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CHAPTER 15

Functional Membranes Based on Amphiphilic Polymer Conetworks

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Abstract

This chapter will present amphiphilic polymer conetworks fabricated as functional membranes and will illustrate related applications. First, the structural features of amphiphilic polymer conetworks rendering them ideal membrane materials will be described. Applications as membranes with a functional performance that is directly based on these structural features are presented. Next, the preparation of conetwork membranes based on stimuli-responsive polymers and their potential for smart membrane systems are detailed. Finally, the functionalization of conetwork membranes with stimuli-responsive units such as organic photochromes and applications as light- or even multi stimuli-responsive drug delivery membranes are described.

15.1 Structural Features of APCN Membranes

Membranes are structures that separate two environments and control the permeation of components from one into the other.[1-3] This control may be employed for the separation of different components from a mixture, by selectively allowing the permeation of some but retarding or prohibiting permeation of other components. A membrane might also be employed to moderate the permeation of components, for example, to release species from a depot at a defined rate. The mechanisms by which membranes control permeation are typically based on the membranes architecture and composition relative to the size, shape and chemical properties of the feed components (Figure 15.1A). Membrane research and development has afforded a wide range of membranes with very different separation properties based on different architectures and different materials. The efficiency and control that has been achieved for many membrane processes has resulted in a rapidly increasing number of industrial applications, ranging from large scale desalination plants and membrane bioreactors to artificial kidneys for blood dialysis. Besides a classification by their actual application, membranes can be classified by the size range in which they operate, from microfiltration down to nanofiltration and reverse osmosis. They can also be classified by the materials they are composed of, most often polymers but also metals, ceramics or composites thereof, and, finally, they can be classified by their internal architecture.

[Figure 15.1 near here]

A very rough categorization of membrane types based on their internal structure is shown in Figure 15.1A. Although membranes often possess complex multi-layered structures, only the layer that provides the actual separation properties will be discussed here. In porous membranes, the pore's dimension and surface chemistry control the passage of species depending on their sizes and chemical properties (pore-flow model). Non-porous membranes, which possess a homogeneous bulk composition, can be further divided into dense membranes and gel membranes. Dense membranes typically do not swell strongly in the feed solution.[4] They

require the feed components to permeate through their molecular structure by a solution-diffusion process that heavily depends on free volume and chain mobility of the polymer material. The permeants dissolve in the membrane material and are then transported through them by diffusion down a concentration gradient (solution-diffusion model). Gel membranes and hydrogel membranes are polymer networks that swell in the solvent of the feed solution. The gel network forms a mesh that excludes or retards larger species depending on its pore size. Accordingly, the network structure, in particular the degree of crosslinking and the degree of swelling, strongly influences its permeability.[5-7] Furthermore, the permeation of feed components depends strongly on the interaction between membrane, solvent and permeants.[8] Due to contributions of these different factors, permeation of components through hydrogel membranes is highly complex and is even further complicated by the often broad distribution of the mesh sizes within typical hydrogel networks.[9] Different theoretical models for permeation through hydrogel membranes have been developed, however, despite their undisputable success they are typically limited in the range of hydrogels that they can accurately describe and, therefore, need to be treated carefully.[10, 11]

Amphiphilic polymer conetworks (APCNs) are closely related to gels and hydrogels in that they possess a macroscopically non-porous structure and that permeation through them is governed by diffusion processes, however, they differ fundamentally when investigated more closely.[12-14] They are composed of two polymer components, one hydrophilic and one hydrophobic, with a nanophase-separated morphology in which the domains of each polymer phase form an interconnected structure. Macroscopic phase separation is prevented by covalent links in between the immiscible polymer segments, an aspect which also distinguishes APCNs from interpenetrating polymer networks (IPNs). APCNs present a unique set of properties that does not only stem from the sum of the individual components but also from their synergistic interaction and from the phase morphology. For example, the ability of the two components to swell either in hydrophilic or hydrophobic solvents is preserved in the APCN due to the interconnected phase domains (Figure 15.1B). Accordingly, different species of opposite polarity can permeate the APCN through the two phases. This is not limited to just hydrophobic and hydrophilic solutes. One of the phases can also provide gas permeability. The synergistic

interaction of the two APCN components manifests itself, for example, in the mechanical properties of APCNs. The mechanical properties of conventional hydrogels are governed by the bulk phase. In APCNs, on the other hand, another phase exists that does not swell under the same conditions and is, therefore, not weakened by solvent uptake. It only stretches to accommodate the expansion of the other phase. Therefore, the swelling behavior of one phase is not only controlled by the degree of crosslinking and the swellability of the polymer, as in conventional hydrogels, but also by the properties of the polymer of the other phase. Accordingly, the two phases can be described as mutually reinforcing each other. For example, a hydrophilic polymer that is normally rigid and brittle in the dry state can be combined with a rubbery hydrophobic phase in an APCN structure to gain overall flexibility. On the other hand, a hydrogel phase with weak mechanical properties may gain improved mechanical strength due to a sturdier reinforcing hydrophobic phase, which is not compromised in its mechanical properties by the plasticizing effect of water. Another fundamental property of APCNs, their optical transparency, is an excellent example for a property which is directly derived from the nanophase-separated morphology and which is independent of the types of polymers used as the hydrophilic and hydrophobic components. The size of the phase domains in the nanometer range is small enough to avoid the scattering of visible light. Another such property is the large interfacial area between the two phases. Species that dissolve in one phase can get close enough contact with species that are restricted to the other phase to enable reactions, for example between water-soluble enzymes and organo-soluble substrates.

One of the biggest benefits of APCNs is that they afford many synthetic handles that can be used to control and adjust their properties for any specific application. Yet the central synthesis challenge, the combination of immiscible components without macrophase separation, is closely related. To understand both it will be beneficial to shortly discuss the synthesis and fabrication of APCNs. Three main synthesis approaches can be distinguished that solve the immiscibility challenge in different ways.[14] For the first one (macromonomer approach), small hydrophilic monomers are copolymerized with hydrophobic macromonomer crosslinkers, or vice versa (Figure 15.2A). Their compatibility is typically ensured either by the use of amphiphilic solvents

or hydrophobic protecting groups for hydrophilic monomers. The macromonomer approach can be considered the historically most employed strategy. For the second approach, preformed polymer segments, with architectures ranging from simple to highly complex, are crosslinked in an amphiphilic solvent to afford the APCN structure (Figure 15.2B). Finally, the third approach is based on the sequential living polymerization of blockcopolymers which are subsequently crosslinked in a last step by the addition of crosslinkers, with all steps occurring typically in the same pot (Figure 15.2C). All these described approaches can provide an excellent control over the APCNs' structure and properties by the careful selection of the type and ratio of the components. For example, the hydrophilic phase may be comprised of an aprotic polymer, such as poly(ethylene glycol) (PEG), or a protic polymer, such as poly(2-hydroxyethyl methacrylate) (PHEMA). The ratio between the hydrophilic and hydrophobic phases can be adjusted to afford the desired swelling and permeation properties. Furthermore, the crosslinking density can be adjusted even without changing the composition of the APCN by variation of the chain lengths in the polymer blocks, or by addition of small molecule crosslinkers. Whereas the macromonomer approach can only provide defined molecular weights for the macromonomer component, the second and third approaches allow the creation of more defined APCN structures, when highly defined polymer precursors are employed. However, the covalent bonds of the network typically do not allow the formation of a long range order that is found with self-assembled blockcopolymers. To summarize, despite the miscibility challenge, the development of different approaches has enabled the synthesis of a wide range of APCNs with well-designed properties. All approaches, however, are more laborsome than the synthesis of most conventional hydrogels. Most approaches are typically also limited in the possible types of polymer or may require the use of large amounts of amphiphilic solvents.

[Figure 15.2 near here]

With their complex and often challenging fabrication, applications for APCNs are best found where their functional behavior and unique set of properties is essential for the required membrane performance. In the

next section, it will be discussed how the special properties of APCNs can be employed in functional membranes and for membrane-related applications. The third section will discuss how the functional behavior of APCN membranes can be further expanded by employing stimuli-responsive polymers for their fabrication. Finally, the last section will discuss how the introduction of functional groups, such as organic photochromes, can add further levels of functionality to APCNs in membrane applications.

15.2 Applications of APCNs as Functional Membranes

15.2.1 Biomedical Applications

The most striking example for an application that specifically requires an APCN structure is presented by extended wear contact lenses based on silicone hydrogels, which also represent the only industrial application of APCNs (see also **Chapter 12**). A contact lens (CL) can be defined as a *clear, transparent shell-like optical appliance that is placed on the front of the eye to correct errors of refraction of the eye*.[15] While, historically, rigid and not water-swellable materials such as poly(methyl methacrylate) (PMMA) have been employed (**Chapter 12**), only the development of soft hydrogel CLs has led to their massive commercial success and today's widespread use of CLs. The development of silicone hydrogel CLs was prompted by the discovery of a serious limitation of hydrogel CLs for extended wear applications, *i.e.* continuous day and night use over several days.[15-17] Their limited oxygen permeability depletes the cornea of oxygen, resulting in hypoxia and, ultimately, in damage to the eye. Oxygen permeability is typically expressed by the oxygen permeability coefficient *Dk* with the unit barrer. Since the oxygen permeability of the water in a hydrogel is much higher than the polymer component, a higher *Dk* of soft CLs can be achieved by high equilibrium water contents (EWC), but also with a reduction of the lens' thickness. However, the former approach is limited by the oxygen permeability of pure water (80 barrer), which is still below the requirement for extended wear that was reported between 87 and up to 125 barrer for a CL of only 100 µm thickness (Figure 15.3A).[18, 19] The latter approach is limited by the decreasing mechanical strength of very thin lenses. In the search for soft CL materials with high oxygen permeability, silicone quickly became a promising candidate due to its extremely high oxygen permeability of about 600 barrer, which far exceeds the requirement for extended wear. However, silicone rubbers are highly hydrophobic and non-wettable. While surface treatments can change surface wettability, a CL must also be permeable for water and ions, which is a necessity for on-eye movement and comfortable use without adverse effect and requires water uptake throughout the lens. To summarize, an extended wear CL must possess silicone-like oxygen permeability but also the wettability and ion permeability

of a conventional hydrogel. Therefore, it must possess properties of two materials on opposite sides of the hydrophilicity spectrum combined with, of course, optical transparency. Clearly, these demands could be perfectly matched by APCNs that combine a silicone phase for oxygen transport with a continuous hydrogel phase for water and ion transport. The necessity of an APCN character for an ideal silicone hydrogel CL has been emphasized by Nicholson and Vogt in their excellent review which appeared shortly after the first silicone hydrogel CLs entered the market and summarizes the lessons learned from their development.[16] They underlined the necessity of a biphasic structure and the importance of co-continuity of the two phases since a most efficient transport of ions and oxygen requires a high degree of percolation (Figure 15.3B).

[Figure 15.3 near here]

The development of silicone hydrogel CLs was faced by the challenges of APCN synthesis, but with the cost and simplicity demands of an industrial setting that does not permit, for example, the use of hydrophobic protecting groups. The requirement of high dimensional stability prohibits the excessive use of amphiphilic solvents. Due to these restrictions, commercialization took a long developmental process. While the first silicone hydrogel patent was issued already in 1977, the first silicone hydrogel CLs entered the market only in 1998. Unfortunately, there appears to be little overlap between the CL industry and APCN academic research, yet the solutions that were found by the silicone hydrogel CL industry could be of high interest for academic researchers and vice versa.

The incorporation of a silicone component into a hydrogel can, in principle, be achieved in two ways.[15, 16, 20, 21] The first one is the use of mono- or bi-functional silicone macromonomers that are copolymerized with hydrophilic monomers, *i.e.* the macromonomer approach for the synthesis of APCNs. This approach results most likely in a biphasic APCN structure, but it also poses the greatest synthetic challenge due to immiscibility of PDMS-based macromonomers with hydrophilic comonomers. This immiscibility is becoming increasingly problematic for longer macromonomer chains due to the general decrease of polymer solubility at higher

molecular weights. However, below a certain chain length of the silicone component, phase separation and domain percolation with the formation of a continuous network with high oxygen permeability is less likely.[22] Furthermore, macromonomer crosslinkers of lower molecular weight result in a high crosslinking density and, thereby, a higher modulus that has been linked to decreased comfort and adverse effects.[23] Much research activity has focused on the design of macromonomers with improved properties and better miscibility.[16] The second approach is the copolymerization of hydrophilic monomers with siloxane monomers that bear silicone-like side groups (Figure 15.4A). The most well-known example is the 3-[tris(trimethylsiloxy)silyl]propyl (TRIS) side group. TRIS-methacrylate was originally developed to enhance the oxygen permeability of rigid CLs based on PMMA. Miscibility of TRIS monomers with hydrophilic monomers such as HEMA, *N*-vinylpyrrolidone (NVP) or *N*,*N*-dimethylacrylamide (DMA) is less restricted for these monomers compared to long chain silicone macromonomers. However, the drawback of this approach is the lack of separate silicone chains due to the random copolymerization with the hydrophilic monomers that makes a well-defined biphasic structure much less likely. These monomers typically increase the oxygen permeability of the bulk phase at the expense of its hydrophilicity, resulting in reduced water uptake and surface wetting. Importantly, the oxygen permeability of a pure TRIS-based network (175 barrer) is also way below the oxygen permeability of a silicone network, *i.e.* TRIS-based strategies have an inherently lower ceiling of achievable oxygen permeabiltiy.[21] The development of silicone hydrogel CLs has typically seen a combination of both approaches, though with an increasing development of more APCN-like structures.

[Figure 15.4 near here]

Typically, three different generations of silicone hydrogel CLs on the market are distinguished.[16, 21, 24, 25] The first generation silicone hydrogel CLs made extensive use of TRIS-type monomers to overcome the miscibility challenges. Balafilcon A from Bausch and Lomb, one of the two first CLs on the market was based on a TRIS vinyl carbamate (Figure 15.4A). This monomer is more hydrophilic than its methacrylate analogue and was

combined with hydrophilic comonomers such as NVP. Accordingly, Balafilcon A did not possess a biphasic structure. The other 1st generation silicone hydrogel CL that entered the market almost at the same time was Lotrafilcon A from CIBA Vision, which has been characterized as truly biphasic. While also employing a TRIS-methacrylate monomer, it also contained poly(siloxane) macromonomers with perfluoropolyether segments to reduce their lipophilicity. Lotrafilcon A possessed an almost 50 % higher oxygen permeability than Balafilcon A, mostly because of its low EWC, but still possessed good ion permeability due to the continuous hydrophilic phase. Therefore, it can be described as the first APCN-type silicone hydrogel contract lens on the market. Nevertheless, both CLs fulfilled the demands of high oxygen permeability with sufficient water swellability and ion permeability. However, the extensive use of TRIS-type monomers had several practical drawbacks. The CLs were very hydrophobic and, for this reason, required surface treatments by plasma polymerization (Lotrafilcon A) or plasma oxidation (Balafilcon A). Furthermore, the low EWC resulted in a high modulus. Biphasic or not, an almost inverse linear relationship exist for these silicone hydrogel Cls between oxygen permeability and EWC. *i.e.* the more TRIS-type monomer, the lower the overall hydrophilicity and the EWC but the higher the modulus and the oxygen permeability (Figure 15.4B).[26]

To improve on the properties of the 1st generation, in particular the low EWC and the related comfort issues, a 2nd generation of silicone hydrogel CLs was developed.[21, 24, 25] This concept was still largely based on the use of small siloxane monomers. However, the oxygen permeability, the monomers were modified with additional polar groups to increase the EWC. The most well-known example is the "Tanaka monomer", named after its inventor Kyoichi Tanaka (Figure 15.4A),[27] which was further developed before its commercial use. Typically, Tanaka-type monomers were also combined with poly(siloxane) macromonomers. Another important development was the incorporation of free high molecular weight PNVP which sequesters on the lens' surface and strongly enhances its wettability, making additional surface treatments unnecessary. Interestingly, some recent studies indicate that silicone hydrogels with only TRIS or Tanaka type monomers as the hydrophobic component may still possess a certain degree of phase separation. [28, 29] A possible explanation could be an enrichment of the siloxane monomers in some polymer chains. Even co-continuity is

indicated by a rapid increase of oxygen permeability at a certain degree of incorporation that can be interpreted as a percolation limit. Overall, however, while 2nd generation silicone hydrogel CLs successfully increased the EWC and decreased the modulus, they still fell within the inverse linear relationship between EWC and oxygen permeability.

To finally break this inverse relationship and achieve silicone hydrogel CL materials with high oxygen permeability but also a high EWC and low moduli, a 3rd generation of silicone hydrogels was developed.[21, 24-26] No TRIS-type monomers were employed in these networks anymore, with poly(siloxane) macromonomers as the only source of silicone components. Furthermore, the inherent wettability of these CLs made the use of surface treatments or internal wetting agents obsolete. Little structural information has been released about the exact composition of these materials. However, based on previous silicone hydrogel CLs and the experiences in the APCN field, it is most likely that these new materials possess an optimized co-continuous biphasic structure. Thus excellent swelling properties and wettability of the hydrophilic phase could be achieved, which is not compromised by a large amount of TRIS-type comonomers. A silicone-based phase with larger molecular weight silicone blocks enables excellent oxygen transport without the necessity for oxygen to pass through the hydrophilic phase or a mixed phase with low or medium oxygen permeability. An idea on how the miscibility problems of monomer components of the earlier generations have been solved can be gained in the patent literature, which indicates a careful optimization of the macromonomer and the composition of the monomer mixtures to achieve compatibility. The following example from the patent literature illustrates the complexity of the composition of such networks.[30] The first component in this example is a high molecular weight poly(siloxane) macromonomer crosslinker with a M_n between 5 kDa and 25 kDa that bears a variety of functional units (Figure 15.4C). While the exact structure is not disclosed, possible elements are detailed and give some insight into the optimization process. Some of these units may be perfluorinated carbon chains and some bear additional trimethylsiloxy (TMS) groups. Most importantly, some of these groups bear hydrophilic grafts that are comprised of, for example, PEG chains, These modifications must achieve compatibility with the other components during the curing process and result in an optimized

phase morphology and oxygen permeability. The high molecular weight macromonomer crosslinkers are combined with mono-functional low molecular weight PDMS macromonomers and this combination is described as having highly beneficial effects on the lens' performance. As the hydrophilic comonomer, preferentially aprotic amide comonomers such as NVP and *N*-methyl-*N*-vinylacetamide are employed. Additional monomers such as isobornyl methacrylate and MMA adjust the hydrophilicity and mechanical properties, while small molecular weight crosslinkers can alter the mesh size and swelling behavior. Strikingly, no amphiphilic solvent was needed due to the excellent miscibility of the other components.

The development of silicone hydrogel CLs over the three generations highlights the superior properties of an APCN structure. Two different components can synergistically contribute to the overall transport properties of a material far beyond their simple combination in the bulk. It also highlights how the careful design of macromonomers and combinations thereof can achieve miscible monomer mixtures without the need for protecting groups or large amounts of amphiphilic solvents. Thereby, APCNs can be fabricated in industrially viable production processes.

The simultaneous permeation of oxygen and ions is not only of interest for extended wear CLs but also for other biomedical applications such as immunoisolation membranes. Type I diabetes requires the injection of insulin to compensate for the loss of the insulin-producing pancreatic β-cells due to an autoimmune reaction. Fine tuning of insulin delivery regimes and new methods of insulin delivery have resulted in a greatly improved life quality of diabetes patients. A new approach with a high potential for further improvement is based on implanted artificial pancreata containing β-cells from a donor.[31] These cells could sense the glucose level and give the proper insulin response. However, the body's immune response would quickly destruct the β-cells if antibodies and cells of the immune system can reach them. The protection by a membrane that allows diffusion of glucose, ions, insulin and other nutrients, but prohibits the contact to large proteins and cells could possibly solve this problem. The use of APCNs as immunoisolation membranes has been spearheaded by the Kennedy and Cakmak groups that have directed their research towards that goal since the early 2000s (see **Chapter 8**).[32-41] APCNs were found to possess great potential for this application due to their size selectivity

which stems from the mesh size of the polymer network and the dimensions of the nanochannels formed by the hydrophilic phase domains. This size selectivity can be adjusted to allow small molecules like glucose, and insulin, but also ions and nutrients to permeate through. At the same time, it poses an impassable barrier to large proteins, antibodies and cells. In addition, a continuous silicone-based phase allows fast diffusion of gases such as oxygen and CO_2.Kennedy and coworkers gauged the viability of an APCN-based approach using APCNs from poly(isobutylene) (PIB) macromonomers and hydrophilic comonomers. They found promising results for the permeation of glucose and insulin with retention of proteins such as albumin.[33-36] In order to improve the gas permeability, they developed a novel synthetic approach that is based on the crosslinking of hydrophilic PEG and hydrophobic PDMS segments. These materials were further developed with silane-based dual purpose chain extenders/crosslinkers that allow the combination of several blocks by hydrosilylation reaction before a final crosslinking by silanol condensation (Figure 15.5A). Such APCNs showed the typical properties of nanophase-separated APCNs with optical transparency, amphiphilic swelling behavior and excellent oxygen permeability. This interesting synthetic approach may result in well-defined phase morphologies. After finding oxidative degradation behavior of the PEG component, the synthetic approach was further developed and based on a combination of random copolymerization of DMA and PDMS macromonomers with a statistical mix of vinyl or methacrylate end groups. Macromonomers consisting of PDMA chains grafted onto PDMS were obtained and could subsequently be crosslinked into APCNs via hydrosilylation.[37-39] Further development of the same approach resulted in bimodal APCNs with both high and low molecular weight PDMS segments, which had greatly improved mechanical properties (Figure 15.5B).[40, 41] The material effectively retained IgG whereas insulin could permeate it.

[Figure 15.5 near here]

PDMS-based APCN membranes were also developed by Bruns, Tiller and coworkers.[42] They synthesized APCNs based on poly(2-hydroxyethyl acrylate) (PHEA) and PDMS via the macromonomer approach. These

PHEA-*l*-PDMS allowed hydrophobic molecules to pass when they were swollen in organic solvents, and hydrophilic molecules to permeate when the material was swollen in water. The permeability of the APCN membranes depended on the PDMS content. It increased for hydrophobic compounds and decreased for hydrophilic compounds with increasing PDMS content. These APCNs were not only employed as interfacial enzyme catalysis membranes,[43, 44] but also as drug delivery membranes (**Section 15.4**).

15.2.2 Other Applications

The applications of APCNs as functional membranes presented above were heavily reliant on the most unique feature of APCNs, the diffusion of different compounds through the co-continuous phases. However, the bi-phasic structure can also be employed to improve and control the mechanical properties and the permeation inside just one phase. An excellent example for the application of APCNs where the hydrophobic phase is mainly responsible for an improvement in the mechanical behavior can be found in the works of Tew and coworkers.[45-47] These authors were interested in the development of a PEG-based matrix for lithium ion salt loading to achieve a highly ion-conducting structure with good mechanical properties. By combining PEG with hydrophobic PDMS or poly(styrene) segments, conetworks were obtained that allowed a high salt loading with improved mechanical properties.

Pervaporation membranes have become one of the most important membrane applications in industrial processes because they enable the highly efficient separation of solvent mixtures with lower energy consumption than thermal processes, such as distillations.[48] A typical industrial application is the removal of water residues from ethanol solutions. Pervaporation membranes typically require a non-porous and mechanically stable membrane with affinity towards the solvent that is to be removed, for example cross-linked PVA for water removal. Du Prez and coworkers were the first to explore APCN-type networks as pervaporation membranes for the separation of water/ethanol mixtures.[49] They copolymerized hydrophilic poly(1,3-dioxolane) macromomoner crosslinkers with MMA into networks of different compositions. They reported homogeneous and mechanically stable networks with little or no phase separation in the dry state,

probably due to the limited difference in hydrophilicity between the two components. However, phase separation may take place at least upon swelling in protic solvent mixtures. The pervaporation properties of these membranes were highly dependent on the exact network compositions, with more tightly crosslinked and less swellable networks showing the best performance. In a follow up study, similar networks were prepared from PEG and different acrylates on top of a porous support that allowed the reduction of the network's thickness to just a few micrometers.[50] These membranes were used not only for pervaporation but also for nanofiltration due to their mechanical stability. Again, the authors found a strong influence of the network composition, its hydrophilic/hydrophobic ratio and degree of crosslinking on the permeation properties of the membranes. Moreover, the chemical nature and properties of the hydrophobic phase were also found to possess a profound influence on membrane performance.

Another example for an application of APCNs as membranes was demonstrated by Bruns and coworkers and is closely related to pervaporation membranes.[51] Breathable but waterproof membranes for weather protective clothing have taken a big role in the textile industry; however, they can be easily compromised if cracks or punctures allow liquid water to penetrate. The authors employed their APCN system based on PHEA-*l*-PDMS as coatings on commercial Sympatex membranes. The APCNs allowed water vapor to pass through and did not compromise the functionality of the Sympatex membrane. If the composite membrane was punctured, however, penetrating water swelled the APCN and, thereby, closed the gap even at elevated water pressures, resulting in an effective self-sealing membrane system (Figure 15.6). While conventional hydrogels could, in principle, show a similar behavior, the authors of the study consciously chose an APCN based system due to the excellent mechanical properties of APCNs that stem from the reinforcing PDMS phase and the ability to fine-tune the swelling and permeation properties of the membrane by adjusting the APCNs composition.

[Figure 15.6 near here]

15.3 Stimuli-Responsive Polymer-based APCNs for Functional Membranes

15.3.1 Stimuli-Responsive Polymer Membranes

We described in the last section how membranes based on APCNs can possess a unique functional behavior when compared to other nonporous membrane systems due to their nanophase separated structure consisting of two very different polymer phases. With the quickly expanding range of membrane applications, especially in the biomedical field, even more complex functional characteristics of membranes are desired. Smart membrane systems can change their selectivity or overall permeability depending on external stimuli. Such membranes either adapt to the properties of their environment, or, are controlled externally. Both possibilities greatly enhance their potential for separation processes and applications in sensors and drug delivery devices. Smart membranes have been the focus of intense research activity and a vast body of work exists both for porous and nonporous membranes.[52-55] Typically, smart membrane systems are based on stimuli-responsive polymers that rapidly change their properties, such as their polarity and conformation, under specific conditions. Stimuli include changes in temperature, pH, ionic strength, but also the presence of external magnetic or electric fields. A schematic depiction of the stimuli-responsive control mechanism for different smart membrane types are shown in Figure 15.7. For microporous membranes, the stimuli-responsive components are typically introduced as surface modifications that can change the pore's surface polarity and wettability. For nanoporous membranes, the pores are often filled with stimuli-responsive polymer brushes or hydrogels that obstruct the flux of components until their stimuli-responsive collapse opens up the pores. The opposite mechanism is also possible, when the stimuli-responsive change in polarity of a pore-filling hydrogel increases the diffusive flux of feed components. The latter mechanism also governs the permeation through hydrogel-based nonporous membranes, for which the stimuli-responsive polymer is typically incorporated in the bulk material. Stimuli-responsive increases in polarity or charge result in an increased mesh size due to swelling, thereby strongly changing the size selectivity as well as the flux through the membrane. APCNs represent a special case of the class of non-porous membrane systems with the possibility of a tailored swelling

behavior, mesh size and permeability of two different polymer phases. If either the hydrophilic or the hydrophobic phase of an APCN is composed of a stimuli-responsive polymer, the APCN membrane can obtain stimuli-responsive permeation properties. The creation of stimuli-responsive APCNs has been a key focus within the APCN field from early on and a large body of work exists despite the challenging synthetic requirements. Much of the reported work has been focused on the fabrication of the APCNs and the investigation of their fundamental properties, but also on membrane-related biomedical applications, such as stimuli-responsive drug release. Though most of those studies were not aimed at the fabrication of stimuli-responsive APCN membranes, they present the methodology for the fabrication of a range of stimuli-responsive APCNs, which may be employed for membrane applications.

[Figure 15.7 near here]

15.3.2 pH-responsive APCNs

The degree of swelling of polymers that contain pH-responsive groups depends strongly on their ionization, which in turn depends on the pH of their environment. Typically, these side groups are weak acids and bases. The earliest study on pH-responsive APCNs was published already in 1988 by the Kennedy group, the early pioneers of APCN research.[56] These authors employed the basic monomer 2-(*N*,*N*-dimethylamino)ethyl methacrylate (DMAEMA) together with a telechelic methacrylate-functionalized PIB macromonomer crosslinker to synthesize an APCN containing a pH-responsive hydrophilic phase. In a follow up study, the same authors investigated the pH-dependent behavior of these ACPNs, and found both pH-responsive swelling behavior and the pH-dependent release of model drugs.[57] Further studies on PDMAEMA/PIB-based APCNs were conducted to give detailed insight into their pH-responsive swelling behavior and their influence on the phase morphology.[58] The DMAEMA monomer was not only attractive for the fabrication of APCNs because of its basicity, with a reported pK_a of 7.3 for the homopolymer,[59] but because it is aprotic. Thus, it gains its water solubility mainly as a proton acceptor, by becoming ionized. Its relatively low hydrophilicity

enables its combination with hydrophobic monomers and macromonomer crosslinkers without macrophase separation problems, which is of the essence for the synthesis of APCNs. Furthermore, its aprotic nature allows its direct use in anionic-type controlled polymerization techniques (classical living anionic polymerization, group transfer polymerization (GTP)) for the synthesis of the APCNs. GTP, for example, requires an aprotic environment and is, therefore, limited in the choice of monomers and solvents. However, these techniques can enable a precise control over the APCN's internal architecture. For the described reasons, DMAEMA has been extensively used for the synthesis of APCNs by the sequential living polymerization and crosslinking approach that was developed in the Patrickios group and is shown schematically in (Figure 15.8A).[60, 61] This synthetic approach is based on the controlled one-pot synthesis of precisely defined amphiphilic methacrylate block copolymers, usually by GTP, and their crosslinking by the addition of multifunctional monomers in a last step. Thus synthesized APCNs have been reported to be close to theoretical model APCNs with perfectly defined architectures since only the crosslinking may proceed in a random fashion. Patrickios and co-workers first reported the synthesis of APCNs from this approach and these APCNs were based on PDMAEMA- and PMMA segments.[60, 61] The authors found profound influences of both the blocks' lengths and also the number and order of the individual blocks on the pH-responsive swelling of the materials. In subsequent detailed studies, they continued to explore more complex architectures, ranging from the introduction of hydrophilic double blocks with one non-pH-responsive component to PIB-based graft copolymer, as well as more refined star block copolymers and interpenetrating double networks.[62-68] Finally, reversible addition-fragmentation chain-transfer (RAFT) living polymerization technique was introduced to the same approach.[69, 70]

[Figure 15.8 near here]

While a basic and aprotic monomer like DMAEMA is well-suited for the synthesis of APCNs, acidic monomers are more demanding because they are protic and, thereby, less miscible with the hydrophobic components. Apart from an early example that was prepared using larger volumes of amphiphilic solvent,[71]

acidic monomers are usually modified with a hydrophobic protecting group that allows their copolymerization with the hydrophobic components to form a homogeneous hydrophobic network (Figure 15.8B). The protecting groups are removed after the polymerization to reveal the acidic functionality, typically resulting in nanophase separation and the formation of the actual APCN phase morphology. One widely employed hydrophobic protecting group is the TMS group, which can be employed not only to mask the hydroxyl side group of HEA and HEMA, but also for the synthesis of methacrylic acid (MAA)-based APCNs (Figure 15.8C).[72-74] Acetal protecting groups are another possibility to mask carboxylic acid groups. An ethoxyethyl acetal protecting group has been employed by Iván and coworkers for both acrylic acid (AA) and MAA.[75] After the network formation together with PIB macromonomer crosslinkers, the ethoxyethyl group was cleaved off under acidic conditions and afforded PIB-based APCNs with pH-responsive swelling. A similar acetal protecting group, the tetrahydropyranyl (THP) group, was used to enable the use of MAA in the sequential living polymerization and crosslinking approach. Furthermore, the THP- protecting of MAA allowed the combination with DMAEMA and, thereby, enabled the synthesis of ampholytic APCNs that contained both basic and acidic pH-responsive monomers.[76-79]

The pH response of basic and acidic monomer units manifests itself in the ionization of their side group at high or low pH, respectively. However, the presence of ionized groups typically makes the properties of these polymers also highly dependent on the ionic strength of their environment. Furthermore, many pH-responsive polymers, including PDMAEMA and copolymers of PAA exhibit temperature dependent phase transitions. Interestingly, polyelectrolyte-modified hydrogel membranes based on PAA have even been shown to allow the control of their permeability with electric fields due to significant contraction and expansion in the on- and off-state, respectively.[53] Accordingly, pH-responsive polymers possess a complex functional behavior.

15.3.3 Thermo-responsive APCNs

Thermoresponsive APCNs that expand and shrink depending on whether the environmental temperature is below the lower critical solution temperature (LCST) or above upper critical solution temperature (UCST) of

their thermoresponsive polymer component have been explored less. One possible reason could be that LCST-type thermoresponsive polymers such as poly(*N*-isopropyl acrylamide) (PNIPAM) provide sharp responses in solution or as polymer brushes, but the limited dynamic movement in a covalent polymer network is often not able to produce an equally fast response.[80] The first study of a thermoresponsive APCN based on a PNIPAM hydrophilic phase was conducted by Kali et al (Figure 15.9A).[81] They employed the macromonomer approach and combined NIPAM with PIB segments using THF as the amphiphilic solvent to avoid phase separation during the synthesis. The authors reported a range of PNIPAM-*l*-PIB conetworks with different compositions. The thermoresponsive response was clearly observable, and though it was less sharp than a PNIPAM homopolymer, the response was more distinct at higher PNIPAM content. Indeed, temperature-dependent swelling in water reflected this thermoresponsive behavior with a massive decrease of swelling from 130 % down to almost 20 % upon heating from 20 up to 40 °C, a change that was reversible when the network was cooled down again.

[Figure 15.9 near here]

Another example of thermoresponsive networks with APCN character can be found in the work of du Prez and coworkers.[82] These researchers synthesized methacrylate end-capped macromonomers of poly(methyl vinyl ether) (PMVE) that possess an LCST of about 37 °C as a homopolymer. Network formation by copolymerization with hydrophilic HEMA or hydrophobic *n*-butyl acrylate (BA) resulted in conetworks with their structure and behavior that depended on the comonomer: PHEMA-based networks are hydrophilic at low temperatures but should possess a hydrophilic-hydrophobic structure after phase separation at elevated temperature. Poly(BA) networks, on the other hand, should possess a hydrophilic-hydrophobic structure until the phase separation of the PMVE component results in an all-hydrophobic network. The authors did not study the temperature-dependent phase separation and morphology in these networks but focused on the thermally responsive swelling of the overall network. Interestingly, they found a strong influence of the monomer type

on the LCST of PMVE with the hydrophobic BA decreasing and the hydrophilic HEMA increasing the phase transition temperature. Interesting for the future design of thermoresponsive conetworks was the faster responsive of networks with additional mono-functional PMVE macromonomers, i.e. with dangling end thermo-responsive chains with increased mobility.

In addition to this work, some highly interesting studies have been conducted in recent years on hydrogels that turn into an APCN upon heating. Shibayama and coworkers developed an approach for the synthesis of near-ideal hydrogel networks with excellent mechanical properties from 4-arm PEG polymers via active ester crosslinking.[83-86] However, when one of the two complementary 4-arm PEG was exchanged for a 4-arm poly(ethylglycidyl ether-*co*-methylglycidyl ether) (PEMGE) star copolymer, the network became thermo-responsive due to the PEMGE that aggregates at elevated temperatures.[87, 88] Accordingly, these networks resemble conventional structurally highly defined hydrogels below the LCST, typically about 20 °C. However, they change into a nanophase-separated hydrophilic-hydrophobic conetwork with close resemblance to an APCN structure when heated above this threshold temperature. Formation of hydrophobic nanodomains was found to be accompanied with a drastic reduction in overall swelling of the networks because the aggregated PEMGE domains frustrated the swelling of the PEG phase. The authors described these networks as "non-swellable" and, therefore, mechanically stable hydrogels since the described temperature effect counteracted water uptake beyond the water already present in the networks during the synthesis. Mortensen and Annaka further built upon this work of crosslinking 4-arm star polymers, however, the authors employed 4-arm star block copolymers that already incorporate both a PEG as the hydrophilic component and a thermo-responsive/hydrophobic poly(propylene oxide) (PPO) component.[89] The highly defined networks that resulted from crosslinking of these building blocks showed similar self-assembly at elevated temperature that resulted in nanophase-separated PPO domains with a hexagonal cylinder structure (Figure 15.9B). The permeability towards water of these networks, as indicated by the water friction coefficient, was tested in a subsequent study.[90] It was found to be strongly dependent on the temperature and, thereby, the internal phase structure. The described work further highlights the possible control over APCN structures and their functional behavior

from highly defined precursor polymers.

The combination of thermo-responsive APCNs with magnetic nanoparticles may open up further possibilities. The excitation of magnetic nanoparticles by a high frequency magnetic field causes local heating, and, thereby, the phase transition of the thermo-responsive polymer. The thermo-responsive component only transduces the magnetic field stimulus into a phase transition response and a change of membrane permeability. Several examples of magneto/thermo-responsive membrane systems have demonstrated the viability of such an approach.[91-93] The few reported studies that exist for the incorporation of inorganic nanoparticles into APCNs indicate the potential for such future work. [94, 95]

15.3.4 APCNs as Chiral Separation Membranes

Selective permeation of feed components can not only be achieved in response to changes in properties of the feed solution, e.g. its pH or temperature, but also in response to the molecular structure of the components of interest. Functional polymers that interact with some feed components can retard their passage or even permit it entirely. One prime example is the use of chiral separation membranes that possess different permeability for one enantiomer over the other. Such membranes enable chiral resolution of racemic mixtures, which is of high interest for many applications, for example in the pharmaceutical sector. For the fabrication of a chiral separation membrane, the membrane material itself must possess chirality on its own. APCN-based chiral separation membranes were first developed by Tiller and co-workers. They prepared hydrophobically protected chiral monomers (R)-*N*-(1-hydroxybutan-2-yl)acrylamide (*R*-HBA) and *S*-HBA and combined them with PDMS macromonomer crosslinkers into APCNs with a chiral hydrophilic phase.[96] The authors also investigated the temperature-dependent swelling behavior. Interestingly, these APCNs possessed thermo-responsive behavior with an almost linear decrease of swelling in water when increasing the temperature. When loaded with the enantiopure forms of the alkaloid cinchonine, release properties were found that corresponded to a four times faster diffusion rate of (+)- over (-)-cinchonine in the *S*-HBA-*l*-PDMS APCN and an about three times faster diffusion rate of (-)- over (+)-cinchonine in the *R*-HBA-APCN. This remarkable

difference was attributed to the interaction of the alkaloids with the chiral APCN matrix. In a follow up study, the same authors investigated the *S*-HBA-based APCN as chiral separation membranes (Figure 15.10).[97] They found excellent permeation selectivity for a number of different compounds that depended strongly on the hydrophilic-hydrophobic phase ratio of the APCNs. Furthermore, selective permeation occurred in water but also in hydrophobic (toluene) solvents. This indicating either a significant swelling of the PHEA phase in toluene or that the close proximity and large interfacial area of the phase domains allows sufficient interaction with the hydrophilic phase. A very similar system was developed by Shi et al. based on a poly(*N*-acryloyl-*L*-alanine) hydrophilic phase.[98] However, it showed a more limited enantioselectivity.

[Figure 15.10 near here]

15.4 Functionalization of APCNs for Stimuli-Responsive Membranes

In addition to the use of stimuli-responsive polymers, such as PNIPAM, PDMAEMA or PAA, smart APCNs-based membranes can also be created by the functionalization of the conetworks with small amounts of more complex stimuli-responsive groups. These moieties can impart functional and stimuli-responsive behavior beyond temperature and pH stimuli. For example, organic photochromes respond to a light stimulus with a reversible change of their molecular structure.[99] A high enough concentration of such groups that function largely independent of each other can suffice to change the overall properties of a membrane (Figure 15.11A). Furthermore, the effect of such groups can be synergistically combined with other stimuli-responsive and phase changing polymers.

[Figure 15.11 near here]

Compared to the use of APCNs based on stimuli-responsive polymers, such functionalized APCNs have received comparably little attention. In contrast, a large body of work exists for porous membranes, hydrogels and IPNs.[11, 53-55, 100] As described in the last section, functional pore surfaces or pore-filling brushes and hydrogels are employed in porous membranes, whereas the bulk material is modified in the case of non-porous membranes. One reason for the lack of comparable work on functionalized APCNs may be related to the demanding nature of APCN fabrication. Incorporation of functional groups via modified monomers is hampered by the often very hydrophilic nature of many of the molecules of interest. Immiscibility with the monomer mixture prohibits copolymerization or requires a large amount of amphiphilic solvents. Incorporation of stimuli-responsive groups by post-polymerization functionalization of APCNs, on the other hand, requires the presence of adequate functional groups, e.g. hydroxyl and carboxylic acid groups, in the conetworks. Many APCNs are based on polymers that lack such functionality. Functional groups which have been successfully incorporated into APCNs or into other membrane systems include light-responsive groups, ion-responsive ligands, molecule responsive groups, such as cyclodextrans or the glucose-sensitive

phenylboronic acid, and redox-responsive groups (Figure 15.11B).[54, 55, 101] Enzymes represent the highest level of complexity of any functional moiety that can be incorporated into APCNs. For example, glucose oxidase-based systems respond to the presence and concentration of glucose.

Light-responsive organic photochromes, such as spiropyrans and azobenzenes, are of special interest for two reasons.[101-105] The first reason is the nature of light as a stimulus; it enables excellent control of the magnitude of the response since the intensity of the light source can be easily adjusted. Also, excellent spatial and temporal precision can be achieved since the light beam can be directed at a specific area for a defined time.[106] Furthermore, the irradiation wavelength can be controlled by employing LEDs and lasers with narrow emission spectra, allowing wavelength-specific activation of different photochrome species.[107] The second reason is the character of ACPNs as an inherently optically transparent material that allows light to penetrate into the structure over its whole thickness without scattering. To change the permeability of a membrane system, a photochrome needs to change other molecular properties, such as polarity, charge, and molecular shape in addition to its color. Only then can the photoswitching result in a switch of the matrix' hydrophilicity and, thereby, its permeability.[99, 104, 108] For this reason, photochromes such as diarylethenes that may possess highly favorable photoswitching properties but change very little in anything but color are of little interest for membrane applications. The light-induced reversible transformation of azobenzenes between their *trans* and *cis* states causes a change in dipole moment, *i.e.* polarity, and molecular shape (Figure 15.11B). Even though these changes are rather small, azobenzene has been employed to introduce stimuli-responsive behavior into different membranes systems.[53, 101] Furthermore, the effect of azobenzene photoswitching can be strongly increased when it is combined with a stimuli-responsive polymer such as PNIPAM, where the light-stimulus synergistically causes a phase change response.[109, 110] For spiropyrans and closely related compounds, such as spirooxazines, the ring-opening reaction during photoswitching results in the transformation of the rather hydrophobic closed form into the open, zwitterionic merocyanine form.[99] This leads to a massive change in dipole moment and molecular shape, basicity and the ability to complex ions, making spiropyrans and their related compounds the primarily employed organic photochromic system for the control of the polarity of

materials by light. Furthermore, spiropyrans do not only respond to light but they can be actuated by a variety of different stimuli, including temperature, pH, solvent polarity, redox potential, metal ion concentration and even mechanical force. Overall, a large body of work exists for membrane systems with light-controlled permeability, usually based on conventional membrane types.[104, 111-114]

The first example of a light-responsive APCN membrane was reported by Schöller et al.[115] These authors aimed for a light-responsive membrane that could be used for the controlled transdermal delivery of hydrophilic drugs from a drug depot through the skin of preterm neonates. At this early stage, preterm neonates possess a highly permeable skin which allows the permeation even of hydrophilic drugs. Thereby, transdermal drug delivery avoids intravenous injections. The control over the swelling behavior and permeability of APCNs via their hydrophobic/hydrophilic composition was described by the authors as an important motivation for the choice of an APCN-based membrane. They employed a PHEA-*l*-PDMS conetwork into which the photochromes were introduced either by functionalization of the APCNs via DCC-mediated ester coupling or by copolymerization of spiropyran monomers. Both approaches resulted in light-responsive ACPNs in which the spiropyrans could be switched between a closed, colorless and hydrophobic state and an open, colored and hydrophilic state (Figure 15.12A). A severe drawback of spiropyrans is that they are prone to photodegradation. However, covalent attachment of spiropyrans to polymer backbones, as demonstrated in this work, can greatly increase their stability. It avoids the close proximity between spiropyrans molecules and, thereby, the aggregation of their merocyanine form, which has been identified as one of the main pathways of photodegradation.[99] A strong increase in the caffeine permeability of the photochromic APCNs was measured under UV light. Subsequent irradiation with visible light leads to recovery of the spiropyran form and, accordingly, resulted in a marked decrease in caffeine permeability. Furthermore, the permeability could indeed be adjusted to the permeability of a porcine skin model for preterm neonate skin by controlling the composition and the thickness of the membranes.

The same authors expanded on their previous work by introducing additional 2,2':6'2''-terpyridine ligands into spiropyran-modified APCNs.[116] These ligands are able to complex heavy metal ions in different oxidation

states and, thereby, add redox-responsiveness to a now multi stimuli-responsive material. These APCNs can exist in a variety of different states which depend on the specific environment, the presence and the type of metal ions and their oxidation state as well as the state of spiropyran, (Figure 15.12B). Using cobalt salt, three different states of the APCN were available based on the terpyridine ligands alone with no metal presence, with cobalt(II), or with cobalt(III). These states could be interchanged with an oxidative environment, a reductive environment or with the presence of free ligands that remove metal ions from the APCNs. Since any of these three states can be combined with UV or visible light irradiation to switch spiropyran, a total of six different functional states were selectively accessible. Indeed, the permeability of these APCN-based membranes towards caffeine in aqueous solution reflected the state of its stimuli-responsive components. While only a slight increase in permeability was observed for complexation of cobalt(II), oxidation to cobalt(III) resulted in a larger effect, which was accompanied by increased swelling. UV light irradiation strongly increased the caffeine flux for any redox state, with the largest increase found for cobalt(III), possibly due to a synergistic effect of the metal ion stabilizing the merocyanine form. The work further underlines the potential of APCNs for smart membrane systems.

[Figure 15.12 near here]

As described before, the functionalization of APCNs is often challenging, especially if good control over the degree of functionalization is required and if the stimulus-responsive groups of interest are too hydrophilic for copolymerization as functional monomers. For example, in the study described above, the degree of DCC functionalization of the PHEA-*l*-PDMS depended on the concentration of the solution as well as the exact mass and composition of the APCN and needed to be confirmed with a complex degradation-based analysis method.[115] Recently, we presented a new modular approach for the controlled functionalization of APCNs using the hydrophobic active ester monomer pentafluorophenyl acrylate (PFPA) in combination with TMS-protected HEA and PDMS macromonomer crosslinkers.[117] This approach employs PFPA as a

hydrophobically protected *N*-alkyl acrylamide due to its high reactivity towards primary and secondary amines. The concept is schematically depicted in Figure 15.13A. First, hydrophobic precursor membranes (preAPCNs) were prepared using the macromonomer approach. Due to the hydrophobic nature of PFPA, it is easily integrated into these networks by copolymerization, providing control over the integrated amount via the ratio between the monomers. Thereby, the degree of functionalization is fixed with the composition of the preAPCN and is independent of the intended functionality, its molecular structure and hydrophilicity. The ratio of PFPA to its comonomer TMS-HEA was varied from 0.1 mol% up to the conetwork poly(PFPA)-*l*-PDMS , consisting entirely of PFPA and PDMS. In a subsequent step, the active esters in the precursor membranes were reacted with an excess of *N*-alkyl amines with the desired functionality, yielding *N*-alkyl acrylamide units in quantitative fashion. Finally, the TMS protecting groups of the HEA units were removed to afford the nanophase-separated APCN structure. The versatility of this approach was demonstrated with different degrees of functionalization and with the incorporation of very different functional groups. For example, poly(PFPA)-*l*-PDMS networks afforded purely poly(*N*-alkyl acrylamide)-based APCNs, whereas reaction of a preAPCN containing 5 mol% of active ester monomer with histamine resulted in a pH-responsive APCN with a defined amount of imidazole-functional acrylamide units. Reaction of one preAPCN (0.1 mol% active ester) with the fluorescent dye EDANS or an amine-modified biotin resulted in a fluorescent APCN and a protein-binding APCN, respectively. The biotin-APCN was able to bind and retain a much higher streptavidin cargo than a comparable control APCN that saw a small amount of non-specifically bound streptavidin mostly washed out in a matter of two days (Figure 15.13B). While this synthesis has not been employed so far for the creation of stimuli-responsive APCN membranes, the facile integration of functional groups into APCNs, potentially also from different synthesis approaches, makes this PFPA-based synthetic platform ideal for future work in this direction.

[Figure 15.13 near here]

15.5 Conclusion and Outlook

In this chapter, we detailed how the structural features of APCNs can result in uniquely functional membranes. APCNs can perform in membrane applications with special demands that cannot be met by conventional hydrogels or any other material class. Developments in the field of APCN synthesis are achieving an ever increasing control over the APCN's properties, their conetwork architecture and chemical composition. For new membrane applications, there exists now a choice from a wide range of different APCN types with different components that can be tailored specifically to the desired properties. Furthermore, silicone hydrogel contact lenses have shown that the fabrication of APCNs for special membranes applications can be achieved within an industrial setting. The incorporation of stimuli-responsive polymers and special functional groups, such as organic photochromes, are adding further levels of functional behavior that make APCNs prime candidates for the development of smart membranes systems. We believe that APCN membranes, especially smart APCN membranes, will find an increasing number of applications, especially in the biomedical sector.

Abbreviations

APCN	Amphiphilic polymer conetworks
PEG	Poly(ethylene glycol)
PHEMA	Poly(hydroxyethyl methacrylate)
CL	Contact lens
PMMA	Poly(methyl methacrylate)
EWC	Equilibrium water content
TRIS	3-[tris(trimethylsiloxy)silyl]propyl
NVP	*N*-vinylpyrrolidone
DMA	*N*,*N*-dimethylacrylamide
TMS	trimethylsiloxy
PHEA	Poly(2-hydroxyethyl acrylate)
PIB	Poly(isobutylene)
DMAEMA	2-(*N*,*N*-dimethylamino)ethyl methacrylate
GTP	Group transfer polymerization
RAFT	Reversible addition-fragmentation chain-transfer
MAA	Methacrylic acid
AA	Acrylic acid
THP	Tetrahydropyranyl
LCST/UCST	Lower/upper critical solution temperature
PNIPAM	Poly(*N*-isopropyl acrylamide)
PMVE	Poly(methyl vinyl ether)
BA	*n*-butyl acrylate
PEMGE	Poly(ethylglycidyl ether-*co*-methylglycidyl ether)
PPO	Poly(propylene oxide)
HBA	*N*-(1-hydroxybutan-2-yl)acrylamide
PFPA	Pentafluorophenyl acrylate

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Figure Captions

Figure 15.1 (A) Simplified depiction of the structural features of typical membrane systems and APCN-based membranes. Selective and controlled permeation through porous membranes (pore-flow model) or non-porous membranes (solution-diffusion model) is based on the size and/or the chemical properties of the feed components. Gel-type membranes are swollen in the feed solvent and permeation strongly depends on the interactions membrane-solvent-solute. APCNs possess two non-porous co-continuous phases through which transport of different species can occur. (B) Amphiphilic swelling ability of APCNs.

Figure 15.2 Schematic depiction of the three main approaches for the synthesis of APCNs. Polymeric precursors may be of different and often more complex architectures than the ones shown here. The hydrophilicity/hydrophobicity, indicated here with blue and grey color, may be inversed for each approach.

Figure 15.3 (A) Relationship between the EWC and the oxygen permeability of conventional hydrogel CLs compared to silicone hydrogel CLs. Adapted with permission from ref. 118. Copyright® (2017), Elsevier. (B) Dependency of ion permeability and on-eye-movement on the EWC with a stark increase above a percolation threshold for the hydrogel phase. A similar percolation threshold exists for a silicone phase providing oxygen permeability. Adapted with permission from ref. 16. Copyright® (2001), Elsevier.

Figure 15.4 (A) TRIS-and Tanaka-type monomers with siloxane side groups for high oxygen permeability. (B) Relationship between the EWC and the oxygen permeability of silicone hydrogel CLs with an almost inverse linear relationship for the 1st and 2nd generation that was only broken by the 3rd generation silicone hydrogels. Reprinted from ref. 26 with permission from Nicole Carnt. (C) Possible structural subunits of a silicone macromonomer found in a patent by Coopervision, one producer of 3rd generation silicone hydrogel CLs.[30]

Figure 15.5 (A) Synthetic approach towards PDMS-based APCN for applications as immunoisolation membranes. Reprinted with permission from ref. 119, Copyright® (2005), Wiley Periodicals, Inc. (B) Schematic depiction of the influence of the polymer precursors on the phase morphology and membrane properties of an APCN from the Kennedy/Chakmat groups. Adapted with permission from ref. 40, Copyright® (2015), American Chemical Society.

Figure 15.6 APCN-coated Sympatex membranes for puncture-resistant waterproof membranes in weather-protective clothing. (A/B) Punctured membrane before (A) and after (B) closure from swelling of the APCN network. Adapted with permission from ref. 51, Copyright® (2015), 2015 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Figure 15.7 Schematic depiction of the typical mechanism of stimuli-responsive membranes with porous or non-porous internal structures.

Figure 15.8 (A) Synthesis of pH-responsive APCNs by the sequential living polymerization and crosslinking approach. Adapted with permission from ref. 67, Copyright® (2006), American Chemical Society. (B) Example of pH-responsive monomers. In contrast to the apolar DMAEMA, the protic MAA requires hydrophobic protecting groups. (C) Response to the solution pH of an acidic APCN obtained with the macromonomer approach. Adapted with permission from ref. 74, Copyright® (2005), International Union of Pure and Applied Chemistry.

Figure 15.9 (A) APCN based on PBI and temperature-responsive PNIPAM segments. Adapted with permission from ref. 81, Copyright® (2013), American Chemical Society. (B) Near-ideal hydrogel networks composed of PEG and thermo-responsive PPO segments. Above the LCST, the PPO segments are water insoluble, resulting in a nanophase-separated APCN-type morphology. Adapted with permission from ref. 89, Copyright® (2016), American Chemical Society.

Figure 15.10 Chiral separation membranes based on APCNs. (A) Chemical structures of the hydrophobically protected chiral monomer (top) and the chiral feed component (bottom). (B/C) Permeation of (*S*)- and (*R*)-BINOL in (B) water and in (C) toluene. Adapted with permission from ref. 97. Copyright® (2011), Elsevier.

Figure 15.11 (A) APCNs with stimuli-responsive functional groups, such as organic photochromes, can change their permeability upon stimulation. (B) Examples of different stimuli-responsive groups that have been employed for membrane applications.[54]

Figure 15.12 (A) Spiropyran-modified APCNs for the light-responsive transdermal delivery of hydrophilic drugs to preterm neonates. Adapted with permission from ref. 115, Copyright® (2014), WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Both redox- and light-responsive APCNs modified with both spiropyrans and metal-complexing ligands. Adapted with permission from ref. 116, Copyright® (2016), Royal Society of Chemistry.

Figure 15.13 (A) Modular approach for the synthesis of amide-functional APCNs from active ester-based precursor networks. A wide range of APCNs is available from functionalized PHEA-*l*-PDMS conetworks to poly(acrylamide)-*l*-PDMS APCNs. (B) Biotin-functional APCNs from the active ester-based functionalization approach specifically bind streptavidin. Adapted with permission from ref. 117, Copyright® (2018), American Chemical Society.

THE FOLLOWING IMAGES SHOULD BE SUPPLIED AS SEPARATE FILES in one of the following formats: TIFF/PDF/EPS/DOC/XLS/PPT/JPEG/CDX

Figure 15.1

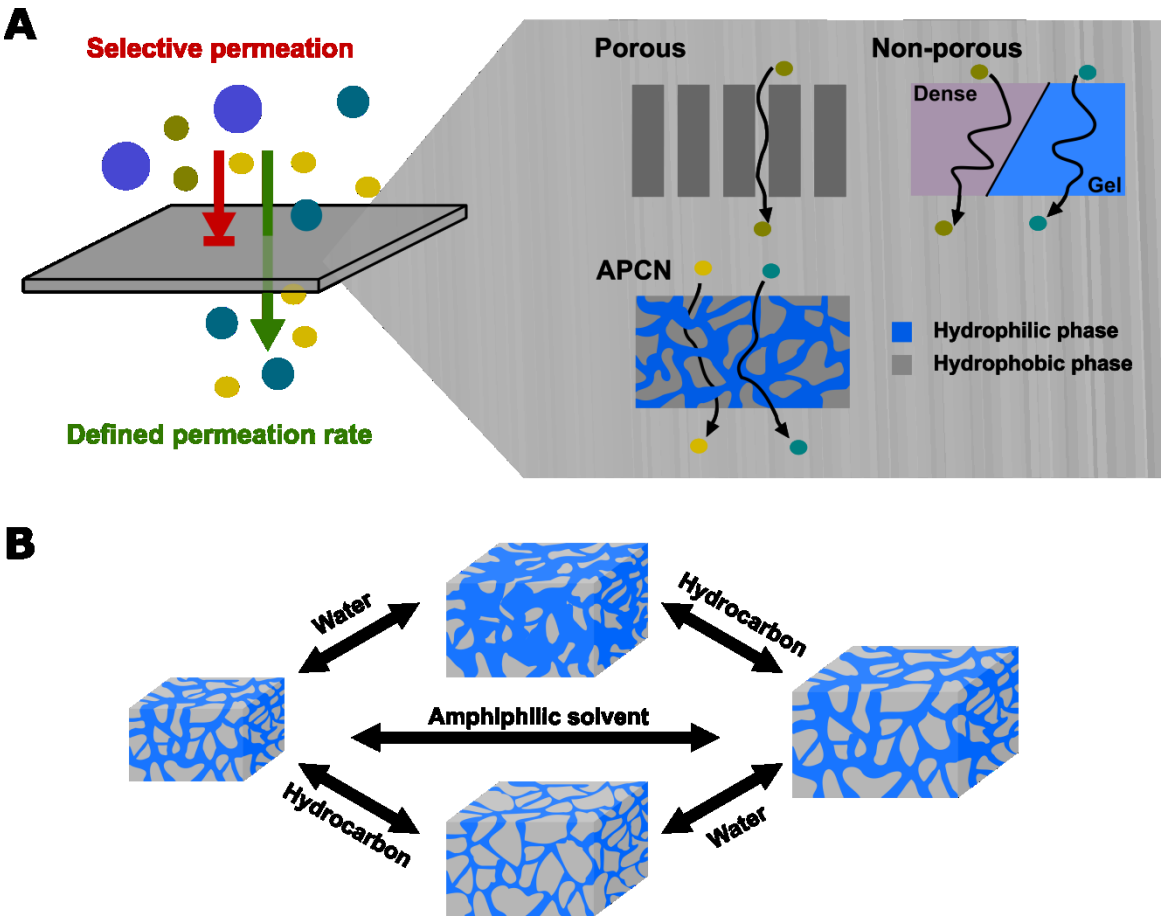


Figure 15.2

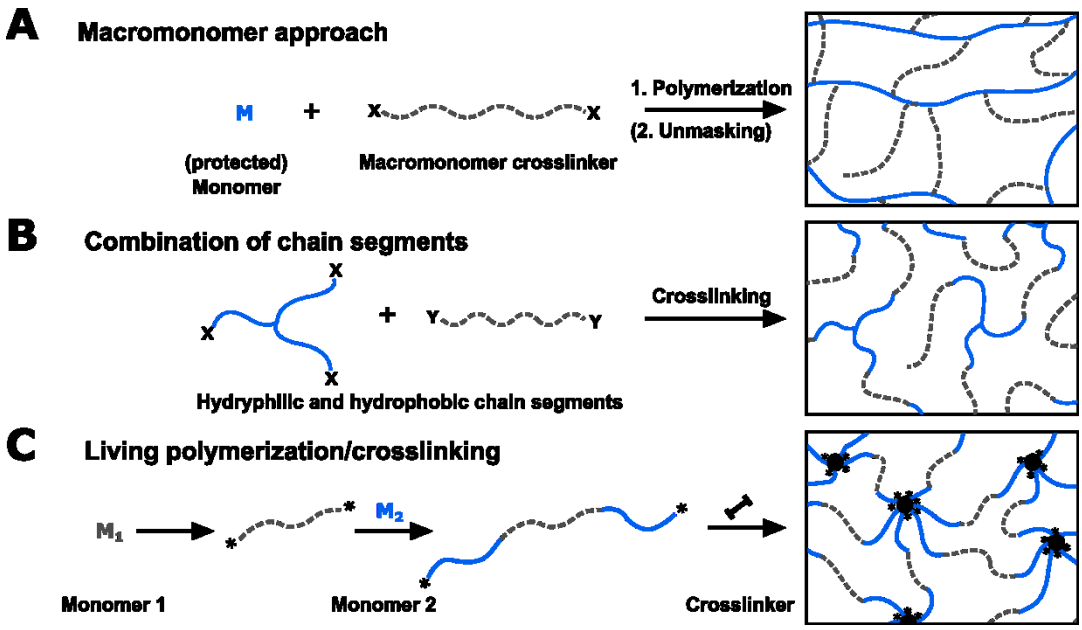

A
Macromonomer approach
M
(protected)
Monomer
Macromonomer crosslinker
1. Polymerization
(2. Unmasking)
B
Combination of chain segments
Hydryphilic and hydrophobic chain segments
Crosslinking
C
Living polymerization/crosslinking
M1
M2
Monomer 1
Monomer 2
Crosslinker

Figure 15.3

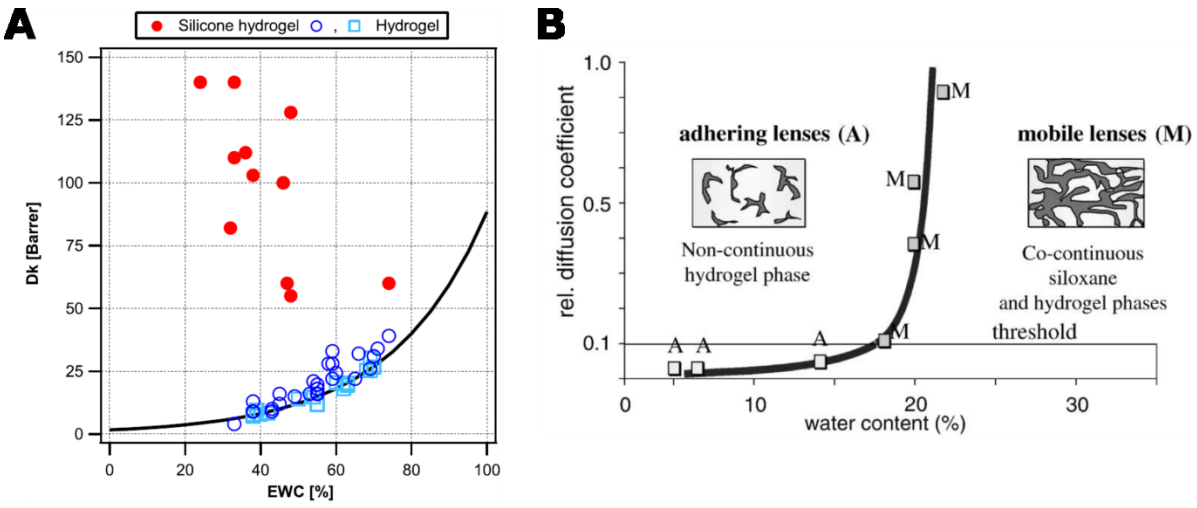

A
Silicone hydrogel
Hydrogel
Dk [Barrer]
EWC [%]
B
rel. diffusion coefficient
water content (%)
adhering lenses (A)
mobile lenses (M)
Non-continuous
hydrogel phase
Co-continuous
siloxane
and hydrogel phases
threshold

Figure 15.4

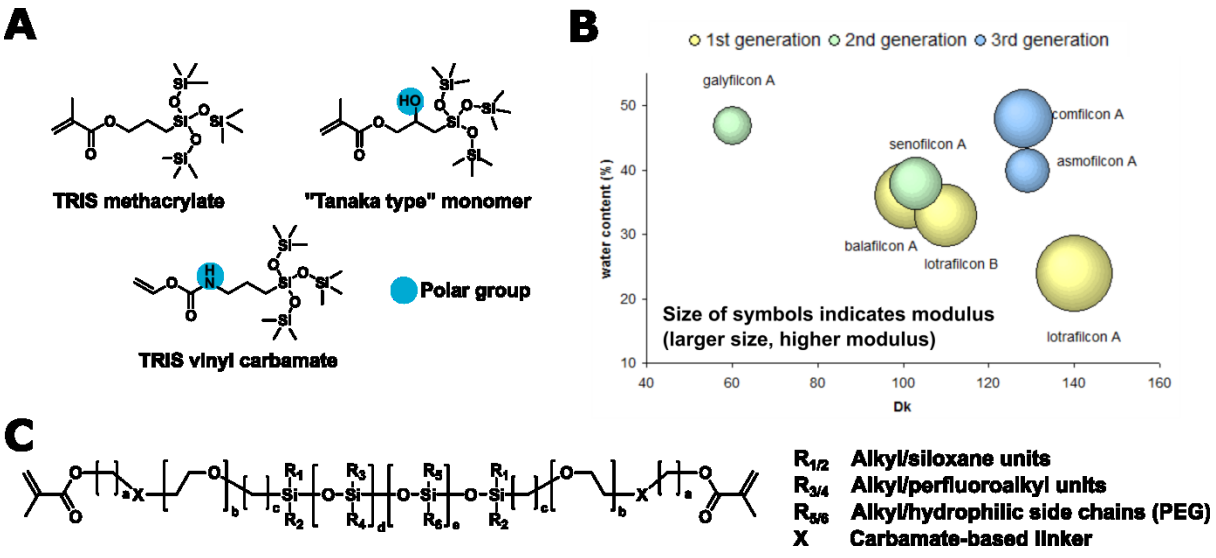

A
TRIS methacrylate
"Tanaka type" monomer
TRIS vinyl carbamate
Polar group
B
1st generation
2nd generation
3rd generation
galyfilcon A
senofilcon A
comfilcon A
asmofilcon A
balafilcon A
lotrafilcon B
lotrafilcon A
Size of symbols indicates modulus
(larger size, higher modulus)
water content (%)
Dk
C
R1/2 Alkyl/siloxane units
R3/4 Alkyl/perfluoroalkyl units
R5/6 Alkyl/hydrophilic side chains (PEG)
X Carbamate-based linker

Figure 15.5

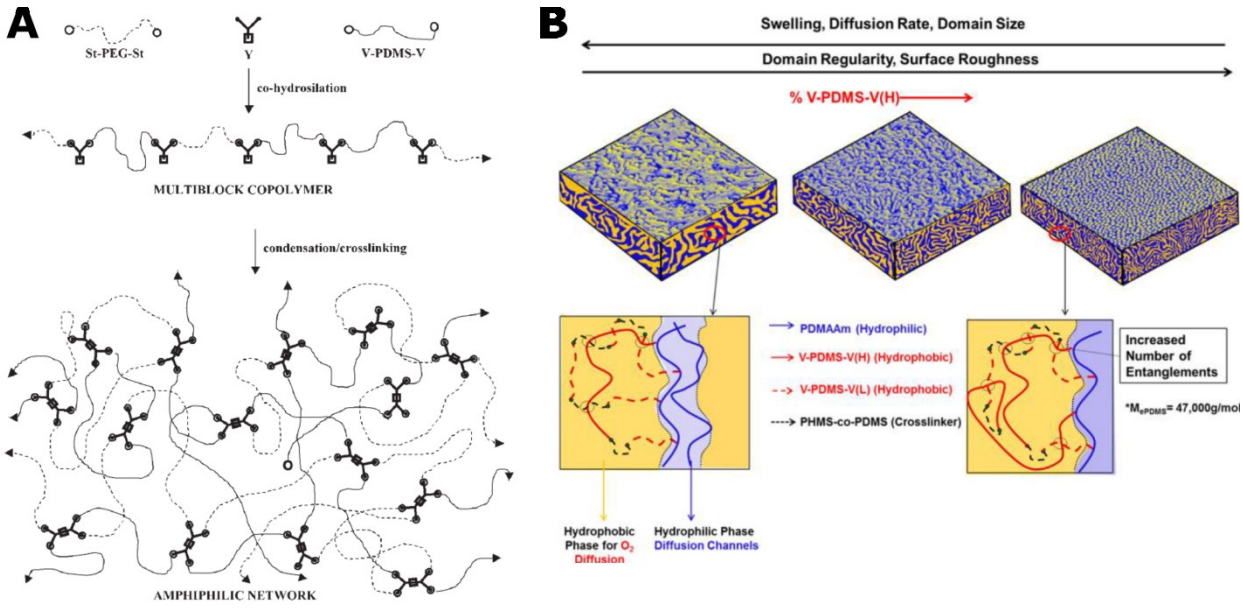

A
St-PEG-St
Y
V-PDMS-V
co-hydrosilation
MULTIBLOCK COPOLYMER
condensation/crosslinking
AMPHIPHILIC NETWORK
B
Swelling, Diffusion Rate, Domain Size
Domain Regularity, Surface Roughness
% V-PDMS-V(H)
PDMAAm (Hydrophilic)
V-PDMS-V(H) (Hydrophobic)
V-PDMS-V(L) (Hydrophobic)
PHMS-co-PDMS (Crosslinker)
Increased Number of Entanglements
Hydrophobic Phase for O2 Diffusion
Hydrophilic Phase Diffusion Channels

Figure 15.6

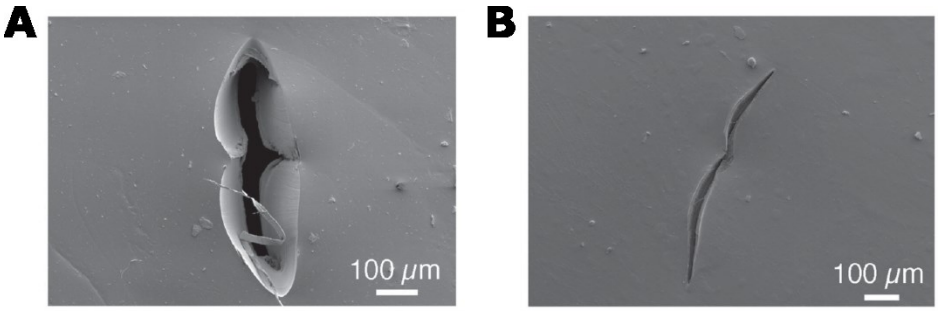


Figure 15.7

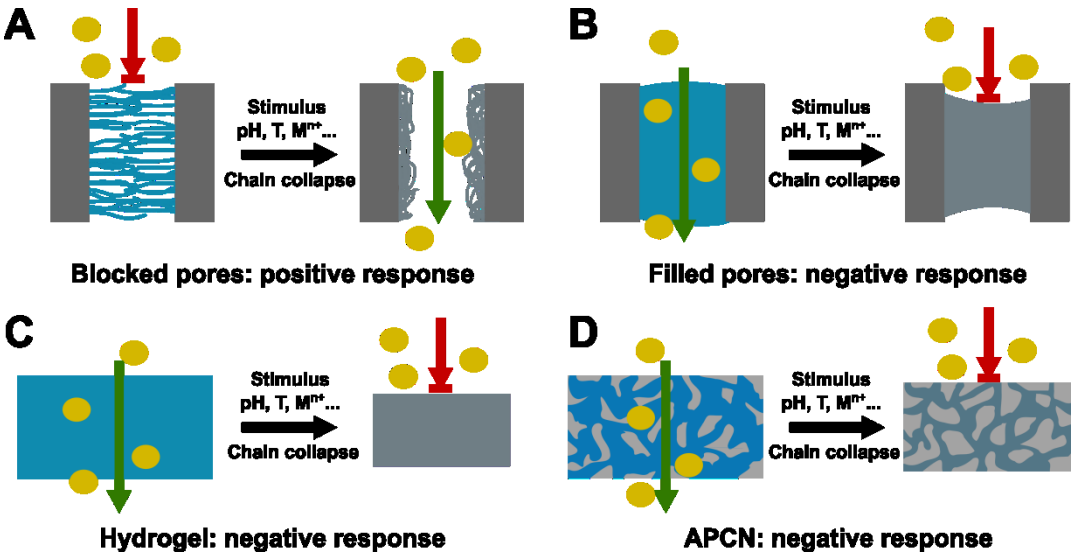

A
Stimulus
pH, T, M^{n+}...
Chain collapse
Blocked pores: positive response
B
Stimulus
pH, T, M^{n+}...
Chain collapse
Filled pores: negative response
C
Stimulus
pH, T, M^{n+}...
Chain collapse
Hydrogel: negative response
D
Stimulus
pH, T, M^{n+}...
Chain collapse
APCN: negative response

Figure 15.8

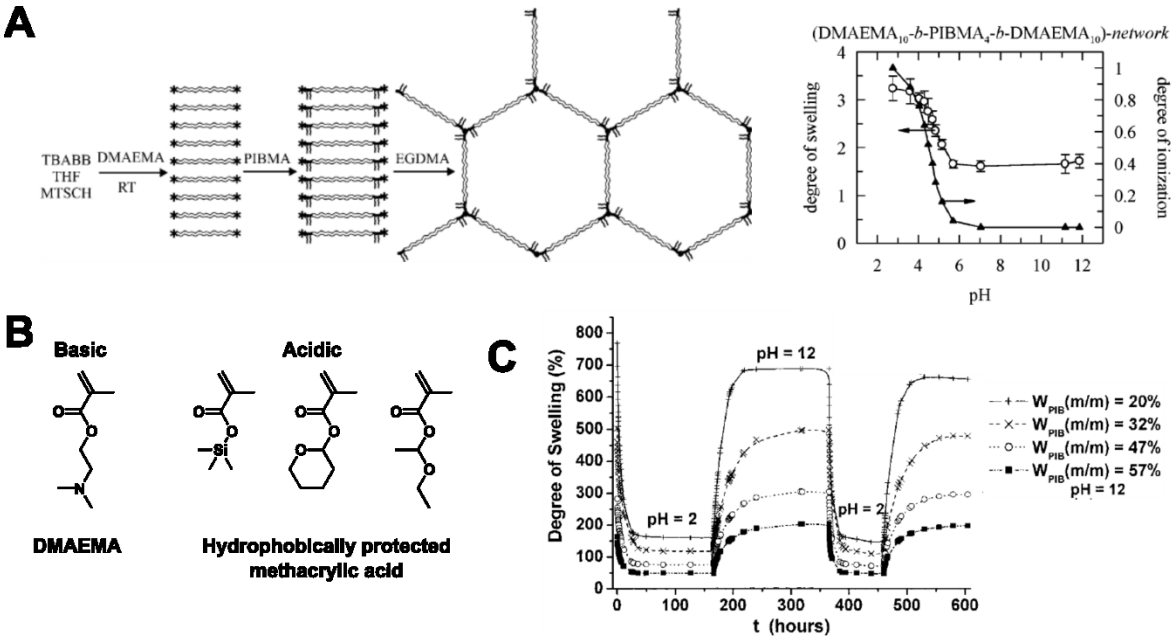

A
TBABB
THF
MTSCH
DMAEMA
RT
PIBMA
EGDMA
(DMAEMA10-b-PIBMA4-b-DMAEMA10)-network
degree of swelling
degree of ionization
pH
B
Basic
Acidic
DMAEMA
Hydrophobically protected methacrylic acid
C
Degree of Swelling (%)
t (hours)
pH = 12
pH = 2
pH = 2
W_PIB(m/m) = 20%
W_PIB(m/m) = 32%
W_PIB(m/m) = 47%
W_PIB(m/m) = 57%
pH = 12

Figure 15.9

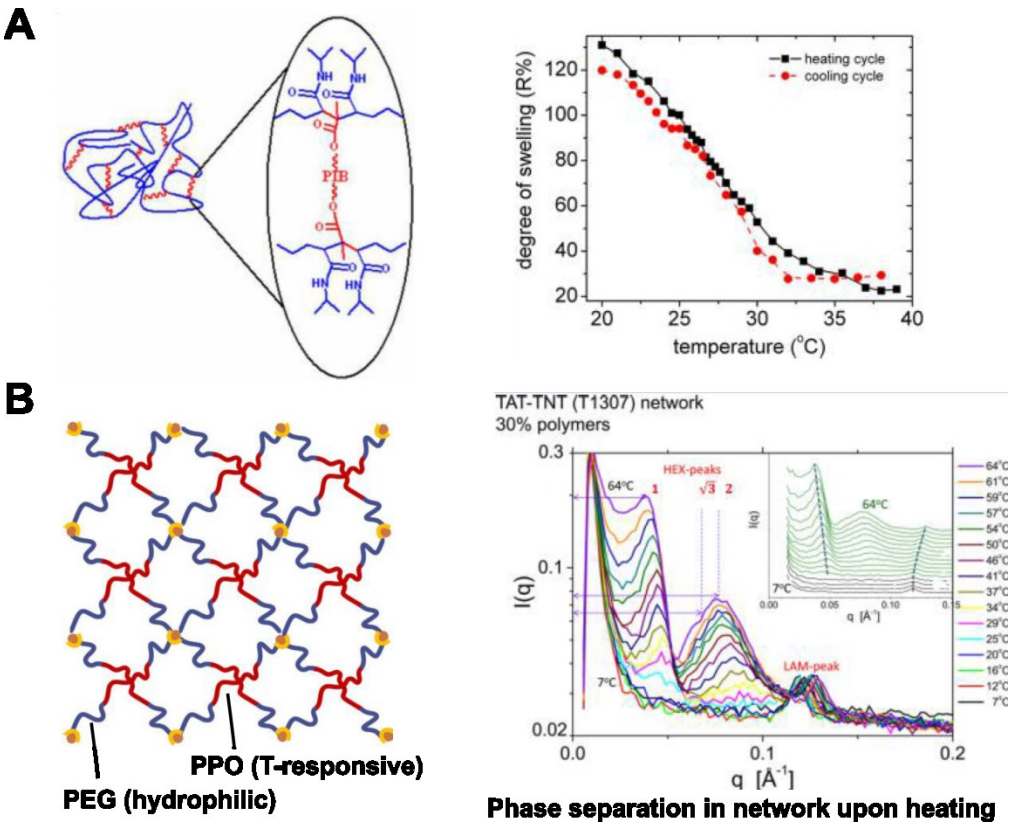

A
B
heating cycle
cooling cycle
degree of swelling (R%)
temperature (°C)
TAT-TNT (T1307) network
30% polymers
HEX-peaks
LAM-peak
I(q)
q [Å⁻¹]
PPO (T-responsive)
PEG (hydrophilic)
Phase separation in network upon heating

Figure 15.10

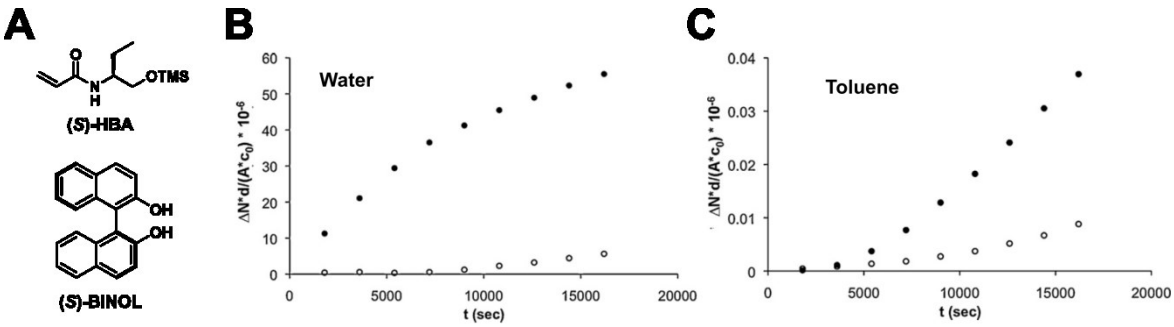

A
OTMS
(S)-HBA
OH
OH
(S)-BINOL
B
Water
ΔN*d/(A*c0) * 10-6
t (sec)
C
Toluene
ΔN*d/(A*c0) * 10-6
t (sec)

Figure 15.11

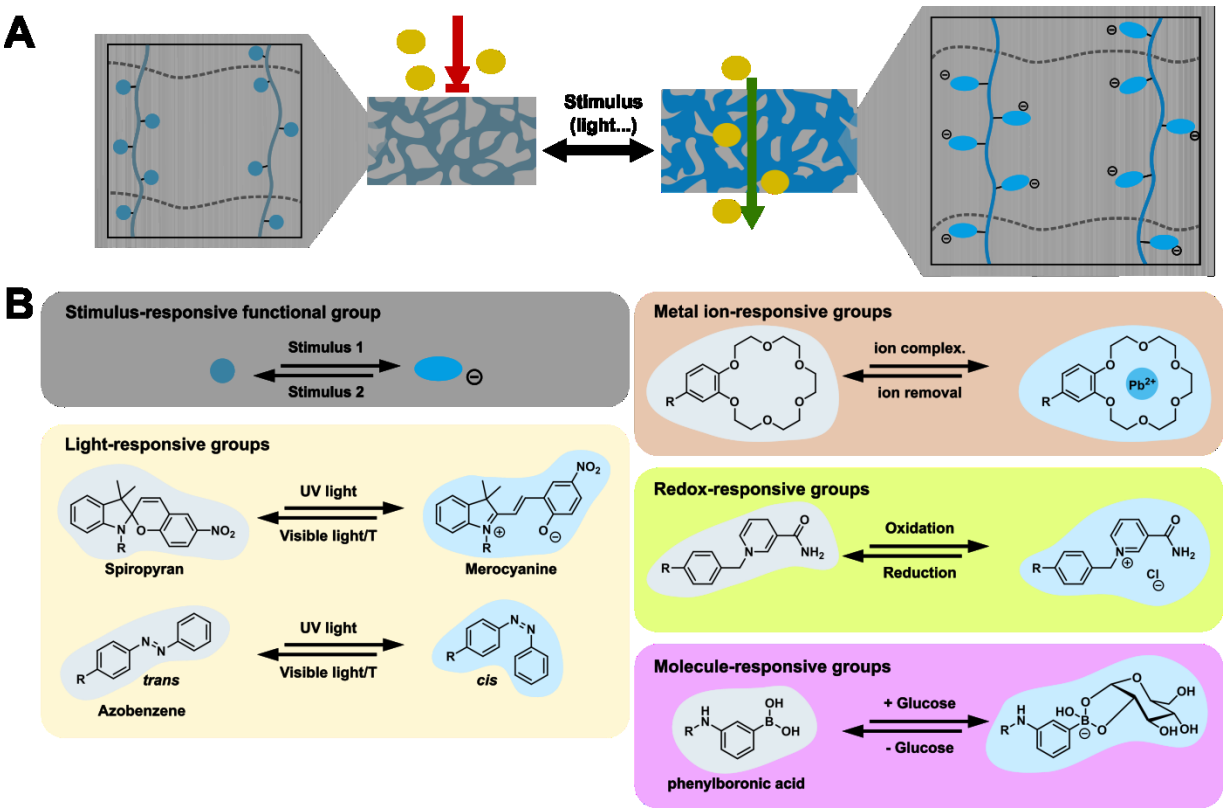

A
Stimulus
(light...)
B
Stimulus-responsive functional group
Stimulus 1
Stimulus 2
Light-responsive groups
UV light
Visible light/T
Spiropyran
Merocyanine
UV light
Visible light/T
trans
cis
Azobenzene
Metal ion-responsive groups
ion complex.
ion removal
Redox-responsive groups
Oxidation
Reduction
Molecule-responsive groups
+ Glucose
- Glucose
phenylboronic acid

Figure 15.12

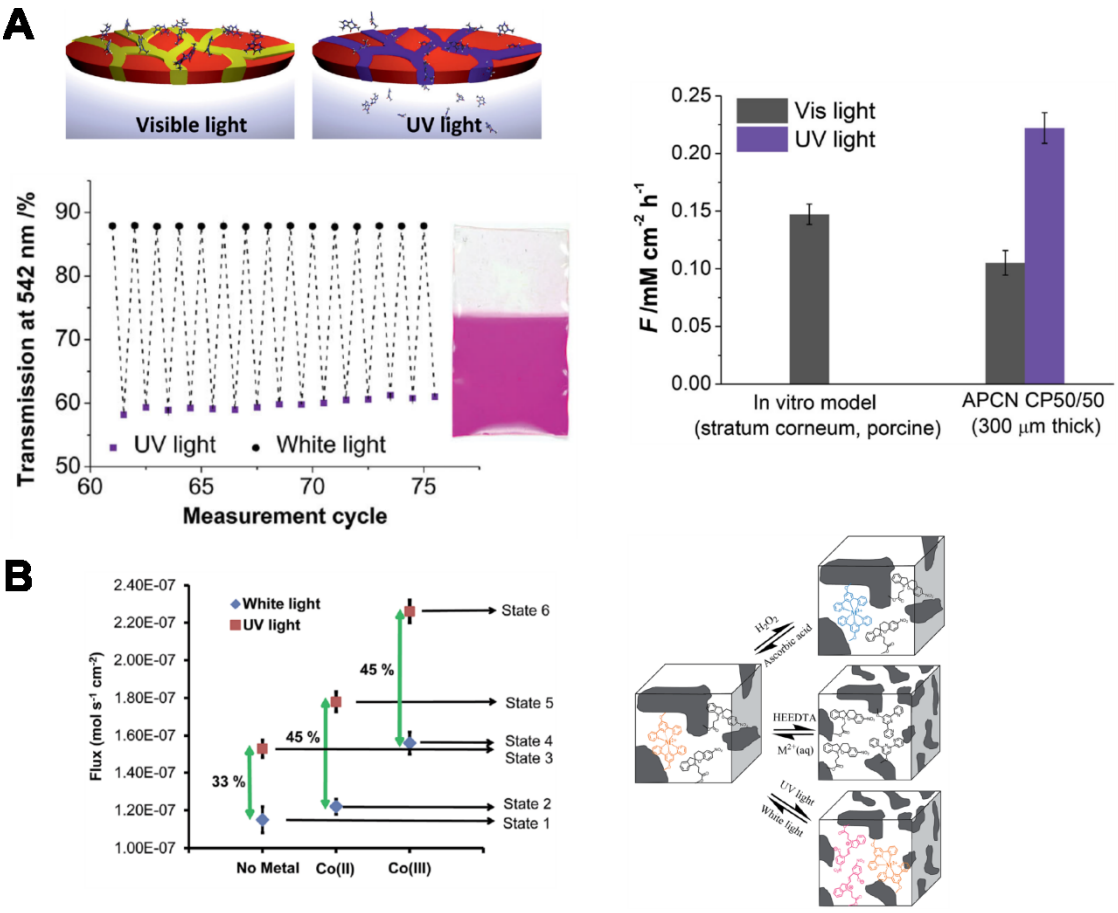
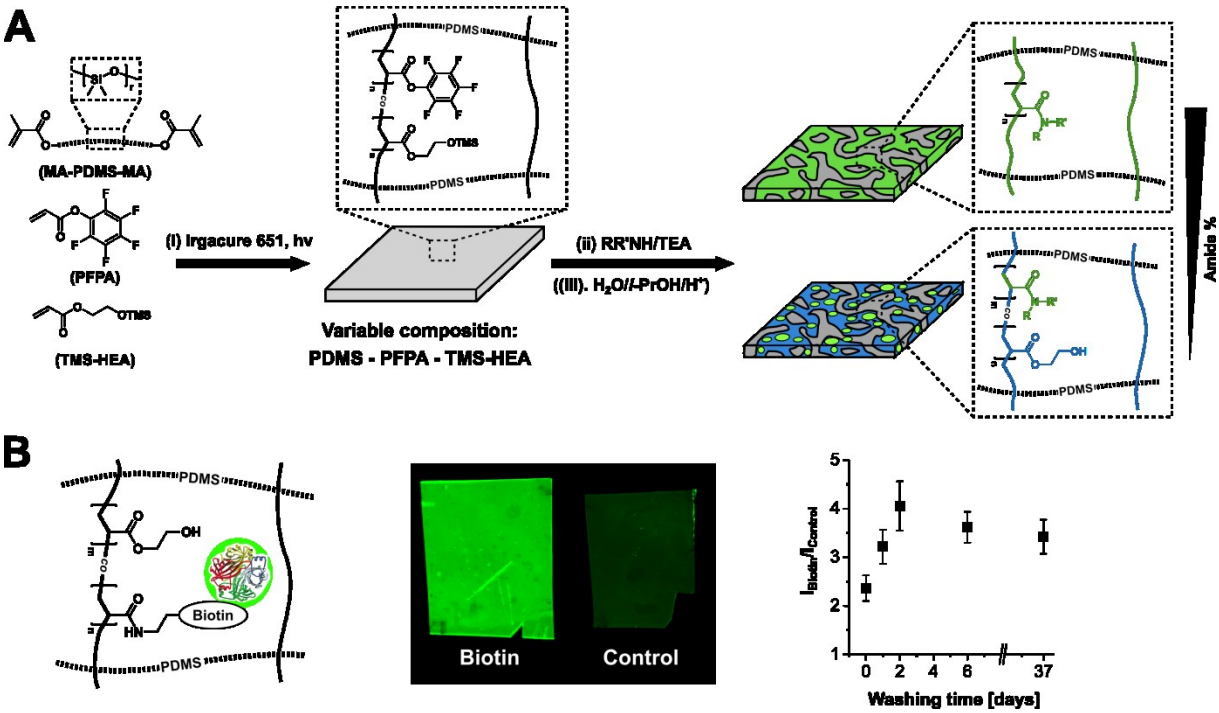

A
Visible light
UV light
Transmission at 542 nm /%
90
80
70
60
50
60
65
70
75
Measurement cycle
UV light
White light
F /mM cm-2 h-1
0.25
0.20
0.15
0.10
0.05
0.00
Vis light
UV light
In vitro model
(stratum corneum, porcine)
APCN CP50/50
(300 μm thick)
B
Flux (mol s-1 cm-2)
2.40E-07
2.20E-07
2.00E-07
1.80E-07
1.60E-07
1.40E-07
1.20E-07
1.00E-07
White light
UV light
State 6
State 5
State 4
State 3
State 2
State 1
45 %
45 %
33 %
No Metal
Co(II)
Co(III)
H2O2
Ascorbic acid
HEEDTA
M2+ (aq)
UV light
White light

Figure 15.13


A
(MA-PDMS-MA)
(PFPA)
(TMS-HEA)
(I) Irgacure 651, hv
Variable composition:
PDMS - PFPA - TMS-HEA
(ii) RR'NH/TEA
((III). H2O/i-PrOH/H+)
Amide %
B
Biotin
Control
I Biotin/I Control
Washing time [days]