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Biomimetic Block Copolymer Membranes

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Abstract: In this article, we review the recent advances in the field of block copolymer membranes. We discuss the similarities and differences between natural membranes and their polymeric counterparts, pointing out the advantages of the latter in applications for biosciences and biomaterials. Membrane properties are discussed in terms of functionality and responsiveness, and the most interesting application possibilities are highlighted.

Keywords: Amphiphilic block copolymers · Biomimetic membranes · Nanocontainers · Nanoreactors

1. Introduction

Membranes are a ubiquitous building component of living organisms. They separate (compartmentalize) and protect cells and cell organelles from their environment, support their vital functions, such as water-, ion- and nutrient transport, and maintain cell integrity by the control of osmotic pressure inside and outside the membrane-enclosed space. Additionally, they are a platform for electron- and proton transfer, essential for cell metabolism. Even more, functions such as cell transportation can be also related to the presence of a membrane, as the flagellum motor is entirely anchored to a double lipid bilayer and so far has not been proven to be active otherwise.

With these selected examples, it is not surprising that the natural sciences are taking a closer look at membrane behavior; a task which is far from trivial. A cell membrane is a uniquely complicated assembly of lipids, sterols, sugars and proteins, and the delicate balance and cooperation of these components assures proper function. Such a system is virtually impossible to reproduce in the laboratory, and even if it were, it would not be scientifically too instructive, as it would be difficult to assign particular functions or processes to individual membrane components.

On the other hand, certain membrane structure details and many functions are known. Models of lipid membranes have been extensively studied, and information is available on self-assembly principles responsible for a bilayer formation,[1–3] interactions between lipids,[4] sterols[5] and membrane proteins.[6] Much interest has been focused on membrane proteins, both in the context of the self-assembly to function relationship, as well as structural details.[7]

The above considerations also apply to membranes from macromolecules, which, although not encountered in nature, have been shown to mimic biomembranes,[8] and to outperform lipid bilayers in some cases.[9] As materials science has made enormous progress recently, it is not surprising that such membranes attract considerable attention. In this article, we will discuss properties of polymeric membranes and specific applications that open a broader perspective for nanotechnology and biomedical sciences.

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2. Membrane Models

We will discuss membrane properties in Section 4 so let us first briefly review the experimentally available models. Membrane models are always simplifications of the living cell membranes, nevertheless, they allow the discrimination of membrane-related processes with respect to the building components.

One of the most frequently studied self-organized structures from lipids, low molecular-mass surfactants and macromolecular amphiphiles are micelles, a very rough approximation of a bilayer structure. Spherical micelles are particularly convenient for investigating solubilization of hydrophobic molecules,[10] and may be relevant for example when looking at micelle diffusion by correlation spectroscopy after a hydrophobic dye has been trapped within the core.[11] They also find applications in the delivery of hydrophobic drugs.[12] Additionally, reports on successful protein shielding by solubilization in micelles have been published.[13]

The disadvantage of a micellar structure when studying membrane mimics is that the 'bilayer' is not hydrated from two sides – in this respect a vesicle comes closer to what occurs in nature: in fact, lipid vesicles do appear in cells. Owing to their structure, vesicles can be applied as transport vehicles for hydrophilic substances[14] or serve as shielding capsules for delicate entities as enzymes to protect them from the environmental stress.[15] Liposomes (lipid vesicles) are commercially used in pharmacy for delivery of toxic drugs such as chemotherapeutics and antibiotics,[16,17] to minimize side effects by slow release.

Apart from spherical models, planar membranes attract much attention: zero curvature is almost what is observed in cells, a valid approximation if small membrane areas are investigated. The disadvantage is that planar membranes are in most cases asymmetric: freely swimming lamellae in solution are difficult to obtain, as they would curve to closed spheres to minimize

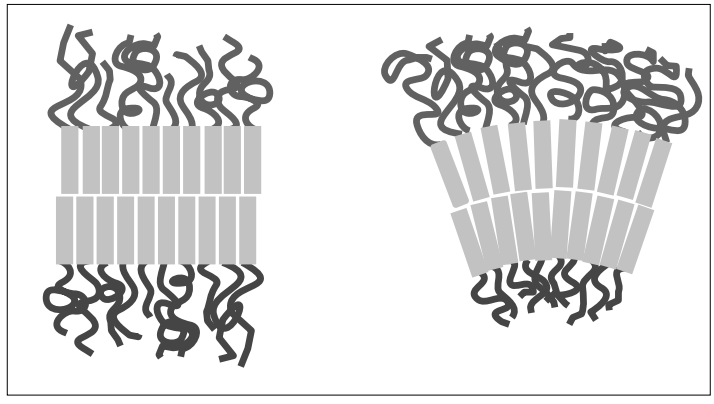

Fig. 1. Chain packing in a planar and curved polymer membrane. Membrane curvature is stabilized by segregation of long and short hydrophilic chains.

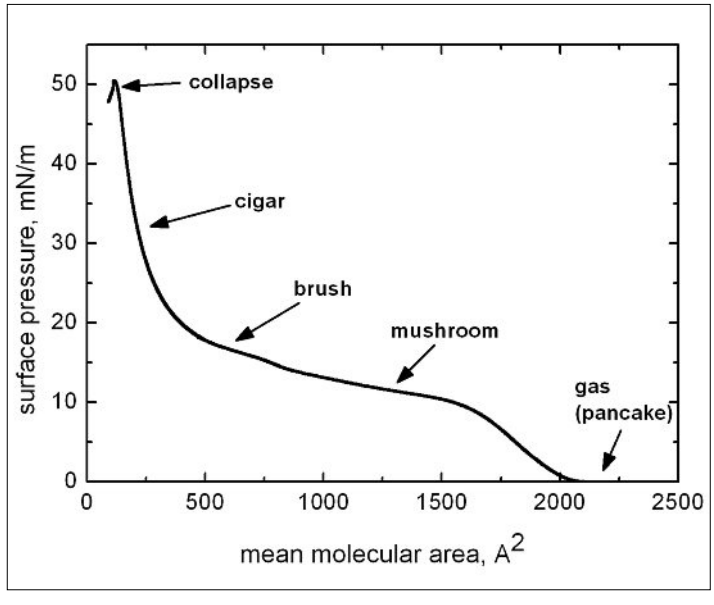

Fig. 2. Surface pressure-mean molecular area isotherm from an ABA triblock copolymer. Nomenclature of polymer phases from ref. [28].

the interfacial energy.[18] Apart from free-standing 'black lipid membranes',[19] the planar self-assemblies are either Langmuir monolayers at the air-water interface,[20] or supported films on solid substrates.[4] In both cases, the environmental asymmetry facilitates membrane formation. With planar membranes, it is possible, for example to study component interactions, energetics of protein insertion, influence of drugs or amphiphile diffusion in two dimensions. Solid supported membranes can also be seen as a perspective platform for sensors[21] or templates for inorganics growth.[22]

3. Membranes from Block Copolymers

Membrane science includes various aspects, from physical chemistry of self-assembled systems, through biological and pharmaceutical applications, to nanoscience and membrane engineering. In our group, the main interest is focused on membranes formed from amphiphilic macromolecules, and in particular from amphiphilic block copolymers. Their underlying principles are essentially the same as for natural membranes, as are the stabilizing factors, such as double layer electrostatics, steric interactions or membrane curvature for vesicles. On the other hand, the 'macromolecular' factors add an energetic contribution in the form of strong hydration, and thus repulsion of large hydrophilic chains,[23] and additionally the entropy of the hydrophobic coil. Altogether, it can be argued that polymer vesicles are actually thermodynamically stable structures,[24,25] whereas liposomes are not.[3]

When discussing polymer membranes for biosciences, the first argument is the membrane composition (chemistry). Polymer membranes are built from synthetic amphiphilic macromolecules, which automatically bring at least two new parameters to the membrane properties, uncommon to lipid membranes. The first one is polydispersity, an intrinsic property of every polymer sample. It may be seen unfavorable when one wants to work with well-defined systems, but on the other hand it adds the possibility of chain segregation, especially when species with non-matching thicknesses are inserted in the membrane.[26] Additionally, vesicle curvature is stabilized by the segregation of shorter hydrophilic chains towards the inside of the vesicle, while longer chains will tend to point outwards (Fig. 1).[27]

The second feature is flexibility of polymer chains: compared to lipids, polymers – due to their size – have many possibilities of conformational arrangements when confined to the membrane. In particular, during compression of Langmuir monolayers, broad transition plateaus are observed in between defined two-dimensional phases, owing to slow polymer dynamics and conformational rearrangements (Fig. 2).[28] In consequence, we can obtain various packing states; an advantage over lipid monolayers, where only discrete states are available.

Polydispersity and flexibility make polymers unique membrane-forming materials, however, for life sciences, biocompatibility is essential. Introduction of a polymer into a living organism may have unfavorable effects, but here chemistry turns out to be actually a very powerful tool. There are many biocompatible polymers known, *e.g.* polyethyleneoxide, polyesters, polypeptides,[29] and combinations of such blocks into amphiphilic molecules is possible. What is more, we are able to choose between blocks of different hydrophilic/hydrophobic properties and fluidity, to construct specific polymers for particular needs. Contrary to lipids, polymer chemistry permits various chemical modifications to introduce functionality and make polymers responsive to environmental stimuli including pH, temperature, ions, light, *etc.* On top of that, thus obtained synthetic polymers form membranes of excellent stability and long shelf-life, where we do not encounter the common problem of lipid oxidation leading to liposome destabilization in solution.

Another important issue is the membrane thickness: if membrane proteins are to be inserted in such a self-assembled structure, its thickness should be similar to that of lipid bilayers. In polymer systems, membrane thickness depends on the polymer size and the ratio between its hydrophilic and hydrophobic block(s),[30] dimensions from 3 up to 40 nm are achievable.[31,32] With respect to the membrane protein insertion, it was shown to be possible with membranes thicker than a lipid bilayer, due to the fact that shorter polymer chains would surround the protein, and their flexibility allows the

protein dimensions to be matched and the hydrophobic interactions in the membrane to be maximized.[26]

4. Responsive Polymer Membranes

The self-assembly processes leading to polymer membranes (vesicles) have been reviewed,[33–35] and so were the characterization methods for polymersomes and membrane characteristics.[36] Here, we will focus on properties that make polymer membranes extremely interesting with respect to their possible applications.

In biosciences, responsiveness to external stimuli is a crucial factor, especially in drug release and construction of biomaterials. For example, poly(N-(3-aminopropyl) methacrylamide hydrochloride)-*block*-(N-isopropylacrylamide), a thermoresponsive block copolymer, produces vesicles only above a critical temperature.[37] The aggregation to vesicles with a hydrodynamic radius of *ca.* 150 nm is sharp and occurs within 1–2 °C, while the transition temperature itself can be adjusted by a block size change. Polymers containing crystalline blocks, *e.g.* polyesters, can be forced to produce vesicular membranes at higher temperature: heating the sample leads to the hydrophobic block melting, and then amphiphilic segregation takes place to produce vesicles.[38] After the system is cooled down, the aggregates are 'trapped' owing to the membrane crystallinity, and remain stable in solution.

Charged polymers are often exploited to produce pH-sensitive membranes: here, polypeptide blocks seem promising, especially those containing poly(glutamic acid) or polylysine.[39] The hydrodynamic radius of polybutadiene-based vesicles with poly(glutamic acid) corona was found to depend on the pH and salt concentration in solution.[40] The permeability and release properties were not studied; however, as the repulsion in corona blocks stabilizes the vesicle curvature, one could expect pH-dependent changes in long-term membrane stability, which could promote this system to a controlled release platform.

A family of propylene sulfide block copolymers was found to build oxidation responsive vesicles,[41,42] which can be employed for drug delivery in sites of increased oxidative stress, such as due to inflammation. The possibility of controlled disintegration of vesicles is a consequence of the change in hydrophilic/hydrophobic balance upon oxidation.

Tong *et al.*[43] reported light-responsive vesicles from an azobenzene-based block copolymer. These structures reversibly disintegrate when exposed to UV light (360 nm) due to conformational changes in the azobenzene, which disturb the hydrophilic-to-hydrophobic balance and thus the self-assembly process. Interestingly, they can be rebuilt after illumination with visible light (440 nm). This is one of the few examples of photosensitive membranes, the main difficulty here lying in the synthesis of the appropriate polymers.

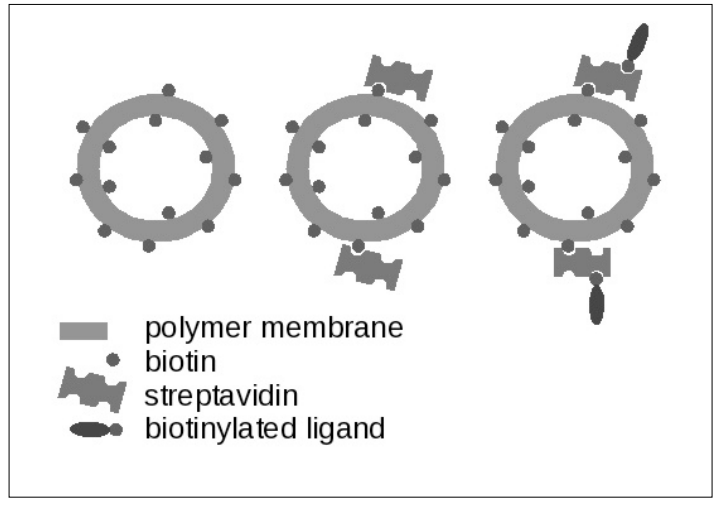

Fig. 3. A schematic representation of a nanoreactor-based therapeutic platform employing the biotin–avidin interactions

5. Polymer Membranes – Applications

5.1. *Therapeutic Applications*

Almost every scientific report on polymer vesicles nowadays will mention 'drug delivery' somewhere in the text. As promising as it may sound, only a few real drug delivery studies have emerged where polymersomes were used.[44,45] A beautiful example of a combined delivery platform comes from Discher's labs.[46] The authors took on board the well-known and toxic chemotherapeutic drugs, taxol and doxorubicin. Both bring unpleasant side effects, and therefore it was desirable to devise new formulations to better control the drug release and minimize the undesired toxicity.[47] The concept involves using poly-ethyleneoxide-poly-(lactic acid) block copolymer vesicles, where doxorubicin is encapsulated in the hollow sphere, while taxol inserts in the polymer membrane. Such two-in-one formulations decreased the size of breast cancer tumors in mice considerably and performed better than free drugs.

In our group, poly(methyloxazoline)-poly(dimethylsiloxane)-poly(methyloxazoline) triblock amphiphilic copolymers were used for drug targeting and delivery. The targeting strategy[48] involved biotin–streptavidin interactions:[49] biotinylated polymers formed vesicles, next avidin was added to attach to the outside of the vesicles, and in the following step biotinylated ligands, poly(guanylic acid) sequences, were bound to the avidin's free sites (Fig. 3).

The ligand was intended to specifically interact with a cell receptor, in this case scavenger receptor A1, present in macrophages responsible for cardiovascular disorders. Microscopy studies revealed very good co-localization of receptors and ligands, while no such effect was observed with control cells, which did not possess the A1 receptor.

The first step of bringing a nanocontainer to a place where it should release a drug was successful, and the question of what happens to the vesicles afterwards was addressed by Meier's and Hunziker's groups in Basel.[50] The biotin–avidin platform described above was used, but this time the vesicles were loaded with a quenching concentration of calcein. Again, the vesicles preferred to attach to macrophages and showed no targeting of control cells. They were observed to actually enter the cells, most likely by endocytosis. After some time, calcein was released, which could be observed by fluorescence microscopy. The mechanisms behind the cell entry and release processes are to be fully understood, however, from the practical point of view the platform offers the possibility to target various cell receptors once appropriate ligands are attached to the vesicles. Another aspect which needs to be considered here is metabolism and accumulation of the used polymers, which is unknown. Nevertheless, once the targeting platform is demonstrated, even with a completely biologically incompatible system, the concept can be easily translated to different, biocompatible polymers.

Another possibility for a therapeutic application of polymer vesicles has been presented recently.[51] Superoxide dismutase, an antioxidant enzyme, was encapsulated in the vesicular cavity and shown to remain

functional in neutralizing superoxide radicals *in situ*. The polymer membranes were proven permeable to superoxide radicals by pulse radiolysis, and the encapsulation of the enzyme prolongs its lifetime, which is only minutes in the bloodstream when non-shielded.

The use of polymer vesicles as artificial oxygen carriers was demonstrated.[52] Compared to liposomes and PEG-ylated liposomes, polymeric carriers had higher capacity for encapsulation of hemoglobin, and thus for oxygen binding. Another advantage of such an oxygen-delivery system is that, unlike lipids, polymers did not induce hemoglobin oxidation.

5.2. *Nanoreactors*

The use of proteins in combination with polymers leads to a new class of biomaterials of potential use in nanotechnology as nanoreactors, nanomachines *etc.*, but also in membrane engineering. Of the many membrane proteins, the most interesting are transporters (active and passive) and enzymes. It was shown that many membrane proteins can be inserted in polymer membranes and remain functional in such an artificial environment;[53–55] experimental data being additionally supported by theoretical considerations.[26]

Two membrane proteins were used in polymer vesicles for ATP production. In this very sophisticated system, bacteriorhodopsin inserted in the polymer membranes pumped protons from the outside to the inside of vesicles when illuminated by light.[56] Next, these protons turned on the ATP-ase, which had also been inserted in the membrane, and when ADP was present, ATP production could be monitored in solution.[57] The above demonstration of a nanomachine can be viewed as a step towards clean energy from protons and light, even if it is a very far perspective from the practical point of view due to its low efficiency in its present form. From the academic point of view, such platforms are excellent model systems for the understanding of protein function, as in the case of ATP-ase.

Different types of nanoreactors (Fig. 4) were prepared using a bacterial pore, OmpF (outer membrane protein F) as a channel for substrates and product of enzymatic reactions taking place within the vesicles.[58,59] Additionally, if the enzyme or the channel protein is pH-dependent, switchable nanoreactors can be produced by changing the conditions in solution.

Cascade reactions in nanovesicles were investigated by Vriezema *et al.*[60] A multistep reaction was sequentially catalyzed by three enzymes: glucose oxidase encapsulated in vesicular cavities, horseradish peroxidase inserted in polymer membranes and *Candida antarctica* lipase B in the outside medium. The reaction turnover was dependent on the positional assembly of the enzymes; removal of any enzyme from the system disturbed the cascade and no product could be obtained.

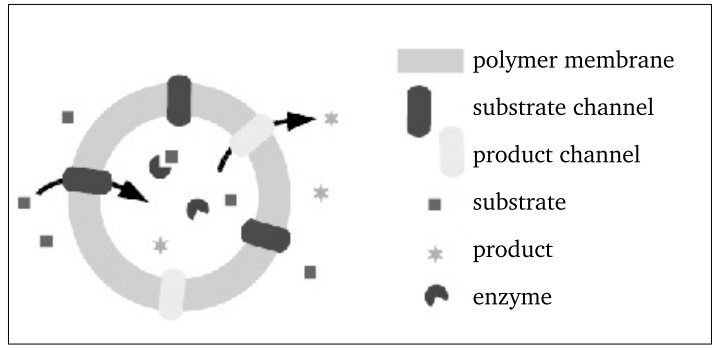

Fig. 4. A schematic representation of a nanoreactor

5.3. *Polymer Membranes for Bio-mineralization*

Bio-inorganics play an important role not only in building teeth and bones, but also find relatively exotic applications such as in the magnetic 'navigation' systems of some bacteria.[61] Templating bio-inorganics *in vitro* is motivated by two factors. Firstly, medical applications are in focus: we want to understand and hopefully mimic the growth of bone minerals with the goal of being able to construct bone replacements. Not surprisingly, self-assembling synthetic polymers are under investigation as scaffolds, as their properties offer new possibilities for controlled inorganic processing.[62]

On the other hand, we wish to take advantage of nature's solutions and implement them in fields such as complex materials or medical imaging. As an example, the aforementioned magnetic particles found in bacteria to navigate them against the Earth's magnetic field, also find applications in medical imaging for detection of liver cancer.[63]

Many studies on calcium phosphate concentrate on templating the growth of this inorganic by various scaffolds.[64] Many particle morphologies can be obtained, depending on the growth conditions and the scaffold chemistry.[65] The understanding of how the particle growth can be optimized is crucial when we do not have at hand all the regulatory mechanisms present in living cells/organisms. So far, many polymeric scaffolds were used for inorganic templating,[66] and very interesting shapes were obtained.[67]

Polymer vesicles were used to achieve spatial control over the mineralization process.[68] Alamethicin, an ion channel peptide inserted in a vesicle membrane, enabled cation (calcium) transport, when phosphate buffer was present inside the vesicles. After a certain incubation time, calcium phosphate crystals were seen inside the vesicles, while no crystallization occurred in the outside medium.

Planar polymer films were recently mineralized with calcium phosphate.[65] By application of the Langmuir monolayer technique, we managed to control the particle growth by manipulating the polymer film properties at the air–water interface, *i.e.* surface pressure, or the degree of packing in two dimensions, and the subphase parameters such as pH and ion strength. With small changes in the growth conditions, we achieved various particle shapes and dimensions: such results are indeed very motivating for further studies towards other templated inorganics using synthetic polymers.

5.4. *Planar Polymer Membranes*

Planar polymer films, either free-standing or at interfaces, are of particular interest; not only are they preferred in many applications, but also allow surface studies which could not be performed on vesicles. Therefore, by combining the investigations of vesicles with those on planar membranes we achieve a more complete picture of membrane self assembly. We have mentioned Langmuir film mineralization, and would like to highlight here other advantages of planar membranes.

Langmuir monolayers from a vesicle-forming amphiphilic triblock copolymer were studied to aid understanding of the polymer interactions with a cation transporting peptide, alamethicin.[28] In lipid bilayers, this amphiphilic helical peptide aggregates to form channels,[69] and thus alters the bilayer properties. Since we found the peptide functional also in polymeric membranes,[68] thermodynamics of interactions in such a composite system was studied, and the results revealed that as long as the aggregation state may be postulated to be similar in both lipid and polymer environments, as visualized by Brewster angle microscopy, the excess mixing energy is lower in polymer films.[28] Interestingly, longer polymers tend to minimize this energy even more. Those results mean that energetically the peptide prefers to be present in films from synthetic polymers, and are explained

by conformational freedom of the soft polymer compared to the relatively rigid lipid molecules, allowing for the optimum packing of the polymer chains in the immediate surrounding of the peptide channels. This fact explains again why many membrane proteins remain functional in polymeric membranes.

Another very interesting aspect was the investigation of the 2D mechanical properties of polymer–peptide films: apparently, by appropriate proportion of the two components the film rigidity and compressibility can be fine-tuned and phases with new properties can be obtained. This fact is of fundamental importance in hybrid material science, where novel features are often sought by a combination of synthetic polymers with biologically active molecules.

In environmental engineering, a crucial problem is the supply of drinking water, which is often produced from sea water by osmosis using desalination membranes.[70] For this purpose, polymer membranes with embedded water transporting proteins, aquaporins, could be used (Fig. 5).

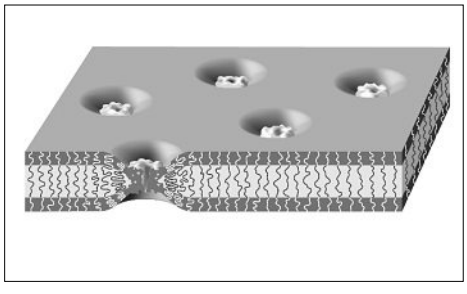

Fig. 5. A scheme of a protein-reconstituted polymer membrane

It was recently demonstrated that permeability of polymer–protein membranes are at least an order of magnitude higher than what can be achieved by commercial desalination membranes.[71] This effect is only observed when aquaporin is used; purely polymeric vesicles have very poor water permeability.

Planar solid-supported block copolymer membranes would not only be interesting for engineering applications, but also for protein insertion in order to study membrane transport or diffusion. So far, concerning organized amphiphilic membranes on solid surfaces, grafted films were produced from poly(butyl methacrylate)-*co*-poly(2,2-dimethylaminoethyl methacrylate).[72] Using the same positively charged polymer, the first planar solid-supported block copolymer films were achieved by vesicle fusion on negatively charged surfaces like mica and silicon oxide.[73] On the other hand, it was shown that tethered lipid membranes can functionally accommodate membrane proteins.[74] Even though the exact protocols from physical chemistry of lipids cannot be always translated to polymers, the concept itself could be employed for applications such as sensor development, given the stability and robustness of the polymer self-organized film. The sensed molecules could be either odorant species, or physiologically relevant ligands.

6. Summary

In summary, we have presented an overview of recent scientific activities in the field of polymer membranes. Whether spherical or planar, they turn out to be excellently suited as biomembrane mimics and enable basic studies and applications at the nanoscale. Self-assembly processes governing the membrane formation can be taken advantage of in order to create submicrometer structures by subtle changes in parameters such as polymer size, block ratio, polydispersity *etc.* Experimental conditions, such as solvent addition, pH and temperature also influence the resulting structures. These factors combined together allow to engineer systems for chemical reactions at the nanoscale, therapeutic applications or inorganic templating.

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