement of our still limited knowledge of the molecular principles/mechanisms governing molecular recognition represents a major challenge for the future.

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