

Nanoporous Membranes Derived from Block Copolymers: From Drug Delivery to Water Filtration

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ABSTRACT With nanoscale pores, high porosity, narrow pore size distributions, and tunable chemical and mechanical properties, block copolymers hold tremendous potential as robust, efficient, and highly selective separation membranes. Recent work by Yang *et al.* illustrates how block copolymers can be employed in the preparation of membranes for use in controlled, long-term, protein-delivery devices. Their work demonstrates that highly efficient and tunable separations are possible with block copolymer membranes. Although significant progress over the past 10 years has advanced the quality, efficacy, and applicability of such membranes, more work is required before benefits are realized for other demanding applications such as water purification.

Block copolymers are a class of fascinating, self-assembling soft materials that are composed of macromolecules with long, covalently connected segments of two or more distinct repeating units. These hybrid molecules combine the physical attributes of the different components and can form ordered structures with nanoscopic heterogeneities. Block copolymers have received much attention over the last five decades as property-enhancing additives, adhesives, and thermoplastic elastomers in applications that benefit from the enhanced physical properties they afford. Since the 1990s, the versatility of block copolymers has dramatically increased; many researchers have exploited the exquisite nanostructures formed in block copolymers for use in various advanced technologies.¹

Effectively capitalizing on the technological capacity of block copolymers requires control of composition, molecular weight, and architecture. Nowadays, controlled polymerization methods provide access to virtually limitless chemical and architectural variety in block copolymers. Combining new synthetic methods with an understanding of phase behavior enables researchers to target a wide range of chemical, mechanical, thermal, optical, and electrical properties. The ultimate utility of block copolymers has been recognized for demanding, size-dependent applications ranging from nanolithography to controlled drug delivery to energy applications.^{1,2} Block copolymers have proven particularly advantageous for templating porous membranes. Some morphologies adopted by block copolymers have nearly ideal attributes for liquid separations, making them attractive candidates for use as ultrafiltration (UF) membranes. The most common implementation involves selective removal

of the minority component in a thin film of block copolymer having hexagonally packed cylinders oriented perpendicular to the membrane surface (Figure 1).^{3,4}

Nanoporous membranes derived from block copolymers are being pursued as desirable materials for controlled separations due to their pore size tunability, narrow pore size distributions, and ability for selective functionalization.

Nanoporous Membranes for Drug Delivery.

Nanoporous membranes derived from block copolymers are being pursued as desirable materials for controlled separations due to their pore size tunability, narrow pore size distributions, and ability for selective functionalization. In this issue of *ACS Nano*, Yang *et al.* demonstrate the outstanding potential of nanoporous membranes from block copolymers for controlled drug release.⁵ They show how pore sizes can be tailored to slow the passage of or completely reject different proteins. Such control over diffusion on the nanoscale is also beneficial for other technically demanding separation processes (*e.g.*, water purification).

Currently, the long-term controlled release of therapeutic proteins is an im-

See the accompanying Article by Yang *et al.* on p 3817.

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mense challenge. Patients who require, for example, interferon, erythropoietin, or human growth hormone (hGH) rely on multiple weekly injections.⁶ Implantable long-term controlled drug release systems, which relieve patients of this hardship, are attractive for improved patient compliance and convenience. Furthermore, much smaller doses should be necessary with controlled-release devices because they offer the potential for localized and continuous release; reduction of toxic side effects or immune reactions associated with high-dose injections may be realized. Patients could see huge benefits from such devices.

Significant attention has been focused on the use of nanotechnology for controlled, long-term protein-delivery systems. In what we consider a significant breakthrough, Yang *et al.* have demonstrated a successful strategy for achieving long-term controlled release of protein drugs by incorporating a nanoporous membrane into a drug-eluting device. The enabling membrane contained an 80 nm thick selective layer of gold-coated nanoporous polystyrene, prepared using a polystyrene-*block*-polymethylmethacrylate (PS-PMMA) copolymer film, laid on a microporous polysulfone-supporting membrane. By exploiting a single-file diffusion (SFD) mechanism through the resulting cylindrical nanochannels, they obtained long-term controlled drug release of both bovine serum albumin (BSA) and hGH as model protein drugs with different sizes (their hydrodynamic diameters being about 8 and 3 nm, respectively) for at least two months *in vitro*.

The SFD mechanism is predicted to occur when the pore diameter is no larger than two times the hydrodynamic diameter of the passing solute. Under these circumstances, solute molecules cannot pass each other in the pore and move “single-file” at a constant rate regardless of the concentration gradient. Using

zeolite membranes, Kukla *et al.* demonstrated this rate-controlling mechanism in 1996.⁷ More recently, Martin and colleagues observed SFD-like behavior for the release of BSA from a drug-eluting device containing 13 nm wide slits in silicon.⁸ These particular nanoporous membranes enabled controlled release of BSA *in vivo* over 50 days. However, true SFD was never fully demonstrated in this device, presumably due to the anisotropic slit structure.

The work by Yang *et al.* is one of the first examples of a functioning device in which a controlled diffusion process was successfully implemented. They tailored their pore sizes to achieve SFD of BSA or the smaller hGH by varying the thickness of a gold layer deposited onto the composite membrane. The gold coating also prevented surface fouling—a critical issue for biological separations and *in vivo* applications. Although this gold-coating strategy was successful, the development of new block copolymers that inherently exhibit even smaller feature sizes than those described by Yang are attractive targets for this and other applications.⁹ Yang *et al.* also tuned the rate of SFD by varying the selective layer thickness. Importantly, the hGH was not denatured during elution; results from the *in vivo* pharmacokinetics demonstrated constant release of hGH over a three week period. Their system is promising for the treatment of a variety of diseases and has the potential to be cost-effective, simple to fabricate, and fouling resistant.

Nuxoll *et al.* recently demonstrated another related size-selective, mechanically robust composite membrane.¹⁰ They prepared a nanoporous membrane on top of a modified macroporous silicon support. Their selective layer, which contained perpendicularly oriented cylindrical channels, was prepared by first spin-casting a polystyrene-*block*-polyisoprene-*block*-polylactide (PS-PI-PLA) triblock terpolymer onto a silicon support

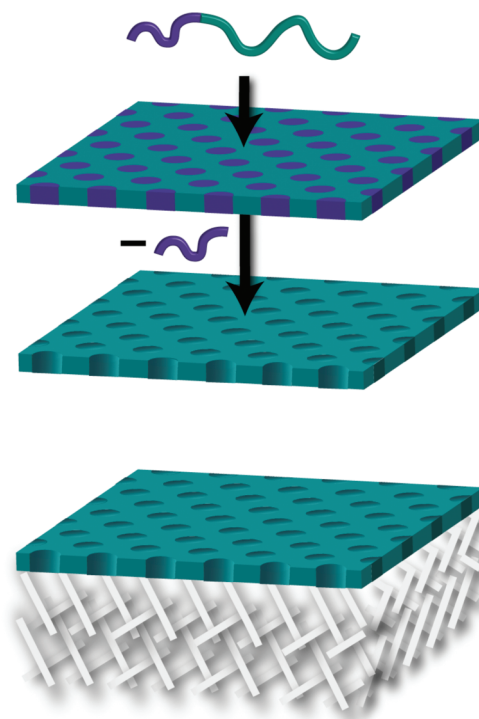


Figure 1. (Top) Schematic representation of a cylinder-forming diblock copolymer thin film and the corresponding nanoporous thin film (green) obtained after selective etching of the minority domains (purple). (Bottom) Composite membrane with nanoporous selective layer on a macroporous support.

followed by etching the PLA with dilute base to give a mechanically robust nanoporous film. Although small molecules could easily pass through, diffusion of the large macromolecule dextran blue was hindered. Furthermore, the PI block had the potential to be chemically modified and thus impart specific pore-wall functionality.¹¹ Uehara and colleagues demonstrated controlled diffusion of BSA and glucose in a series of tough and flexible nanoporous polyethylene membranes.¹² Their membrane was prepared by fuming nitric acid etching of polystyrene from a polyethylene-*block*-polystyrene (PE-PS) copolymer. Controlling the PS etching time resulted in controlled pore sizes and allowed selective transport of glucose over BSA. The controlled selectivity and robust mechanical properties of these membranes highlight their potential for improved glucose or other biosensing devices. Collectively, these results exemplify the versatil-

ity of block-copolymer-derived membranes for size-selective separations with biomedical relevance and will pave the way for other important separation processes such as water purification.

Block-Copolymer-Derived Water Purification Membranes. Providing access to clean water is a global challenge that will ultimately require improvements in the current state of water filtration systems.¹³ Improvements in the technology of filtration systems could provide more affordable clean water for all through industrial, municipal, or small-scale filtrations. Ultrafiltration is just one of the current technologies that could realize significant improvements in separation efficacy from the incorporation of nanoporous membranes prepared using block copolymers.

Typical UF membranes are either quite permeable and not very selective, as in the case of phase-inversion-type membranes, or selective and not that permeable, as in the case of track-etched membranes.¹⁴ To compete successfully in the UF arena, four main criteria are typically needed: high selectivity, high permeability, mechanical integrity, and resistance to fouling.¹⁵ Nanoporous membranes derived from block copolymers have tremendous promise to fulfill all four of those requirements due to their narrow pore size distributions (high selectivity), high porosity (high permeability), and tunable chemical and physical properties, yet research in the science and engineering of such membranes is needed to combine all of these attributes into practical systems. Because flux is inversely proportional to thickness and costs are directly related to amount of material used, separation membranes containing thin, selective block copolymer layers are most desirable.¹⁶ Creative strategies, such as that demonstrated by Yang *et al.*, are needed to produce selective membranes that are mechanically stable and compatible with application-

specific chemical, thermal, and biological environments. Furthermore, fabrication hurdles such as achieving proper pore alignment and scalable fabrication steps must also be overcome.³ We highlight recent progress made toward other block-copolymer-derived nanoporous separation membranes and some of the obstacles that still remain.

Ultrafiltration is just one of the current technologies that could realize significant improvements in separation efficacy from the incorporation of nanoporous membranes prepared using block copolymers.

In important early work, Liu *et al.* showed that water-permeable nanoporous films could be made from poly(*tert*-butyl acrylate)-*block*-poly(2-cinnamoyl ethyl methacrylate) (PtBA-PCEMA) block copolymers.¹⁷ Hydrolysis of the PtBA block left the films with water-compatible poly(acrylic acid) (PAA) cylinders, and pores were effectively formed by soaking the films in high or low pH solutions. They noted that the permeability of their films was comparable to that of PAA-grafted, track-etched membranes and suggested higher permeabilities would have been possible if all channels had been oriented perpendicular to the film surface. In 2006, Cooney *et al.* studied the diffusion of water through a 2 mm thick nanoporous monolith they prepared from a PLA-etched, channel-die aligned polystyrene-*block*-polylactide (PS-

PLA) diblock copolymer.¹⁸ Unlike Liu *et al.*, they observed good orientation of PLA cylindrical domains and complete etching of the PLA phase. After wetting of the pores, the expected steady state flux was observed. Also in 2006, Phillip *et al.* estimated that both higher separation factors and higher permeabilities than are currently possible with commercially available membranes could be achieved using related hydrophilic, nanoporous polystyrene-*block*-poly(dimethylacrylamide) (PS-PDMA).^{14,19} In 2009, Phillip *et al.* showed that high selectivity could be achieved from newly developed, mechanically robust, nanoporous membranes derived from block copolymers.^{20,21}

To compete with phase-inversion membranes, highly selective block copolymer membranes must also provide high flux. Strategies for creating composite membranes—like those described by Yang *et al.*—that combine a thin block copolymer selective layer on top of a porous support layer are important research targets for high-flux membranes. Similar composite membranes for water filtration are also highly desirable but can be more demanding due to the high degree of mechanical integrity needed. Improving mechanical strength of nanoporous films is necessary during fabrication processes and for durability in devices requiring high pressures. For example, Yang and colleagues prepared a composite membrane intended for virus filtration that contained a PS selective layer with 15 nm diameter pores on top of a polysulfone-supporting membrane.²² When the cylinders were perpendicularly aligned, the material was limited by lack of dimensional stability, crack formation, and poor adhesion to the underlying support.²³ In a distinct strategy, thin films made from polybutadiene-*block*-poly(2-vinyl pyridine)-*block*-poly(*tert*-butyl methacrylate) (BVT) terpolymers showed potential as

tough selective layers for composite filtration membranes.²⁴ By selectively UV cross-linking the polybutadiene matrix, Sperschneider *et al.* toughened their thin film without affecting the resulting perpendicular cylinder nanostructure. Because they could easily transfer the film off of a supporting NaCl plate onto another substrate without damaging the film, they suggested that these films could also be combined with a support layer to create a composite membrane. In 2007, Peinemann *et al.* formulated a robust asymmetric membrane by combining block polymer self-assembly with a commercially employed nonsolvent induced phase separation process.²⁵ The membrane, which is composed entirely of a polystyrene-*block*-poly(4-vinylpyridine) (PS-P4VP) block copolymer, exhibited a 250 nm thick nanoporous layer on top of a disordered support layer containing a much larger pore structure.

The use of more complex multiblock polymers, as described above, offers the potential for enhanced mechanical properties and also allows for simultaneous control of pore wall and matrix chemistries. For example, the previously mentioned PS-PDMA monoliths also contained tunable functionality in their design. In 2005, Rzayev *et al.* reported hydrophilic pore walls from a polystyrene-*block*-poly(dimethyl acrylamide)-*block*-polylactide (PS-PDMA-PLA) terpolymer.²⁶ Hydrophilicity is attractive for filtration membranes because it can render them more fouling resistant. Etching the polylactide (PLA) exposed the PDMA midblock and rendered the pores hydrophilic. This PDMA block could be converted into PAA and subsequently modified using a variety of functionalized amines.²⁷ Mao *et al.* incorporated hydrophilic poly(ethylene oxide) (PEO) chains on the pore walls by preparing blends of polystyrene-*block*-poly(ethylene oxide) (PS-PEO) and PS-PLA diblock copolymers followed by etching of the PLA

block.^{28,29} Again, membrane hydrophilicity was achieved by exploiting the miscibility and differing etch sensitivity of PEO and PLA. In 2006, Bailey *et al.* used an alternative, post-etch chemical transfor-

mation step to obtain functionalizable pore walls in a series of PS-PI-PLA block terpolymers that exhibited the core-shell cylinder morphology.⁹ These examples showcase three different methods that can be used to incorporate desired functionality into a nanoporous membrane.

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Block copolymers have also been used to develop chemically and thermally robust membranes. For example, Pitet *et al.* recently developed robust nanoporous polyethylene membranes exhibiting a bicontinuous structure (Figure 2).³⁰ These membranes are attractive

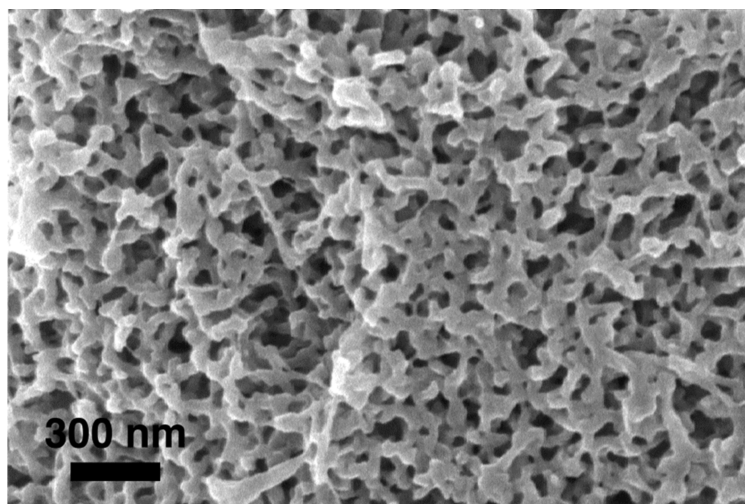


Figure 2. Bicontinuous nanoporous polyethylene membrane prepared from a block copolymer precursor. Reproduced with permission from ref 30. Copyright 2010 American Chemical Society.

precursors for water purification, battery separators, or other demanding applications due to their high porosity and robust nature. Bicontinuous structures such as these do not require separate pore alignment steps, but the increased tortuosity leads to lower permeabilities. Cylindrical morphologies, like those exploited by Yang *et al.* are often appealing because they provide straight paths and therefore minimal resistance.

OUTLOOK AND CONCLUSIONS

More work is needed to develop practical fabrication process for thin film composite membranes that use block copolymers as the selective layer. Most nanoporous thin films for separation membranes have been made from polymers that form cylindrical morphologies. Such films oftentimes must be solvent or thermally annealed after casting to achieve perpendicular orientation of cylinders.³¹ Although these methods can be reliable, processes that are more appealing for large-scale membrane fabrication are desirable. For example, casting blends of block copolymers with either a small amount of dissolved homopolymers or copolymers, as shown by Yang *et al.* and others, is a successful strategy for achieving perpendicular cylinder orientation in BCP films without the need for

post-cast annealing steps. Work is also needed to reduce the overall number and complexity of fabrication steps required to prepare composite membranes. An attractive strategy may be to cast a selective layer directly onto a support layer. Recently, Phillip *et al.* demonstrated this strategy by casting a polystyrene-*block*-poly(lactide) (PS-PLA) diblock copolymer film directly onto water-filled polyethersulfone support membrane.¹⁵

The progress highlighted here provides compelling evidence for the technological power and sophistication afforded by block copolymers. The work by Yang *et al.* demonstrates how a nanoporous membrane prepared from a block copolymer can successfully be used to control diffusion of molecules of different sizes over a long time without membrane fouling. Their work calls attention to the outstanding performance of block copolymer membranes and how, with creative strategies, these materials can be made into useful separation devices. Such composite membranes can combine high flux, mechanical strength, and enhanced selectivity. Fine-tuning the design of block copolymers for such membranes can also provide a wide range of material properties. As discussed here, multiple strategies are being pursued for the development of membranes with chemical, mechanical, and biological integrity. The possibilities for creating advanced separation membranes from block copolymers are truly exciting, and we look forward to the next set of advances in this technologically important arena.

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