High Affinity Polymers by Molecular Imprinting for Drug Delivery

Mara Soares da Silva and Teresa Casimiro

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/50162

1. Introduction

Molecular recognition processes found in nature have always inspired scientists to mimic these systems in synthetic materials such as molecular imprinted polymers. Selective receptors within a polymer have a huge range of applications such as in separation processes, analytical chemistry, sensors, catalysis, drug discovery and therapeutics. In this last area in particular, polymers are having a central role in recent developments and materials with molecular recognition ability can respond to new challenges and opportunities.

The synergy of traditional pharmaceutical formulations with new polymers and hybrid and conjugated materials is leading to new approaches of treating diseases in medicine. In 2003 Langer and Peppas have identified the combination of new polymers with molecular imprinting, as a new field in drug delivery but with applications not immediately forthcoming [1]. Since then the field has grown with increasing reported applications of molecular imprinted polymers for drug delivery and pharmaceutical applications, although not at the expected rate. From a literature search (Web of Knowledge database, April 2012) one can see that from the ca. 13000 published papers on molecular imprinting only less than 170 are related to drug delivery. We believe this relatively small number of contributions can be attributed to difficulties in the synthesis and especially in the optimization of the polymers. Traditional methods are time-consuming involving multi-steps and in general MIPs are prepared using organic solvents which eventually leave toxic traces, incompatible with pharmaceutical and biomedical applications. Also safety, in particular biodegradability and cytotoxicity issues, must be addressed in applications where MIPs are in contact with biological tissues. In addition there is an extra difficulty of preparing MIPs with performance in aqueous solutions which is crucial to in vivo applications.

It has already been demonstrated that MIPs are highly promissory drug delivery systems (DDS). Not just because of the high specificity of the active sites but also due to the
possibility of introducing stimulus-responsiveness by choosing appropriated monomers. In addition the physicochemical properties of MIPs are able to protect the drug from enzymatic degradation during trafficking in the body [2]. However, only recently MIPs have been applied to drug release [3]. The possibility of preparing cheaper robust materials with molecular recognition capability and with tailored properties, is highly attractive to pharmaceutical applications and in particular for drug delivery.

This Chapter will focus on the use of supercritical fluid technology as a viable and greener alternative to the synthesis and processing of molecularly imprinted polymers for potential pharmaceutical applications in particular for drug delivery.

2. Molecular imprinting

Molecular recognition comprises the specific interactions that enable one chemical entity to selectively recognize its physical and chemically complementary target molecule. The recognition mechanism is mainly mediated by weak non-covalent interactions, such as hydrogen bonding, ion-pairing, hydrophobic interactions and dipolar associations that as a whole govern the structural conformation of macromolecules and influence their interaction with other molecules. In nature there are several examples of successful recognition mechanisms, such as DNA-protein, RNA-ribosome and antigen-antibody. Biomolecules however tend to lose their recognition properties in abiotic environments. Furthermore they are considerably expensive, which limits their applicability. For those reasons scientists have shown a great interest in the design of artificial supramolecular systems that exhibit molecular recognition. Examples of these materials are crown ethers and calixarenes, that selectively bind specific cations [4], derivatives of parental cyclodextrins [5], dendrimers [6] and molecularly imprinted polymers (MIPs).

Molecular imprinting is an emerging technique to create high affinity polymeric matrices, MIPs, for target molecules. The methodology relies on the stabilization of the monomers-template assembly in the pre-polymerization step and posterior copolymerization with a crosslinking agent, in the presence of a porogen [7]. Template removal from the imprinted polymer at the end of the reaction leaves accessible chemical and sterically complementary binding sites. The generally accepted mechanism for the formation of MIPs is schematically presented in Fig. 1.

![Figure 1](image-url)
Imprinted polymers are synthetic receptors with binding constants comparable to natural receptors [9,10], but capable of withstanding harsh conditions of pressure [11], temperature and extreme pH [12], and organic solvents [13]. They are cheap to synthesize and can be manufactured in large quantities with good reproducibility. These properties explain the growing interest in imprinted materials in the last decades, resulting in a significant increase in reported works in such diverse areas as in synthesis and catalysis [14,15], solid-phase extraction [16,17], chromatography [18,19], sensing [20,21] and in drug delivery [22,23].

In literature one can find many functional monomers and their combinations, typically used in molecular imprinting. Mayes and Whitcombe listed a significant part of monomers typically used in non-covalent molecular imprinting and corresponding literature [24]. The most common monomers are methacrylic acid (MAA), acrylic acid (AA), 4-vinilpyridine, diethylaminoethyl methacrylate (DEAMA), acrylamides, 2-hydroxyethyl methacrylate (HEMA), etc. Typical cross-linkers used in molecular imprinting are acrylated-based (e.g. ethyleneglycol dimethacrylate EGDMA, trimethylolpropane trimethacrylate TRIM, etc), styrenic-based (e.g. divinylbenzene DVB), water soluble cross-linkers (e.g. ethylene-bis-acrylamide), among many others. In 2004 Hilt and Byrne reported a quite complete list of molecularly imprinted biologically significant molecules, where is visible that methacrylic acid and ethylene glycol dimethacrylate are probably the most common monomer and cross-linker used in the synthesis of MIPs [25].

3. Synthetic approaches and design of MIPs

Molecularly imprinted polymers can be prepared according to a number of approaches that essentially differ in the way the template interact first with the functional monomer and later with the polymeric binding sites. Although the divisions among them are becoming somewhat blurred due to the emergence of more complex hybrid strategies, the main molecular imprinting approaches considered are covalent, non-covalent, semi-covalent and metal ion-mediated imprinting.

Covalent imprinting, first developed by Wulff [26], was the initial strategy to introduce molecular affinity in polymeric matrices. By means of this imprint methodology, templates with polymerizable groups are reacted to prepare the recognition matrix. At the end of the polymerization the template is cleaved from the matrix and the functionality left in the binding site is available for future covalent rebind of the target molecule. The great advantage of this approach is that the functional groups are only associated with template sites. However, difficulties in the cleavage of the template and limitations found in the type of compounds that can be imprinted by this way led to the development of other imprinting methodologies.

Non-covalent imprinting, pioneered by Mosbach [27], is currently the most used approach to produce molecular recognition matrices because of its simplicity and easy availability of the commercial monomers used. The efficiency of MIPs prepared by non-covalent methodology relies in the successful stabilization of template-monomer (T-M) complexes formed in the pre-polymerization step, through numerous non-covalent interactions such as
hydrogen bonding, ion-pairing and dipole-dipole interactions. After the matrix prepared and template-cleaved, the rebinding is achieved also via non-covalent interactions, providing higher kinetic constants than MIPs prepared by covalent imprinting. The simplicity of the method, allied with the easy and cheap preparation, as well as the high selectivity that the polymers can have, seem to overcome potential complex stabilization issues.

Semi-covalent imprinting route combines both covalent and non-covalent interactions during the synthesis and rebinding process, respectively. When using this approach, a template with covalently bound polymerizable groups is used to prepare the recognition matrix, affording polymers with narrower distribution of the binding sites. Also, the inexistence of other kinetic restrictions than those encountered by diffusion can be considered a big advantage of this methodology. Two different approaches have been developed in which the template and the monomer are directly connected or, hence, have a sacrificial spacer group between them. This latter has been intensively developed by the group of Whitcombe [28].

Metal ion-mediated imprinting uses metal ions to target a wide range of functional groups through the donation of electrons from heteroatoms of ligands to the unfilled orbitals of the outer coordination sphere of the metal. By means of this approach, a polymerizable ligand is used to complex the metal ion that coordinates to the template [29], yielding therefore matrices with highly specific active sites.

The development of molecular recognition polymers involves the optimization of a number of experimental variables that determine the thermodynamic balance of the system and consequently the specificity of the matrix towards the template molecule. The most important parameters that have to be carefully optimized are the choice of the functional monomers according to the template nature, monomer: template (M:T) ratio, the crosslinking degree and the solvent of the polymerization.

The non-covalent approach is the most widely adopted method due to the reasons already exposed above. M:T ratio has a major influence in non-covalent imprinting as it directs the equilibrium of formation of template-monomer complexes. Functional monomers are typically used in excess to shift the equilibrium towards complex formation, that results in some of functional groups being randomly distributed throughout the polymer, leading to non-specific binding [30]. Although there is no straightforward correlation between the amount of template and the formation of specific sites within the polymer, a slight decrease in the absolute number of high-affinity sites has been reported when low template concentrations are used while the relative yield in high-affinity sites increased [31].

This is extremely important in order to extend the application of non-covalent molecular imprinting to expensive or poorly soluble template molecules. On the other hand high concentrations of template lead to an increased number of random affinity binding sites, increasing non-specific interactions [31,32].

The cross-linker agent fulfils three main purposes in imprinting technique: 1) it controls the polymer morphology (whether the matrix formed is of gel type, macroporous or microgel powder); 2) it freezes the functional monomer-template complex within the matrix; and 3)
imparts mechanical stability to the polymeric network. The integrity of the binding sites responsible for the recognition mechanism usually requires a rigid structure, with high crosslinking density, which minimizes the possible conformations of the matrix. However, when lower ratios of cross-linker are used, the matrix is more flexible, which can turn the equilibrium between drug release and uptake in the recognition site faster. Therefore, a compromise between the rigidity and flexibility of the network is necessary [23]. The imprinted cavities should be stable enough to maintain the conformation in the absence of the template, but also flexible enough to ease the fast equilibrium between the release and re-binding of the template in the cavity during its application.

The solvent or porogen used in the imprinting process has also a significant effect in surface morphology and molecular recognition properties of the polymers [33,34], particularly in the case of non-covalent imprinting. The success of imprinting relies on the relative amount of cross interaction between the solvent and the intended non-covalent interactions employed during T-M complex formation. If the solvent interferes or competes with any of these interactions, less effective recognition will occur. Furthermore it is well known that the performance of the MIP is usually optimized in the solvent used in the synthesis achieving better selectivity and rebinding results, i.e., there is a memory effect [35].

The influence of pressure in the imprinting process was studied by Sellergren and co-workers, by means of hydrostatic pressure, using three different solvents (dichloromethane, methanol and 2-propanol) and two different triazines as templates [36]. Their results support the idea that high-pressure could be used to stabilize template-monomer complexes and result in higher affinities.

The increasing restrictions in the use of organic solvents prompted the development of new greener methods for the preparation of MIPs. Some efforts have been made in the synthesis of imprinted polymers in aqueous environment; however it presents many problems since the high concentration of water molecules weakens the interactions between the monomer and the template, decreasing the selectivity of the MIP for the template molecule [35]. Attempts have been made by using functional monomers that may stabilize the complexes through hydrophobic interactions, such as cyclodextrins [37], metal coordination [38] or by multi-step polymerization procedure which is time-consuming and energy intensive drying steps are required.

4. Applications of MIPs

Imprinted polymers play an important role in separation processes. MIPs can be used as absorbents in solid phase extraction [39,40], extraction of contaminants from environmental samples [41], food analysis [42], analytical chemistry [43] and chromatography, which is the most traditional application of MIPs. In particular, MIPs can be used as chiral stationary phases, replacing expensive chiral columns and avoiding chiral mobile phase additives and derivatisation with chiral reagents. Successful imprinting systems are able to deliver polymeric networks with effective enantiomeric recognition properties when templating a chiral molecule. Higher affinity to the template enantiomer is translated in a predictable
order of elution when using MIPs as chiral stationary phases, as the template establishes a higher number of interactions with the polymeric matrix and therefore is more retained. The use of MIPs as stationary phases has been object of intense research, with many papers published in the area [44,45,46,47,48].

Membrane technology is an active, growing field, which has gained a huge importance in the last forty years, as high-throughputs membranes were developed. New trends encounter the development of affinity membranes, with molecular recognition character inspired in natural mechanisms. Molecularly imprinted membranes (MIMs) emerge as potential affinity materials due to their low cost, ease of preparation and good molecular recognition performance [49]. Also the development of sensors and biosensors are gaining significant interest in the last years. MIPs have been used in transducers and integrated in sensors [2].

Another very promising area is the application of MIPs in catalysis. The robustness and high selectivity of molecular imprinted polymeric materials turn possible their use at harsh conditions of temperature and pressures, in a wide range of organic solvents and pH conditions, replacing for instance enzymes [50].

The use of molecular imprinted polymers in drug delivery systems is a new and attractive area of research. Developments in the field of polymer synthesis and polymerization mechanisms are being reflected in MIPs synthesis, where various mechanisms can be followed to obtain more controlled macromolecular architectures [51] and by exploring new intelligent analyte-sensitive hydrogel co-polymers [1]. We believe that the development of new biomimetic materials for controlled and targeted drug delivery will be for sure one of the most active areas of molecular imprinting in the next years, and where supercritical fluid technology can have a relevant role by delivering materials with the required features for pharmaceutical and biomedical applications.

5. Supercritical fluid technology

A supercritical fluid is a substance above its critical temperature and pressure but below the pressure required to condense it from the fluid to the solid state [52]. The properties of supercritical fluids are somewhat intermediate between those of liquids and gases (Table 1), they have gas-like diffusivities and liquid-like densities, in addition to an easily tuneable solvent power [53].

<table>
<thead>
<tr>
<th></th>
<th>Diffusivity (cm$^2$/s)</th>
<th>Density (g/mL)</th>
<th>Viscosity (Pa.s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gases</td>
<td>0.1</td>
<td>$10^{-3}$</td>
<td>$10^{-5}$</td>
</tr>
<tr>
<td>Supercritical fluids</td>
<td>$10^{-3}$</td>
<td>0.3</td>
<td>$10^{-4}$</td>
</tr>
<tr>
<td>Liquids</td>
<td>$5 \times 10^{-6}$</td>
<td>1</td>
<td>$10^{-3}$</td>
</tr>
</tbody>
</table>

*Table 1.* Physical properties of gases, liquids and supercritical fluids (adapted from [53]).
Supercritical carbon dioxide (scCO₂), in particular, possesses numerous properties that made it emerge as the most extensively studied supercritical fluid. It has a low critical point, is inexpensive, readily available in high purity and is a gas under ambient conditions, meaning that by simple depressurization of the system no solvent residues will be found in the final product. It is a GRAS solvent (Generally Recognized As Safe) ([http://www.fda.gov) and considered a “green” alternative solvent.

In the last years, scCO₂ has already proved to be an excellent medium for the synthesis and processing of polymers [54,55,56], impregnation of active substances [57], formation of porous structures [58,59], textile cleaning [60], chemical reactions [61], extraction [62], etc.

Polymers and other high average molecular weight macromolecules and polar materials are typically not soluble in supercritical carbon dioxide, with exception of silicones and fluorinated polymers. On the other hand monomers are usually very soluble. This means that initial homogeneous phases are easily obtained at mild pressure conditions at the beginning of the reaction and when the polymer reaches a certain threshold molecular weight it precipitates being collected inside the reactor (Fig. 2b). This is a typical heterogeneous reaction by precipitation. Depending on the solubility of template and monomers in the scCO₂ medium, different polymerization approaches can be followed such as dispersion and emulsion [63].

Typically a polymer is synthesized in scCO₂ inside a stainless steel high-pressure vessel equipped with a pressure transducer. Several types of reactors can be used with magnetic or mechanically stirring or equipped with visual windows to allow full observation of the inside (Fig. 2a).

Figure 2. a) 33 mL high-pressure visual reactor used in our lab and b) ready-to-use dry MIP polymer powder synthesized in scCO₂.

Polymerization of the typical monomers used so far in scCO₂-assisted molecular imprinting is radical initiated, usually with AIBN. That is why typical reactions are carried out at around 65°C, the optimal initiation temperature. Initial pressure of the reaction is chosen in order to have a one single phase at the beginning of the reaction, with all reactants, monomers, cross-linker and initiator soluble in the CO₂ continuous phase, as well the
template molecule. There is the possibility of adding a stabilizer that can further control the morphology of the polymer by minimizing the surface area of the particles forming spherical particles with monodisperse particle size distribution [64,65].

Phase behaviour studies such as cloud point curve determination for the reaction mixture are important for the polymerization optimization [66]. In addition, as organic solvents are typically soluble in scCO2, a small amount of an organic solvent co-solvent can be added in order to tune the polarity of the medium, and help dissolving more polar molecules.

6. Supercritical CO2-assisted synthesis of MIPs

Supercritical CO2-assisted molecular imprinting has recently demonstrated to be a clean and one-step synthetic route for the preparation of MIPs, with attested performance in chromatography [47], drug delivery [67,68,69], and extraction [70,71,72,73]. The advantages of using scCO2 as solvent in the molecular imprinting process go beyond environmental concerns. By performing the synthesis in an apolar aprotic porogen, such as scCO2, the T:M complexes can be highly stabilized giving rise to well-defined active sites and leading to materials with high affinity [74]. Furthermore the matrices can have a controlled morphology and are obtained as dry powders, with no solvent residues, avoiding posterior purification and drying steps, which are major advantages over conventional methods. Moreover the use of supercritical fluids in the removal of template molecules can increase the diffusion coefficient at least 10-fold [75], which can overcome this actual limitation of conventional molecular imprinting. Thus the use of scCO2 can bring not just advantages in the synthesis of the polymers but also in the template desorption from the matrix at the end of the polymerization, and it can be further used in the impregnation of the bioactive molecules in the matrix by scCO2-assisted impregnation.

Imprinted polymers have gained much importance over the last years, and their potential use in drug delivery applications, as unique delivery systems or incorporated into other drug delivery devices, are being widely studied. The use of MIPs could improve the control over the therapeutic release by sustaining the delivery of the agent and intelligently releasing the drug in response to small variations in the environment. Moreover the majority of the drugs act by a molecular recognition mechanism and molecular imprinting technique also enhances the loading capacity of the polymers towards the template drug.

The first work reporting the potential use of MIPs as sustained drug delivery carriers was conducted by the group of Nicholls [76] and studied the drug dissociation kinetic from theophylline-imprinted polymers, at different pH and loaded with different amounts of drug. The imprinted polymers synthesized demonstrated higher affinity towards theophylline than to caffeine and displayed a more sustained delivery than the corresponding control polymer. This work was followed by many others reporting the development of MIPs with potential use as DDS. Some recent developments include the use of molecular imprinting in the preparation of materials for ocular, transdermal and oral drug delivery. Templates such as theophylline, histamine, ephedrine [77], propranolol [77,78,79,80,81], citalopram [82], H1-antihistamines [83], sulfasalazine [84], 5-Fluorouracil
[85], norfloxacin [86], hyaluronic acid [87], levofloxacin [88] among many others have been used with success. Propranolol a β-blocker widely used for hypertension treatment, is one of the most used templates, and is indeed the most successful imprinted molecule. Its choice is not only justified by its clinical relevance, inherent chirality and availability in enantiomerically pure and radio-labelled forms, but also because of its ability to establish strong ion-pair interactions as well as hydrophobic [89]. The actual great challenge in the synthesis of MIPs is to imprint other interesting molecules such as macromolecules, charged or low functionality molecules [90].

Over the last years a great effort has been made to develop imprinted matrices for drug delivery applications with some chain flexibility. Although the majority of imprinted polymers reported possess high crosslinking degree and therefore limited chain mobility, a certain degree of flexibility can be found in biological systems, with recognition occurring in aqueous environment as the result of numerous non-covalent interactions. Much of the theory concerning conformational memory in biological macromolecules, such as proteins, is valid for molecularly imprinted polymers. Thus, the design of imprinted matrices with a certain mobility of the polymeric chains has been studied to improve the properties of common hydrogels.

Hydrogels are networks of hydrophilic polymers that have attracted wide research interest as controlled release devices due to their tunable chemical and three-dimensional physical structure, good mechanical properties, high water content and biocompatibility [1]. Hydrogels can be successfully synthesized in scCO2 [91,92]. Poly(N-isopropylacrylamide) (PNIPAAm) hydrogel with controlled morphology was synthesised in scCO2, with advantages when compared with conventional polymerization since there is no need for intensive drying of the material before further processing or characterization steps. Thus the combination of hydrogel development using supercritical fluid technology with molecular imprinting has a strong potential in the design of new targeted DDS therapies.

Supercritical CO2-assisted synthesis of MIPs as potential DDS was first developed by Casimiro and collaborators [67]. The work reports the synthesis in supercritical medium of spherical particles of poly(diethylene glycol dimethacrylate), PDEGDMA, using a carboxylic acid end-capped perfluoropolyether oil as stabiliser. Polymerisations were carried out in the presence of different concentrations of salicylic acid and acetylsalicylic acid and results showed that MIPs were able to uptake higher amounts of template drug during scCO2-assisted impregnation and release it in a more sustained way when compared with non-imprinted polymers (NIPs). In addition there was an evident correlation between the amount of template used in the synthesis and the loading capacity in the impregnation of the polymers using scCO2. These promising results prompted the optimization of other imprinting systems, through the study of the influence of some experimental variables in the performance of MIPs as drug delivery carriers.

Copolymers of methacrylic acid (MAA) with ethylene glycol dimethacrylate (EGDMA) and N-isopropylacrylamide (NIPAAm) with EGDMA were designed in scCO2 to have molecular recognition to flufenamic acid (FA) [68]. The synthesized polymeric matrices with different
ratios between template and functional monomer and different crosslinking degrees were further impregnated with FA in scCO₂ and the drug release profiles evaluated in vitro. The results showed that by changing the experimental parameters above mentioned it is possible to tune the molecular recognition of MIPs and therefore the drug delivery. Although highly cross-linked matrices possess higher imprinting factor, all the imprinted polymers presented more sustained release of FA than control polymers, due to the affinity introduced by molecular imprinting. High-pressure NMR was used to study the interactions between the template and the monomers in the pre-polymerization mixture. The results confirm that there are hydrogen bond interactions between the carboxylic acid groups of FA and monomers, which are responsible for the specificity of the binding sites.

Figure 3. a) SEM image of MIP polymer and b) MIP particles in contact with Caco-2 cells (1500×, 20 kV) from [69].

Low cross-linked polymeric networks composed of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and EGDMA with molecular recognition to ibuprofen were developed using supercritical fluid technology [69]. After impregnation of the matrices with the drug using scCO₂-assisted impregnation, the polymers were evaluated as potential DDS in two different in vitro situations. In the first the polymers were allowed to release the drug over several days and in the second an oral administration situation was simulated and the polymers were subjected to different pHs and the drug release profiles studied for a period of 8 hours. The results show that MIP had an extraordinary ability to uptake the template drug during scCO₂-assisted impregnation, when compared with the NIP (33.1 wt% versus 10.2 wt%). Further, cytotoxicity experiments performed with Caco-2 cells revealed that the polymers are biocompatible and could therefore be used in biomedical applications. Fig. 3a shows the MIP particles synthesized in scCO₂ and Fig. 3b the proliferation and the adhesion of Caco-2 to the particles which shows its compatibility.

Furthermore, the affinity structures were able to maintain their selective recognition properties in aqueous environment. Water-compatible molecular recognition is a real challenge as traditionally MIPs present better performance in hydrophobic organic solvents. Supercritical CO₂ can provide a potential alternative to the synthesis of MIPs with good performance in biological fluids, crucial for in vivo applications.
Though we believe the use of supercritical fluid technology is very promising and challenging in the development of MIPs, there are of course still some limitations. An example is the development of molecularly imprinted contact soft lenses where transparency of the polymer is a required parameter. Typically polymers are obtained as amorphous white powders not in accordance with this specific requirement. However even in these cases supercritical fluid technology can be beneficial for instance in the impregnation of drugs into the lenses taking advantages of the high diffusivity of scCO₂ [93].

Very recently a MIP was developed for the first time using the semi-covalent approach using supercritical fluid technology [71]. Molecularly imprinted polymeric particles with molecular recognition towards bisphenol A (BPA) were synthesized using bisphenol A dimethacrylate, a monomer containing the template. Bisphenol A was then cleaved from the polymeric matrix by hydrolysis with tetrabutylammonium hydroxide (n-Bu₄OH) with scCO₂, taking advantage of its high diffusivity. Once again the MIP showed a good performance in aqueous solutions, due to the fact of CO₂ is an aprotic solvent, as explained above. This could open up a new possibility of molecular imprinting for drug molecules, which however needs the use of a template-containing molecule with polymerizable backbones. Still it could lead to a stricter control over the functional group location and uniform distribution binding sites, characteristic of covalent imprinting, and the reduced kinetic restriction during rebinding, characteristic of non-covalent imprinting approach.

Recently supercritical fluid technology has also been proposed as a viable alternative to prepare hybrid MIMs [70]. This methodology took advantage of the ability of scCO₂ to induce phase inversion of poly(methyl methacrylate), to prepare PMMA-based membrane with imprinted particles casted. Results showed that the immobilization of imprinted polymers by incorporation of MIPs into a casting solution for membrane production is a viable method to produce affinity membranes, which are able to be loaded with higher amounts of the template molecule than the non-imprinted membrane, even in dynamic conditions. This means that it is possible to confer molecular recognition to other types of structures and scaffolds by immobilizing MIP particles.

7. Final remarks

The continuous advances in materials science, in particular in the development of smart targeted DDS and materials with molecular recognition will for sure bring important progresses in biomaterials applications. The development of molecularly imprinted polymers as drug delivery systems although in an emerging stage, has already shown its high potential. The affinity to the target molecules, introduced by molecular imprinting, provides polymers with the ability to load higher amounts of the template molecule, compared to the non-imprinted polymers, either in aqueous solutions or in supercritical environment. In addition in vitro drug delivery experiments revealed that the macromemory effect yields polymeric DDSs able to release the drug in a more sustained way. Additional degrees of control in drug release can be introduced by tuning the MIP composition for instance with stimulus-responsive polymers. Furthermore the immobilization of imprinted
Polymerization of particles within porous structures, such as membranes, seems to be a feasible option for the preparation of affinity devices with potential application as DDS.

Supercritical fluid technology is a very promising way to prepare MIPs. While it provides a clean route for the synthesis, since it avoids the use of organic solvents and multistep processes, it can also bring high control over the morphology of the polymers. We believe that this technology has still much to offer to molecular imprinting and that the combination of both technologies is a good synergy to design new materials and structures with a high purity level and tunable molecular recognition, with the needed requirements for biomedical and pharmaceutical applications.

Author details
Mara Soares da Silva and Teresa Casimiro*
REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, FCT, Universidade Nova de Lisboa, Caparica, Portugal

Acknowledgement
The authors would like to thank Fundação para a Ciência e Tecnologia (FCT-Lisbon) for financial support through project PTDC/QUIQUI/102460/2008 and contract PEst-C/EQB/LA0006/2011.

8. References

* Corresponding Author


[58] Reverchon E, Cardesa S. Production of controlled polymeric foams by supercritical CO2. J. Supercrit. Fluids. 2007; 40(1): 144-152.
[71] Soares da Silva M, Viveiros R, Aguiar-Ricardo A, Bonifácio V, Casimiro T. Novel supercritical CO2-based strategy to prepare semi-covalent molecularly imprinted...


