Nanoporous Materials for Biomedical Devices

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Nanoporous materials are currently being developed for use in implantable drug delivery systems, bioartificial organs, and other novel medical devices. Advances in nanofabrication have made it possible to precisely control the pore size, pore distribution, porosity, and chemical properties of pores in nanoporous materials. As a result, these materials are attractive for regulating and sensing transport at the molecular level. In this work, the use of nanoporous membranes for biomedical applications is reviewed. The basic concepts underlying membrane transport are presented in the context of design considerations for efficient size sorting. Desirable properties of nanoporous membranes used in implantable devices, including biocompatibility and antibiofouling behavior, are also discussed. In addition, the use of surface modification techniques to improve the function of nanoporous membranes is reviewed. An intriguing possibility involves functionalizing nanoporous materials with smart polymers in order to modulate biomolecular transport in response to pH, temperature, ionic concentration, or other stimuli. These efforts open up avenues to develop smart medical devices that respond to specific physiological conditions.

INTRODUCTION

There is a great interest in incorporating the capabilities of biological membranes in nanoscale medical devices. In nature, cell membranes are equipped with nanometer-scale protein pores to regulate the movement of biological molecules. Another example of a natural filter is the glomerular basement membrane in the kidney.[1] This natural blood filter allows water and small waste molecules to pass into the urine, but prevents proteins (e.g., albumin) and cells from passing into the urine. Similarly, a porous biosensor membrane would allow passage of glucose, oxygen, and other small molecules, but exclude passage of proteins and other large molecules. Researchers have actively sought the development of nanoporous membranes for a variety of implantable medical devices, including diffusion-controlled drug delivery devices, signal-responsive drug delivery devices,[2] immunoisolation devices,[3] and microdialysis systems.[4] Size-sorting and filtration of biomolecules is crucial for these applications.[5]

How would you…

…describe the overall significance of this paper?

The work presents an overview of critical issues in designing nanoporous biosensor membranes for biomedical implants and various materials fabrication strategies explored to address these issues. The possibility of achieving signal-responsive drug delivery by utilizing smart polymers is also discussed.

…describe this work to a materials science and engineering professional with no experience in your technical specialty?

The need for highly selective, biocompatible, and fouling-resistant membranes for implantable biomedical devices has led research into novel nanoporous materials and new fabrication techniques. An overview of research directions toward achieving ideal membrane properties is given.

…describe this work to a layperson?

Nanoporous membranes with superior biocompatibility and higher selectivity for screening biomolecules continue to be developed for implantable devices to achieve controlled drug delivery and immunoisolation. This review presents a materials science perspective on designing ideal membranes.

Nanoporous materials are desirable for the treatment of several chronic medical conditions, including diabetes mellitus. Diabetes mellitus is a group of metabolic diseases that result from defects in insulin action or insulin secretion. Insulin is a hormone produced by the pancreas that promotes the storage of glucose, primarily in the liver. Currently, there are several in-vitro blood glucose monitors (e.g., the MediSense® device) that enable patients to check their blood glucose at home and make adjustments in their insulin doses. These portable blood glucose meters require patients to stick their fingers with a needle to obtain blood samples. These blood samples are placed on test strips, which are analyzed by portable instruments.

The fingerstick procedure can become stressful and painful when repeated several times over the course of a day. Patients, physicians, and medical engineers have sought to replace the current fingerstick testing and subcutaneous injection treatment regimen with a closed-loop system. This ideal closed-loop artificial pancreas would be an entirely implantable device that performs blood glucose sensing and insulin delivery over several months or years. Fast sensing of blood glucose and actuation of insulin delivery would be integrated in order to mimic the physiologic glucose control provided by the pancreas. Insulin delivery systems are continually being reduced in size; over the past two decades, bedside insulin pump systems have been replaced by wearable programmable insulin pump systems. The development of ideal in-

terfaces for such implantable systems will rely on artificial membranes capable of size-sorting and filtration of biomolecules.[5]

A key challenge has been to fabricate membranes with appropriate pore size, pore density, and pore size distribution properties, in order to maximize passage of analytes and minimize passage of fouling materials.[3–5] Recent progress in fabrication techniques has made it possible to make such ideal membranes inexpensively. The major difficulty in creating closed-loop systems that function over long periods of time within the body is the poor in-vivo performance of implantable biosensors. Two phenomena, biofouling and tissue encapsulation, create permeability barriers that decrease analyte flux from the tissue to the sensor.[6] These "sensocompatibility" issues, involving the biological response to sensor materials, have been far more challenging than electrical failure, electrode passivation, enzyme degradation, or other device-related issues.

Many promising biomedical applications for nanoporous materials have recently been discovered, and several of these are currently being explored. Potential applications include use in implantable devices as well as in-vitro analytical systems. In implantable drug delivery or immunoisolation devices, the membrane would function as a semipermeable compartment that holds the implant or drug while allowing passage of desired molecules in a controlled manner.[3] Nanoporous membranes are also the obvious choice for in-vitro analysis, including medical diagnosis, cell evaluation, and protein separation.[7] Enormous research efforts in the past decade have been applied to automate biological analysis, reduce sample consumption, and minimize cost. For example, commercialized micro total analysis system or lab-on-a-chip devices are now available for examining many biological processes.[8] These microfabricated devices are able to perform separation, mixing, reaction, detection, or preconcentration processes using small sample quantities. In particular, extraction of analytes from complex samples has been achieved using variations in diffusivity as well as selective transport through membranes. The range of potential applications for microfabricated systems will depend on the ability of nanoporous materials to sort, detect, and analyze biological molecules. This article will review design considerations for nanoporous materials used in biomedical applications. A current trend is to build smart nanoscale pores capable of signal-responsive flow regulation; in other words, control the pore size dynamically in response to a stimulus such as pH, temperature, or ion concentration. This intriguing possibility will be discussed with respect to recent experiments that involve modification of nanoscale pores with stimulus-responsive polymers.

DESIGN CONSIDERATIONS FOR MOLECULAR SORTING

One of the fundamental issues involved in designing a nanoporous biosensor is to characterize both biomolecule diffusion and size selectivity properties as a function of pore size and pore surface chemistry. The optimal pore size for the semipermeable biosensor membrane must be determined using size and diffusion considerations. An implantable biosensor must be able to dynamically respond to analyte concentration changes by allowing rapid diffusion of relatively small analytes on one hand and preventing diffusion of relatively large molecular weight proteins and undesirable biological materials (e. g., antibodies) on the other hand.

Separation by nanoporous membranes is important for many technological applications, including water desalination, waste treatment, and biological molecule separation. As such, this process has been extensively described in the literature. Since the basic principles that govern size-separation through nanoporous membranes remain the same, we will summarize the existing theory of solute transport through nanoporous membranes.

The figure of merit of a nanoporous membrane is evaluated in terms of hydraulic permeability (L_p) and some sort of pore-size rating.[9] The hydraulic permeability indicates the porosity of the membrane. It is defined as the solvent flux through unit area of the membrane under a unit pressure difference, and it is given by Equation 1, where r_p is the pore radius, η is the solvent viscosity, and $(A_k/\Delta x)$ is the ratio of surface porosity to the pore length. (All equations are presented in the table.) The pore-size rating is usually expressed as molecular-weight cutoff (MWCO). The MWCO is generally defined as the molecular weight for which 90% of the solute is rejected.[10] Rejection (R), which is related to ratio of the analyte concentration in the permeate (c_p) and in the feed solution (c_f), is given by Equation 2.

Equations

$$L_p = \left(\frac{r_p^2}{8\eta}\right)\left(\frac{A_k}{\Delta x}\right) \quad (1)$$

$$R = 1 - \frac{c_p}{c_f} \quad (2)$$

$$D_\infty = \frac{k_B T}{6\pi\mu r_s} \quad (3)$$

$$f = \frac{D_m}{D_\infty} = \frac{(1-\lambda)^2}{(1+2.4\lambda)} \quad (4)$$

$$f = (1-\lambda)^2(1-2.104\lambda + 2.09\lambda^3 - 0.95\lambda^5) \quad (5)$$

$$R = \frac{\sigma(1-F)}{1-\sigma F} \quad (6)$$

$$\sigma = 1 - 2(1-\lambda)^2 - (1-\lambda)^4 \quad (7)$$

HINDERED DIFFUSION OF RIGID MOLECULES

When the pore size of a filtration membrane is comparable to the molecular size of the diffusing species, the diffusion rate is slowed as compared to the bulk and the phenomenon is called hindered or restricted diffusion. Diffusion inside nanometer-scale pores has been the subject of extensive research, and theories of hindered diffusion have been developed, for example, by J.R. Pappenheimer,[11] E.M. Renkin,[12] W.M. Dean,[13] and J.L. Anderson and J.A. Quinn.[14] In general, these models consider idealized membranes with cylindrical capillaries that run parallel to each other across the membrane. In a bulk fluid, the diffusion coefficient D_∞ determines how fast a molecule undergoes Brownian motion. In the Stokes–Einstein equation (Equation 3), k_B is Boltzmann's constant, T is absolute

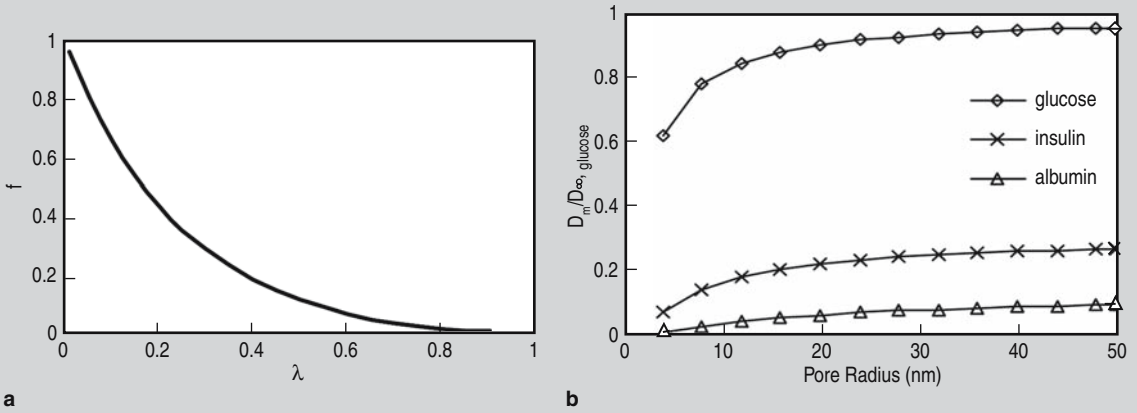

Figure 1. (a) A plot of the ratio f between restricted diffusion and bulk diffusion as a function of the ratio λ between solute radius and the pore radius. (b) The restricted diffusion coefficient of glucose, insulin, and albumin normalized by bulk diffusion coefficient of glucose as a function of pore radius.

temperature, μ is solvent viscosity, and r_s is the hydrodynamic radius of the solute. The ratio f between the restricted diffusion coefficient through the membrane (D_m) and the free diffusion coefficient (D_∞) is generally expressed in terms of the ratio (λ) between r_s and r_p. Several expressions relating f and λ have been used in the literature. For example, J.R. Pappenheimer[11] derived Equation 4 that considers two effects, the wall drag effect and the steric hindrance effect, which come into play when solute molecules pass through tiny pores. A more commonly used expression is E.M. Renkin's equation (Equation 5).[12]

While Renkin's equation quite accurately describes diffusion of rigid molecules through cylindrical nanoscale pores for λ values <0.4, many modifications based on it have been developed. An extensive review of this topic can be found elsewhere.[13,14] In Figure 1a, f is plotted as a function of λ. It is observed that D_m is less than half of D_∞ for solutes as small as a tenth of the pore size. At extremely small values of λ, the bulk diffusivity value is recovered. The effect of spatial confinement on the diffusivity is further illustrated by comparing the diffusion coefficients of glucose (r_s = 0.45 nm), human albumin (r_s = 3.75 nm), and insulin (r_s = 1.5 nm) as a function of pore size (Figure 1b). For example, glucose diffuses about 30 times faster than albumin inside a pore of radius 10 nm, while it is only eight times faster in the bulk.

Solute flux and solvent flux through membranes are often expressed using three transport parameters, L_p, the Staverman reflection coefficient (σ), and the solute permeability through the membrane (P). The rejection of a given solute is given in Equation 6, where $F = \exp\left(-\frac{(1-\sigma)J_v}{P}\right)$ and J_v is the solvent volume flux. There are many expressions relating the Staverman reflection coefficient with λ. For example, J.D. Ferry[15] derived Equation 7. Other models for modeling the reflection curve are present in the literature. The reader is referred to work by W.L. Haberman and R.M. Sayre,[16] as well as reviews by M. Soltanieh and W.N. Gill.[17]

HINDERED DIFFUSION OF FLEXIBLE MOLECULES

The hindered diffusion theories discussed above consider the diffusing molecule to be a rigid sphere whose size is taken as the hydrodynamic radius of the molecule in bulk solution. The assumptions about rigidity and size are not justified for molecules that are flexible, including polymers, nucleic acids (DNA and RNA), unstructured random-coil proteins, and proteins with several rigid domains that are connected by flexible components. This is especially true when the molecule size is equal to or greater than the pore size. In this case, the molecules can deform and orient as dictated by the pore confinement effect. For example, a flexible polymer chain in bulk solution is a random coil with a size quantified by the average radius of gyration r_g, which is a statistical average of monomer distribution around the center of mass for the polymer over all allowed conformations. The radius r_g of the chain in bulk solution varies with the degree of polymerization as $r_g \sim N^\nu$, where ν has values of 3/5 and 1/2 for good and theta solutions, respectively.[18] For modeling bulk diffusion in dilute solutions, polymer chains are appropriately described as rigid spheres of radius r_h, the hydrodynamic radius of the chain, which is closely related to r_g. Hence, the bulk diffusion coefficient of the polymer chain varies as $D_\infty \sim N^{-\nu}$. However, in the case of polymer diffusion through porous media, the chains inside a nanoscale pore can be constrained. As a result, the application of the rigid sphere model is not straightforward. The dynamics of polymer diffusion inside nanoscale pores has been extensively studied, and detailed information can be found elsewhere.[18,19] Studies of diffusion for a wide range of λ values have revealed that there are three regimes, which are derived from the molecular diffusion coefficient dependence on the polymer chain length (N). The rigid sphere model is appropriate under weak confinement ($\lambda < 0.2$), and the hindered diffusion theory can be applied to study diffusion. For $0.2 < \lambda < 0.5$, the chain experiences the confinement in such a way that hydrodynamic interactions between monomers are screened by the pore walls. As a result, diffusion follows Rouse behavior, which is characterized by a diffusion coefficient that varies with chain length as $D_m \sim N^{-1}$ (as opposed to $D_m \sim N^{-\nu}$ for the equivalent sphere model). Stronger confinements ($\lambda > 0.5$) cause chains to further elongate. As a result, reptation be-

comes the main mechanism of diffusion, with a diffusion coefficient $D_m \sim N^{-2}$.

Numerous theoretical studies of macromolecular diffusion in porous media have been developed that essentially fall into two methods, namely the porous-body approach[20] and the scaling approach.[18] The porous body approach has been successful in modeling situations in which $\lambda << 1$, and the scaling approach has been successful in modeling situations in which $\lambda > 1$. Experimental evaluation of these theories has been difficult because the pores in traditional membranes are far from ideal, since they exhibit a wide range of pore size distributions as well as a random network of pores.[21] Recent studies have examined polymer diffusion in well-defined and ordered pores.[22] The use of nanoporous membranes with well-ordered capillary pores is particularly attractive in size sorting and molecular analysis applications. Another emerging area is single molecule analysis, in which long chain molecules (e.g., DNA and RNA) are passed through engineered nanoscale pores and the linear composition of the molecule is determined by examining current variations. In these experiments, the pores are narrow enough ($\lambda > 1$) to enable detection of individual components within the molecule. Theoretical and experimental work describing this process exists in the literature.[19]

It is worthwhile to point out that the advances in nanoscience will aid in fabrication of nanoporous materials that contain small pore sizes with great precision in a pursuit to achieve greater control over molecular transport. Subsequently, transport theories based on ideal pore geometries will more closely correspond with experimental systems, and atomistic computer simulations will be able to more accurately model diffusion processes. Insights from theory and simulations will be important in order to design nanoporous materials for future biomedical applications. In particular, molecular level information on the interaction of diffusing molecules with the pore surface that computer simulations provide can help in designing nanoscale pores with selectivity based on a variety of parameters, including size, charge, and chemical composition.

TYPES OF NANOPOROUS MEMBRANES

Nanoporous membranes can be fabricated using inorganic materials, organic materials, and composite materials. Nanoporous alumina, titania, zirconia, and silica have been developed for liquid phase separation.[9] However, the majority of the commercial filtration and liquid phase separation applications involve the use of polymeric ultrafiltration or microfiltration membranes. The most commonly used polymeric materials contain Nafion®, polycarbonate, polyethylene terephthelate, or polysulfone. Two of the most common techniques that are used to create nanoporous polymeric films are ion-track etching and phase separation.[23] Nanoporous materials can also be made using conventional microfabrication techniques, including lithography and focused ion beam etching.[24] Composite membranes containing both polymer and ceramic components have also been prepared.[9]

Commercial porous membranes generally exhibit broad pore size distribution values and relatively high thickness values. As a result, these materials generally possess poor size cutoff properties and low transport rates. In addition, many polymeric membranes perform poorly in in-vivo environments due to inadequate chemical and mechanical properties. Alternate synthesis methods have been developed in order to fabricate nanoporous materials with very narrow pore size distributions and precise pore geometry properties. For example, anodized nanoporous materials with long, columnar, well-ordered pores including nanoporous alumina[25] and nanoporous silica[26] have gained considerable attention for use in biomedical applications. Recently, C.C. Striemer et al.[27] have fabricated nanoporous silicon membranes from a deposited layer of amorphous silicon using rapid thermal annealing. Membranes with relatively narrow pore size distributions and with pore sizes between 5 nm and 25 nm were fabricated using appropriate annealing temperatures. Another widely used method is the sol-gel process. This process has been used to fabricate nanoporous ceramic materials that contain multiple components.[9]

IN-VIVO APPLICATIONS: CHALLENGES AND PROMISING SOLUTIONS

When biomedical implants come in contact with physiological environments, primarily three types of reactions limit the long-term usage. These are biofouling, implant-tissue interaction, and degradation due to corrosion or wear. Several different approaches are being explored to address these issues such that the future medical implants interact with the host in a controlled and a predictable manner. Biofouling is the accumulation of proteins, cells, and other biological materials on the sensor surface. This process starts immediately upon implantation, when small (<3 kDa) proteins experience adhesive and adsorptive interactions with the biosensor membrane surface.[28] In some cases, larger proteins and cells may impregnate pores and other features on the biosensor surface. The thickness of these fouling layers has been estimated to be in the range of 20 nm to 0.5 μm.[29] In-vivo microdialysis, in-vitro cell, and protein fouling studies have confirmed that membrane biofouling results in decreased sensor signal strength.[30,31]

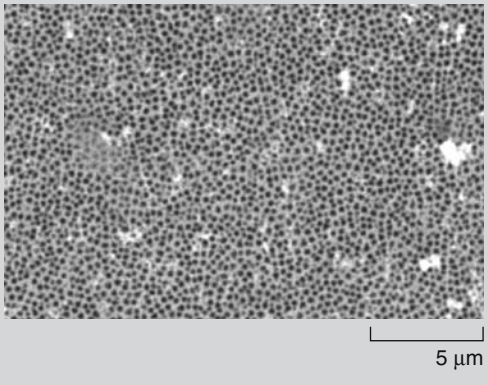

Figure 2. A scanning-electron micrograph of PEGylated, platinum-coated nanoporous alumina membrane after exposure to human platelet-rich plasma. The pores largely remain free of fouling. In addition, fibrin networks or platelet aggregation were not observed on the surface of the platelet-rich plasma-exposed membrane.

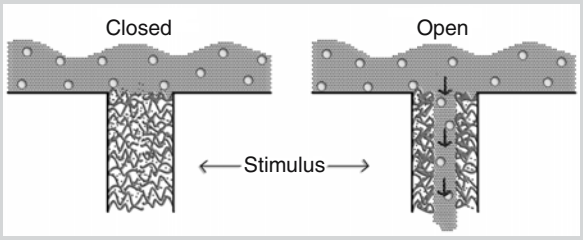

Figure 3. A schematic illustration of nanoscale pores functionalized with responsive polymers for smart drug delivery.

For example, W. Kerner et al.[32] demonstrated that an implantable sensor signal was lost only six hours after implantation, and regained after explanation and recalibration. The gain in sensitivity after sensor removal and recalibration suggested that protein biofouling was a major cause of implantable sensor failure.

Several materials have been employed to modify the tissue-material interface of implantable biosensors, including Nafion, hydrogels, phospholipids, surfactants, materials with covalent attachments, diamond-like carbon coatings, and flow-based systems.[33] These materials are employed to maintain the passage of desired analyte molecules over time. Specifically, these surfaces must reduce protein adsorption and promote integration of the sensor with the surrounding tissues. Furthermore, these surfaces must be sufficiently thin and/or porous in order to allow the sensor to rapidly respond to fluctuations in analyte concentration.

One promising method to modify the surfaces of nanoporous membranes is atomic layer deposition (ALD). Atomic layer deposition is a thin film growth technique that utilizes alternating, self-limiting, chemical reactions between gaseous precursor molecules and a surface in order to create thin film in an atomic layer-by-layer fashion. A wide variety of materials may be processed using ALD, including inorganic oxides, nitrides, and metals. Saturation of the individual reactions during the ALD process ensures that all surfaces of a given substrate, including surfaces that are deeply embedded within a porous material, receive coatings with uniform thickness values. Consequently, ALD can be used to deposit conformal thin films with precise thickness values on nanoscale pores within nanoporous membranes.[34] As such, an ALD-deposited protective coating may be used to deposit corrosion-resistant or protein biofouling-resistant surfaces (Figure 2). In addition, the conformal nature of the ALD coating allows one to reduce the pore diameter in a nanoporous membrane to below ten nanometers while retaining a narrow pore size distribution.[35]

Recently, much success has been obtained by functionalizing implant surfaces with polyethylene glycol (PEG).[36] These water-swellable, cross-linked polymers line up parallel to each other in order to create a hydrophilic interface between the biosensor surface and the largely aqueous surroundings that resist protein penetration. Water-soluble analytes can diffuse easily through these water-swollen polymers. This material is soluble in several organic solvents, including alcohol, benzene, toluene, and water. Unlike ethylene glycol, which can be enzymatically degraded to glycoaldehyde, glycolate, glycolic acid, glyoxylate, and other toxic metabolites, triethylene glycol and larger polyethylene glycol molecules have been proven to be nontoxic. Animal reproductive and developmental studies have shown no biologically significant embryotoxicity or teratogenicity associated with triethylene glycol ingestion. In addition, triethylene glycol and polyethylene glycol oligomers (e.g., PEG-4 and PEG-8) were shown not to be mutagenic or genotoxic in chromosomal aberration or Ames assays.[37] In-vivo studies using mouse and rabbit models have shown that polyethylene glycol does not elicit antibody formation and is nonimmunogenic.[38] Polyethylene glycol materials are considered safe for in-vivo use, and are currently used in drug-delivery products.[39]

Novel surface modifications on nanoporous alumina membranes have been explored to improve biocompatibility. Platinum was conformally deposited on the membranes using ALD to prevent aluminum release. Subsequently, the membranes were modified with polyethylene glycol to impart antifouling properties. In-vitro studies of protein adsorption on these modified membranes performed using a polydisperse protein solution showed that the coated membranes remained free from fibrin or platelet aggregation after exposure to human platelet rich plasma (Figure 2).

TOWARD SIGNAL-RESPONSIVE MEMBRANES

In an effort to mimic the ability of biological systems to respond to specific molecules or other stimuli, the development of biomimetic synthetic nanoporous membranes that change their permeability in response to environmental stimuli has been recently pursued. Fabrication of such novel membranes has significance to applications in smart drug delivery systems, biosensors, and biomolecular separation devices. The interest mainly stems from the intriguing possibility of autonomous flow control/sensor devices. One possible application is self-regulated drug delivery, in which transport of an encapsulated drug is regulated based on a change in a given physiologic parameter. The functionality of the majority of these smart membranes is based on reversible expansion and collapse of responsive polymers incorporated into the membranes that regulate fluid/molecular transport through the pores and provide a chemomechanical effect (Figure 3). These hybrid nanoporous membranes have been prepared by functionalizing responsive polymers into a wide variety of porous supports, including nanoporous alumina membranes, silica membranes, track-etched polycarbonate membranes, and other polymer membranes. By functionalizing the membrane with a suitable responsive polymer, switchable membrane permeability in response to variation in temperature,[40–42] pH,[43] ionic/solute concentration,[44] and light[45] has been demonstrated. Similarly, polymers that respond to electric fields[46] offer an additional triggering mechanism.

These nanoporous stimuli-responsive flow-gating systems are attractive alternatives to conventional flow-control systems in micro/nano fluidic chan-

nels. Conventional mechanical flow-control systems include sensors, actuators, and sources of energy. The nanovalve system based on smart polymers could potentially combine both sensor and actuator functionalities. As a result, the system would allow for efficient combination and analysis of biological samples in miniaturized lab-on-chip devices. Some novel smart flow control valves have already been investigated for autonomous flow control in microfluidic systems. In addition, they have also been explored for smart drug delivery, chromatography, and selective transport of analytes. This class of smart materials is of particular interest in smart drug delivery systems, tunable membrane separation, and catalytic reactions. Additionally, one could envision a variety of other applications for signal-responsive flow-control valves including molecular pumps, solute storage/release systems, and chemical-to-mechanical energy conversion systems.

In general, three distinct approaches have been used to functionalize membranes with smart polymers. In one widely used method, polymer chains are densely end-grafted onto the surface to form a polymer brush layer inside the pore and/or on the surface of the porous support. The brush layer can stretch and collapse in a reversible manner to open and close the pores in response to a stimulus. In the second method, responsive cross-linked polymer gels are incorporated into a nanoporous support. In the third method, porous membranes are modified by depositing layer-by-layer assembled polyelectrolyte multilayers inside pores; changes in film thickness are utilized to produce membrane responsiveness.

Temperature-sensitive grafted polymers have been exploited to achieve flow regulation in synthetic membranes. For example, S. Akerman et al. prepared PNIPAAM grafted poly(vinylidene fluoride) (PVDF) membranes and measured transport of model compounds across the grafted membranes. They demonstrated that movement of large molecules can be controlled as a function of temperature. The flow regulation was shown to be a function of grafting density, degree of polymerization, and ionic concentration.[41] In another study, L.Y. Chu et al. synthesized membranes composed of a porous substrate membrane, polyacrylamide (PAAM), and polyacrylic acid (PAAC)-based interpenetrating polymer networks (IPNs) in the pores. In this system, the pores act as thermoresponsive gates with a temperature response reverse to that of PNIPAAM. In other words, the "opening" of the membrane pores is enabled by a decrease rather than an increase in the environmental temperature.[47] G.V.R. Rao and G.P. Lopez synthesized a hybrid membrane composed of temperature-sensitive poly(N-isopropylacrylamide) (PNIPAAM) in a dense silica matrix using sol-gel process. PNIPAAM is a thermo-responsive polymer that exhibits a hydrophilic (stretched conformation) to hydrophobic (collapsed conformation) transition at its lower critical solution temperature (31°C). By cycling the temperature between 25°C and 40°C, they demonstrated reversible gating and size-selective permeation through this membrane.[48] They have also fabricated functional membranes containing elastin-like polypeptides in the place of PNIPAAM. Elastin-like polypeptides may exhibit a wide range of lower critical solution temperature values, depending on the primary sequence and the length of these materials.[49]

pH-sensitive materials have also been utilized to achieve flow regulation in synthetic membranes. For example, D.J. Beebe et al. recently used pH-sensitive hydrogel methacrylate to regulate flow inside microfluidic channels.[50] Y.S. Park et al. demonstrated a pH-responsive nanometer-scale gate in which a polypeptide brush was grafted into a gold-plated nanoporous membrane.[51] Water permeation through the material was regulated by helix-coil transformation of grafted poly-(L-glutamic acid) chains in response to pH. At low pH values, grafted poly-(L-glutamic acid) has a helical conformation. As the pH is increased, the helical conformation expands to a random coil conformation. This transition reduces the effective pore diameter and hence the system permeability. M. Mika et al.[43] synthesized smart membranes with inverse pH behavior. They reported that polypropylene microfiltration membranes containing poly(4-vinylpyridine) anchored within the pores that exhibited very large chemical valve effects, specifically, an increase in pressure-driven permeability by more than three orders of magnitude when the pH was increased from two to five.[43] J.B. Qu et al.[52] demonstrated a novel composite membrane system which utilized both grafted polymers and gels to produce a large pH-responsive release. Their membrane consisted of a porous PVDF membrane grafted with positively pH-responsive poly(methacrylic acid) (PMAA) linear chains. These smart pores in the membrane acted as flow control valves to a reservoir inside which a crosslinked, negatively pH-responsive poly(N,N-dimethylaminoethyl methacrylate) (PDM) hydrogel functioned as a functional pumping element. The cooperative action of the pH-responsive gating and pumping systems produced responsive release rates much higher than either of the mechanisms used alone.[52] Next-generation nanoporous materials are envisioned with multiple biological functionalities, including size screening, responsive flow regulation, and dynamic pore sizing.

CONCLUSIONS

Nanoporous materials may be used to enhance the performance of many biomedical devices, including immunoisolation devices, dialysis, targeted drug delivery systems, bioanalytical devices, and biosensors. Some of the key properties that nanoporous membranes are required to possess for biomedical applications include a pore size of a few tens of nanometers or less; a narrow pore size distribution in order to achieve high biomolecule selectivity; high porosity as well as low thickness in order to enable high analyte flux; mechanical stability; and chemical stability. Pore geometry, biocompatibility, and biofouling resistance are central issues for membranes that are used as interfaces in implantable devices. Studies are currently underway that involve fabricating nanoporous membranes that exhibit good compatibility with surrounding tissues as well as low protein adsorption. Many challenges lie ahead when developing nonfouling nanoporous materials that are suitable for long-term in-vivo biomedical applications.

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