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Surface modification of polymeric membranes for low protein binding

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Abstract. Surface modification of microfiltration and ultrafiltration membranes has been widely used to improve the protein adsorption resistance and permeation properties of hydrophobic membranes. Several surface modification methods for converting conventional membranes into low-protein-binding membranes are reviewed. They are categorized as either physical modification or chemical modification of the membrane surface. Physical modification of the membrane surface can be achieved by coating it with hydrophilic polymers, hydrophilic-hydrophobic copolymers, surfactants or proteins. Another method of physical modification is plasma treatment with gases. A hydrophilic membrane surface can be also generated during phase-inverted micro-separation during membrane formation, by blending hydrophilic or hydrophilic-hydrophobic polymers with a hydrophobic base membrane polymer. The most widely used method of chemical modification is surface grafting of a hydrophilic polymer by UV polymerization because it is the easiest method; the membranes are dipped into monomers with and without photo-initiators, then irradiated with UV. Plasma-induced polymerization of hydrophilic monomers on the surface is another popular method, and surface chemical reactions have also been developed by several researchers. Several important examples of physical and chemical modifications of membrane surfaces for low-protein-binding are summarized in this article.

Keywords: surface modification; ultrafiltration; microfiltration; fouling; biofouling; low-protein-binding.

1. Introduction

Microfiltration (MF) and ultrafiltration (UF) are commonly used in the biotechnology industry to concentrate and/or purify desired proteins, sugars, fruit juices and pharmaceuticals. It is desirable to enhance membrane performance through concentration and purification processes, because the loss of membrane performance over time, due to biofouling, is a major limitation of using pressure-

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driven membrane processes.

Most MF and UF membranes are conventionally made from so-called engineering plastics, such as polysulfone (PSf), polyethersulfone (PES) and polyvinyldinefluoride (PVDF), which are hydrophobic materials. Hydrophobic materials are used because of the need for sterilization with hot water in the food, medical and biotechnological industries.

It is known that hydrophobic membrane surfaces exhibit much higher protein adsorption than hydrophilic membrane surfaces; this leads to biofouling, because the hydrophobic interaction between proteins and the hydrophobic surface of the membrane results in irreversible adsorption of proteins on the surface (Higuchi, *et al.* 1988, Toyomoto and Higuchi 1992).

Hydrophilic membranes, such as cellulose acetate, poly(vinyl alcohol) and polyacrylonitrile (PAN) membranes, are sometimes used as low-protein-binding membranes. These membranes, however, do not exhibit good thermal stability and are susceptible to chemical and bacteriological agents, whereas hydrophobic membranes (i.e., PVDF, PSf and PES) show thermal stability and some chemical resistance.

Surface modification of hydrophobic membranes to introduce hydrophilic segments only on the surface is a way to exploit the advantages of both hydrophilic and hydrophobic membranes. The original characteristics of mechanical strength and thermal stability are retained in the membranes since only the surface is modified. On the other hand, the hydrophilic skin layers of the membranes govern the transport characteristics. Therefore, surface modification has been widely used to improve the protein adsorption resistance and permeation properties of hydrophobic membranes. Several surface modification methods have been reported in the literature to convert conventional membranes into low-protein-binding membranes (Hatakeyama, *et al.* 2009, Nunes, *et al.* 1995). They can be categorized as either physical modification or chemical modification of the membrane surface. The physical modification of membrane surfaces can be achieved by coating with a hydrophilic polymer, a hydrophilic-hydrophobic copolymer, surfactants or proteins (Louie, *et al.* 2006, Ghosh and Cui 1998). Other methods of physical modification are plasma treatment with O_2, Ar, He, NH_3, CO_2 and other gases (He, *et al.* 2009, Kull, *et al.* 2005, Yu, *et al.* 2008). A hydrophilic surface can be also generated on the membrane surface by phase-inverted micro-separation during membrane formation, using a blended polymer of hydrophilic or hydrophilic-hydrophobic copolymers with a hydrophobic base membrane polymer (Hester and Mayes 2002, Zhao, *et al.* 2008a, 2008b).

There are several methods for chemical modification of a membrane surface. The most widely used method is the surface grafting of hydrophilic polymers by UV polymerization (Hatakeyama, *et al.* 2009, Tian, *et al.* 2007, Zhang, *et al*. 2009). This is the easiest method; membranes are dipped into monomers with and without photo-initiators, and then irradiated with UV light. Plasma-induced polymerization of hydrophilic monomers on the surface is another popular method (Ulbricht and Belfort 1996, Chang, *et al.* 2008a). Also, several researchers have developed surface chemical reactions on membranes (Barona, *et al.* 2007, Higuchi, *et al.* 1990, 2002). Some interesting examples of physical and chemical modification of membrane surfaces for low-protein-binding are discussed in the upcoming section.

2. Physical modification of the surface

Coating hydrophobic membranes with hydrophilic polymers is a popular physical surface modification method for preparing protein-resistant membranes. Some examples of coating materials that produce low-protein binding are listed in Table 1.

Table 1 Coating materials on the surface of the membranes for low-protein binding

Coating materials	Charge of coating materials	Specificity	Base membrane materials coated[a]	Ref
PEBAX 1657[b]	Neutral	Hydrophilic-hydrophobic block copolymer	Polyamide (RO) ESPA1, ESPA3, SWC4[c]	Louie, *et al.* (2006)
PEBAX 1657[b]	Neutral	Hydrophilic-hydrophobic block copolymer	PVDF (MF)	Nunes, *et al.* (1995)
PVP	Neutral	Hydrophilic polymer	PP (MF)	Liu, *et al.* (2005)
Myoglobin	zwitterion	Protein pretreatment	PSf (UF)	Ghosh and Cui (1998)

[a]UF: ultrafiltration membrane, MF: microfiltration membrane, RO: reverse osomosis membrane
[b]PEBAX1657: Nylon-polyethylene oxide block copolymer
[c]ESPA1, ESPA3, and SWC4: RO membranes produced by Hydranautics (Oceanside, CA)

Nunes, *et al.* (1995) prepared microporous poly(vinylidene fluoride) (PVDF) membranes coated with different grades of hydrophilic polyether-polyamide (PEBAX^{R}) to generate non-porous ultrafiltration (UF) membranes. The PEBAX-coated membranes demonstrated higher permeate fluxes than porous, uncoated PVDF membranes during filtration of an oil-water emulsion. This is because the relatively hydrophobic surfaces of the uncoated membranes were more susceptible to hydrophobic foulants than the membranes coated with hydrophilic PEBAX. The coated membranes had higher permeate fluxes when operated with a fouling feed solution, while the fluxes of pure water through the coated, nonporous membranes were lower than those of the microporous PVDF membranes. An ideal fouling-resistant coating would be an ultrathin, highly water-permeable surface layer that does not significantly increase resistance to water flux. The effect of such a coating layer on membrane flux can be predicted using the series resistance model (Nunes, *et al.* 1995).

Louie, *et al.* (2006) prepared PEBAX-coated reverse osmosis (RO) polyamide membranes, where the coating not only covered the surface of the polyamide membrane but also penetrated into its porous ridge-and-valley structure. A long-term (106-day) fouling test with an oil/surfactant/water emulsion demonstrated that the flux through the uncoated membranes declined more rapidly than the flux through the coated membranes.

Phosphorylcholine (PC) is an electrically neutral zwitterionic head group, which represents the dominant property of the phospholipids that exist on the external surfaces of cell membranes, and can effectively reduce protein adsorption. An artificially synthesized monomer of 2-methacryloyloxyethylphosphorylcholine (MPC) has been prepared, and many MPC-based materials bearing PC groups on side chains have been developed by several researchers, with the goal of inhibiting protein adsorption and platelet adhesion (Feng, *et al.* 2005, Ishihara, *et al.* 2000, Su, *et al.* 2008). Ishihara, *et al.* (1999a and 1999b) reported that blending membranes with the MPC copolymer was an effective treatment for both improving hemocompatibility and reducing protein fouling. They also showed that blended membranes of polysulfone (PSf) and MPC polymers could improve blood compatibility and reduce protein adsorption and platelet adhesion.

Su, *et al.* (2008) blended an amphiphilic random copolymer, composed of MPC and *n*-butyl methacrylate (BMA) synthesized by radical copolymerization with polyethersulfone (PES), to fabricate antifouling ultrafiltration membranes. The amounts of adsorbed bovine serum albumin (BSA) on the MPC-modified PES membranes were dramatically decreased when compared against the control PES membrane. In ultrafiltration experiments in which BSA solution flowed through the MPC-

modified PES membranes, BSA rejection was decreased through the membranes, while the flux recovery ratio was remarkably increased, and the degree of irreversible fouling decreased significantly. The MPC-modified PES membranes were reported to be able to run several cycles without substantial flux loss (Su, *et al.* 2008).

Hester and Mayes (2002) prepared PVDF membranes blended with an amphiphilic comb polymer with a methacrylate backbone and poly(ethylene oxide), PEO, side chains. The surface coverage of the amphiphilic comb polymer increased with the comb molecular weight, providing hydrophilic surfaces with high stability by surface localization. The resulting blend membranes exhibited substantially reduced flux decline during filtration of a protein solution, compared to pure PVDF membranes with similar pore sizes and separation characteristics relative to BSA. Fouling resistance increased as the PEO side chain length was increased from 5 to 45 ethylene oxide (EO) segments, at constant overall PEO content in the comb. The membrane containing 10 wt% of the comb with 45-unit PEO side chains had a pure water permeability nearly five times than that of a pure PVDF membrane with equivalent separation characteristics. This is because the surface segregation modified the pore channel surfaces throughout the membrane cross-section, in contrast with other surface modification techniques, which generally modify pore channel surfaces in the region of the separation surface. This may have important consequences with respect to fouling in situations where foulants are sufficiently small to pass through the membrane (Hester and Mayes 2002).

Table 2 Blending materials of the membranes for low-protein binding

Blending materials	Charge of blendingmaterials	Specificity	Base membrane materials blended	Ref
Pluronic F127	Neutral	Hydrophilic-hydrophobic block copolymer	PES	Yu, *et al.* (2008)
Poly(amide-imide)	Neutral	Aromatic copolymer	PES	Rahimpour, *et al.* (2008)
Pluronic	Neutral	Hydrophilic-hydrophobic block copolymer	PVDF	Zhao, *et al.* (2008a)
Comb-like copolymer	Neutral	Hydrophilic-hydrophobic block copolymer	PVDF	Zhao, *et al.* (2008a)
Amphiphilic comb polymer[a]	Neutral	Hydrophilic-hydrophobic copolymer	PVDF	Hester and Mayers (2002)
MPC copolymer	Twitterion	Hydrophilic-hydrophobic copolymer	PSf	Ishihara, *et al.* (1999a) Ishihara, *et al.* (1999b)
MPC copolymer	Twitterion	Hydrophilic-hydrophobic copolymer	PES	Su, *et al.* (2008)
Polyaniline	Neutral	Hydrophilic nanofiber	PSf	Fan, *et al.* (2008)
PEGlated PSf	Neutral	Hydrophilic sgments grafted hydrophobic polymer	PES	Shi, *et al.* (2007)
Amphiphilic heperbranched-star poymer[b]	Neutral	Hydrophilic-hydrophobic copolymer	PVDF	Zhao, *et al.* (2007)
PVP	Neutral	Hydrophilic polymer	PSf	Kim, *et al.* (2005)

[a]Polymethacrylate backbone and poly(ethylene oxide) side chain
[b]Hyperbranched polyester-g-methoxy poly(ethyleneglycol)s

The use of other hydrophilic polymers, such as pegylated PES (Shi, *et al.* 2007), amphiphilic hyperbranched-star polymers (i.e., hyperbranched polyester grafted with methoxy poly[ethylene glycol]s) (Zhao, *et al.* 2007), pluronic (PEO-PPO-PEO triblock copolymer) (Wang, *et al.* 2006) and poly(*N*-vinyl-2-pyrrolidone), PVP, (Kim, *et al.* 2005) as blended polymers in hydrophobic membranes to prepare protein-resistant membranes has also been reported. Table 2 summarizes some examples of the blending materials used on membranes for low-protein binding.

Another physical modification of membrane surfaces that can prevent protein fouling is plasma treatment of hydrophobic membranes. Glow discharge (plasma deposition) under several gases (i.e., N_2, O_2, CO_2, NH_3 and Ar) is known to increase the surface energy and to decrease the contact angle of water on a membrane surface (He, *et al.* 2009, Kull, *et al.* 2005, Yu, *et al.* 2008).

He, *et al.* (2009) used CO_2 plasma to modify hydrophobic polypropylene (PP) MF membranes and create hydrophilic surfaces. The relative pure water flux through the modified membranes had a maximal value for a plasma treatment time of 2 min. The amount of protein adsorption decreased by over 50% in the treated membranes. The results demonstrated that BSA fouling was significantly suppressed by plasma surface modification (He, *et al.* 2009).

Kull, *et al.* (2005) used nitrogen-based plasma systems such as N_2, NH_3, Ar/NH_3 and O_2/NH_3 to modify microporous PES membranes. Their treatments were designed to alter the surface chemistry of the membranes to create permanently hydrophilic surfaces. Contact angle measurements taken initially and 1 year post-treatment confirmed that treatments using O_2/NH_3 plasmas (with a 5:3 gas flow ratio) successfully achieved their design goals. The plasma was found to penetrate the thickness of the membrane, thereby modifying the entire membrane cross-section. Optical emission spectroscopy studies of excited state species present in the modifying gases revealed the presence of OH*, which was not present in a 100% ammonia plasma, suggesting that OH* must play a critical role in the membrane modification process (Kull, *et al.* 2005). The treated membranes exhibited increased water flux, reduced protein fouling and greater flux recovery after gentle cleaning when compared to an untreated membrane.

3. Chemical modification of the surface

Surface reactions between active reagents and membranes are useful methods for introducing various functional groups, such as hydrophilic non-charged segments, negatively charged segments, positively charged segments and zwitterionic segments. There are three major methods of chemical membrane surface modification for low-protein binding membranes: surface modification by plasma-induced polymerization, by photo polymerization and by chemical reactions. Table 3 and 4 summarize some examples of chemical modification of membrane surfaces for low-protein binding. These methods are described below.

3.1. Surface modification by plasma-induced polymerization

Plasma-induced graft polymerization has the advantage that the graft polymer is not chemically altered by the plasma (Ulbricht and Belfort 1996). Modification of membrane permeability by graft polymer layers of this type has been reported for polypropylene (PP), polysulfone (PSf), polyethersulfone (PES) (Chen and Belfort 1999), polycarbonate (PC) (Ito, *et al.* 1990), poly(tetrafluoroethylene) (PTFE) (Chang, *et al.* 2008a) and poly(vinylidene fluoride) (PVDF) (Takahashi and Hisatomi 2009)

Table 3 Surface reaction for the surface modification of the membranes for low-protein binding (Introduction of neutral segments)[a]

Functional group or segments introduced	Membrane materials for surface reaction	Reaction method	Ref.
Hyperbranched-star PEG			
PEG	-COOH	Estification reaction	Nie, *et al.* (2004)
PEG methacrylate	PES	UV copolymerization	Susanto, *et al.* (2007)
PEG methacrylate	Teflon	Plasma-induced Polymerization	Chang, *et al.* (2008a)
PEG-MA	PES	Redox reaction	Belfer, *et al.* (2000)
PEG methacrylate	PSf	ATRP	Li, *et al.* (2009)
PEG methacrylate	PAN	UV polymerization	Ulbricht, *et al.* (1996a)
PEG methacrylate	PVDF	Ozone & thermally induced polymerization	Chang, *et al.* (2008b)
MPEG	PSf	UV grafting	Tian, *et al.* (2007)
ABIMPEG	PSf	UV grafting	Tian, *et al.* (2007)
HEMA	PSf	ATRP	Li, *et al.* (2009)
HEMA	PES	UV copolymerization	Taniguchi, *et al.* (2003)
HEMA	PP	UV copolymerization	Hu, *et al.* (2006)
HEMA	PAN	UV polymerization	Ulbricht, *et al.* (1996a)
HEMA	PSf, PAN	Plasma polymerization	Ulbricht and Belfort (1996)
HEMA		Ozone-induced polymerization	Wang, *et al.* (2000)
NVP	PES	UV copolymerization	Taniguchi, *et al.* (2003)
NVP	PES	UV copolymerization	Zhang, *et al.* (2009)
NVP	PES	UV copolymerization	Pieracci, *et al*. (1999)
NVP	PES	UV copolymerization	Kaeselev, *et al.* (2001)
NVP	PES, PSf	UV polymerization	Kaeselev, et al. (2001)
NVP	PES	Plasma-induced polymerization	Chen, *et al.* (1999)
NVF	PES	UV copolymerization	Pieracci, *et al.* (1999)
NVC	PES	UV copolymerization	Pieracci, *et al.* (1999)
NVP	PVDF	Plasma-induced polymerization	Takahashi and Hisatomi (2009)
ACMO	PVDF	Plasma-induced polymerization	Takahashi and Hisatomi (2009)
Pluronic	ADCS coated on MCE	Chemical reaction	Rajam and Ho (2006)
GAMA	PAN	UV copolymerization	Dai, *et al.* (2008)
GAMA	PP	UV copolymerization	Gu, *et al.* (2009)
PVA	PES	Interfacial polymerization	Liu, *et al.* (2009)
PVA	Nylon	Chemical reaction	Castilho, *et al.* (2000)
Dextran	Nylon	Chemical reaction	Castilho, *et al.* (2000)
PEG	PES	Interfacial polymerization	Liu, *et al.* (2009)
$-CONH_2$	PP	Plasma-induced Polymerization	Yu, *et al.* (2008)

[a]ABIMPEG: 4-azidobenzoy-limino-monomethoxypoly(ethylene glycol), ACMO: acryloyl morpholine, ADCS: allyldimethylchlorosilane, GAMA: d-gluconamidoethyl methacrylate, MA: methacrylic acid, MCE: mixed cellulose ester, MPEG: methoxypoly(ethylene) glycol, NVC: N-vinylcaprolactam, NVF: N-vinylformamide, PAN: polyacrylonitrile, PP: polypropylene, PVA: polyvinyl alcohol

Table 4 Surface reaction for the surface modification of the membranes for low-protein binding (Introduction of electrically charged segments)[a]

Functional group or segments introduced	Membrane materials for surface reaction	Reaction method	Ref.
(a) Negatively charged group or segmenrs			
$-SO_3H$	PVDF	Chlorosulfonation	Barona, *et al.* (2007)
$-SO_3H$	PEK-C	UV copolymerization	Qiu, *et al.* (2007)
-COOH	PEK-C	UV copolymerization	Qiu, *et al.* (2007)
-COOH (AAG)	PES, PSf	UV polymerization	Kaeselev, *et al.* (2001)
$-SO_3H$ (AAP)	PES, PSf	UV polymerization	Kaeselev, *et al.* (2001)
$-SO_3H$ (SPM)	PES	Redox reaction	Belfer, *et al.* (2000)
-COOH	PP	Plasma-induced Polymerization	Yu, *et al.* (2008)
-COOH	PSf, PAN	Plasma-induced polymerization	Ulbricht, and Belfort (1996)
-COOH	PAN, PES	UV polymerization	Ulbricht, *et al.* (1996b)
-COOH (AA)	PES	Plasma-induced	Wavhal, *et al.* (2002)
-COOH (MA)	PES	Redox reaction	Belfer, *et al.* (2000)
-COOH (IDA)	PSf	chemical reaction	Nabe, *et al.* (1997)
$-SO_3H$	PSf	chemical reaction	Nabe, *et al.* (1997)
$-SO_3H$ (AMPS)	PVDF	UV copolymerization	Hilal, *et al.* (2004)
DNA	PSf	UV grafting	Zhao, *et al.* (2003)
BSA	PES	Chemical reaction	Fang, *et al.* (2009)
(b) positively charged group or segmenrs			
$-P^{+}-(CH_3)_3$	PSf	UV polymerization	Hatakeyama, *et al.* (2009)
$-P^{+}-(R_3)_3$	PSf	UV polymerization	Hatakeyama, *et al.* (2009)
$-N^{+}-(R'_3)_3$	PSf	UV copolymerization	Hatakeyama, *et al.* (2009)
$-N^{+}-(R'_3)_3$	PSf	Chemical reaction	Nabe, *et al.* (1997)
$-NH_2^{+}$	Cellulose	Epichlorohydrin activation	Mehta, *et al.* (2008)
qDMAEM	PVDF	UV copolymerization	Hilal, *et al.* (2004)
Chitosan	PES	Interfacial polymerization	Liu, *et al.* (2009)
Chitosan	PAN-co-MA	Carbodiimide reaction	Dai, *et al.* (2005)
(c) Zwitterionic group or segmenrs			
Phosphorylcholine	-OH group	Chemical reaction	Zhou, *et al.* (2007)
Phosphorylcholine	PDMS	UV copolymerization	Goda, *et al.* (2006)
SBMA	PVDF	ATRP	Chiag, *et al.* (2009)
Gelatin	PAN-co-MA	Carbodiimide method	Dai, *et al.* (2005)
SPE	PSf	Chemical reaction	Higuchi, *et al.* (2004a)
Aspartic acid	PSf	Chemical reaction	Higuchi, *et al.* (2004b)

[a]AA: acrylic acid, AAG: 2-acrylamidoglycolic acid monohydrate, AAP: 2-acrylamido-2-methyl-1-propane-sulfonic acid, ACMO: acryloyl morpholine, AMPS: 2-acrylamido-methyl-propane sulfonic acid, IDA: iminodi-acetic acid, SBMA: zwitterionic sulfobetainemethacrylate, qDMAEM: quaternized 2-(dimethylamino)ethyl metacrylate, MA: methacrylic acid, PAN: polyacrylonitrile, PP: polypropylene, PEK-C: carbo polyetherketone, PVDF: poly(vinylidene fluoride), SPM: sulfopropylmethacrylate, SPE: sulfoalkylbetaine

membranes (Tables 3 and 4).

Ulbricht and Belfort (1996) investigated the graft polymerization of hydrophilic monomers such as 2-hydroxy-ethylmethacrylate (HEMA) and acrylic or methacrylic acid onto PAN and PSf UF membrane surfaces initiated by plasma-induced polymerization. The degree of modification could be adjusted by the polymerization conditions. The hydrophilicity of the modified membrane surfaces was increased relative to that of the unmodified membranes. With about 1-1.4 mmol/cm^2 grafted HEMA, the contact angles (captive bubble technique; $\theta_{\text{octane/water}}$) for PAN and PSf were reduced from 48 to 34^o and from 92 to 43^o, respectively (Ulbricht and Belfort 1996). The PAN UF membrane water permeability was clearly observed to depend on the amount of grafted monomer. Hydrophilic PAN membranes modified by HEMA graft polymerization showed improved protein UF performance and significantly reduced fouling from static protein adsorption. Hydrophilized PSf-*g*-HEMA membranes could also provide improved performance in protein ultrafiltration over unmodified PSf UF membranes, because the pore etching effects are compensated by the grafted layer, yielding both improved filtrate flux (>30%) and BSA protein retention (Ulbricht and Belfort 1996). Hence, plasma-induced graft polymer modification of UF membranes can be used to adjust membrane performance by simultaneously controlling the surface hydrophilicity and permeability.

Chen and Belfort (1999) modified commercial PES membranes by low-temperature helium plasma treatment followed by grafting of *N*-vinyl-2-pyrrolidone (NVP). Helium plasma treatment and post-NVP grafting substantially increased the surface hydrophilicity of the PES membranes. The degree of modification depended on the plasma treatment time and polymerization conditions (temperature, NVP concentration and graft density). A filtration protocol to simulate protein fouling and cleaning potential demonstrated that the surface modified membranes were notably less susceptible to BSA fouling than the unmodified PES membrane or a commercial low-protein binding PES membrane. The absolute and relative permeation fluxes of the NVP-grafted membranes were found to be notably higher than those of the unmodified membrane.

It is challenging to control the grafting of highly polar material to the chemically inert Teflon-based membrane surface. Chang, *et al.* (2008a) investigated the surface modification and characterization of expanded poly(tetrafluoroethylene) (PTFE) membranes grafted with poly(ethylene glycol) methacrylate (PEGMA) macromonomers via surface-activated plasma treatment and thermally induced graft copolymerization. The biofouling properties of the modified membranes were evaluated by measurements of the plasma protein (γ-globulin, fibrinogen or albumin) adsorption, determined using an enzyme-linked immunosorbent assay (ELISA). The hydrophilicity of the surfaces of PTFE membranes increased with increasing grafting of copolymerized PEGMA. The highly hydrated PEGMA chain on the resulting PTFE membranes was found to form a surface hydrogel-like layer with regulated coverage in the aqueous state, which could be controlled by the PEGMA macromonomer content of the reaction solution (Chang, *et al.* 2008a). The relative protein adsorption decreased with the increasing hydration capacity of the PEGMA chain grafted onto the PTFE membrane surface. Results of both protein adsorption and platelet adhesion tests in vitro showed that the PEGMA-grafted hydrophilic PTFE membranes could provide good biofouling resistance, substantially reducing plasma protein and blood platelet fouling on the membrane surface at the temperature of the human body (Chang, *et al.* 2008a).

3.2. Surface modification by photo polymerization

The photochemical surface modification technique is attractive and has several advantages. Mild

reaction conditions and moderate temperature may be applied, high selectivity is possible by choosing the reactive groups or monomers and respective excitation wavelength, and it is easily incorporated into the end stages of a manufacturing process (Tian, *et al.* 2007). In general, there are two approaches to immobilizing polymer chains on the surfaces of materials by UV irradiation (Tian, *et al.* 2007). One is direct grafting of polymer chains containing photoreactive groups under UV irradiation (simultaneous method); the other approach is grafting the photoinitiator onto the substrate by means of UV irradiation, followed by covalent coupling of the target polymer chains (sequential method). In the literature, most studies were carried out with the former approach; the latter method is not common.

Tian, *et al.* (2007) attempted to use both the simultaneous and sequential methods to graft polyethylene glycol (PEG) chains onto the surface of PSf film and reduce the surface protein adsorption of the PSf surface. With the simultaneous method, PEG chains were directly grafted onto the PSf surface under UV irradiation; in the sequential method, 4-azidobenzoic acid (AzBA) was grafted onto the PSf surface with UV irradiation first and then reacted with *o*-amino-monomethoxypoly(ethylene glycol) (MPEG–NH_2). The grafting efficiencies of the simultaneous and sequential methods were reported to be 20.8% and 10.2%, respectively. Protein adsorption measurements showed that the surface protein adsorption of the modified film was significantly reduced compared with that of the unmodified PSf surface (Tian, *et al.* 2007).

Hatakeyama, *et al*. (2009) prepared several lightly cross-linked quaternary phosphonium- and ammonium-based polymer coatings on PSf ultrafiltration membranes by photo-polymerization. The membranes were found to effectively resist the non-specific adsorption of proteins (i.e., BSA and fibrinogen (Fg)) in aqueous solution under both static exposure and dynamic membrane fouling conditions. Under specific conditions, their protein-resistance performance was comparable to, or even better than, cross-linked PEG-based polymers, which are generally considered benchmark protein-resistant coating materials. These quaternary phosphonium and ammonium polymers exhibited comparable or better resistance to protein adsorption than polymeric analogues of some of the best organic functional groups identified in prior self-assembled monolayer-based protein-resistance studies (Hatakeyama, *et al.* 2009). In particular, initial results of dynamic membrane fouling experiments showed that lightly cross-linked poly[trimethyl-(4-vinyl-benzyl)-phosphonium bromide] has exceptional protein-fouling resistance and better water transport properties than a representative PEG-based polymer coating on the membranes (Hatakeyama, *et al.* 2009).

PVDF membranes are widely used in MF and UF due to their excellent chemical resistance, well-controlled porosity and good thermal and mechanical properties (Zhang, *et al.* 2009). However, the higher hydrophobicity of the membranes limits their application in the fields of biotechnology and pharmaceuticals, where the fluid phases to be treated are generally complex and heavily loaded with colloidal matter, and require hydrophilic membranes with better fouling resistances. Zhang, *et al.* (2009) investigated the graft polymerization of NVP onto a PVDF-based microporous membrane containing a small quantity of PES under UV irradiation (Zhang, *et al.* 2009). The addition of up to 3.3% by weight PES in PVDF did not change the membrane's mechanical properties, but made photo grafting onto PVDF possible. The grafting rate increased with irradiation time, and the contact angle of water on the modified membrane surface decreased from 86 degrees to 32 degrees after 10 min of irradiation. The modified membrane exhibited good fouling resistance (Zhang, *et al.* 2009). The amount of BSA adsorbed on the membranes was reported to decrease from 159±2 μg/cm^2 to 13±2 μg/cm^2 after 10 min of grafting. Furthermore, the filtration of a 0.1% BSA solution showed that the modified membrane had lower BSA adsorption and better flux recovery. The degree of

fouling of the blend membrane after 7 min of grafting was found to decrease by 66%, and the flux recovery after chemical cleaning increased by about 32% compared with that of the unmodified PVDF membrane (Zhang, *et al.* 2009).

Kaeselev, *et al.* (2001) modified the surface of polyether sulfone and polysulfone UF membranes using UV-assisted graft polymerization, at 300 nm, of three hydrophilic monomers: NVP, 2-acrylamidoglycolic acid monohydrate (AAG) and 2-acrylamido-2-methyl-1-propanesulfonic acid (AAP) (Kaeselev, *et al.* 2001). The modified membranes were characterized by their filtration performance with a 0.1 wt.% BSA solution in phosphate buffered saline (PBS) at pH 7.4. The modified UF membranes showed superior filtration performance over the unmodified PES and unmodified PSf regenerated cellulose (RC) control membranes. Slightly compromised protein solution permeabilities were compensated by low fouling modified membranes that exhibited excellent cleaning characteristics (Kaeselev, *et al.* 2001). All of the best cases were at the highest monomer concentrations (5 wt.%) and lowest irradiation energy (<65 mJ/cm^2 for PES and <130 mJ/cm^2 for PSf). This work suggested that low degrees of grafting and intermediate wettabilities ($0.74 < \cos\theta < 0.82$) were sufficient to obtain attractive non-fouling membranes. Since BSA is strongly negatively charged at pH 7.4, it is not surprising that AAP was the monomer that exhibited the best performance in two of the four best cases. It was found that PES membranes are far more sensitive to UV-assisted graft polymerization than PSf membranes, and thus require far less energy to attain the desired degree of grafting (Kaeselev, *et al.* 2001).

3.3. Surface modification by chemical reaction

Membrane surface modification by chemical reaction can be realized by the simple approach of dipping into active reagents. Sulfonation (Higuchi, *et al.* 1990, Barona, *et al.* 2007) is one of the most common surface reaction reagents, and the degree of sulfonation can be controlled by the reaction time.

Crassous, *et al.* (1985) reported the chemical surface modification of a styrene-isoprene-styrene block copolymer and succeeded in introducing -SO_3H, -COOH and -CONH onto the membrane surfaces. This membrane was chemically modified by reaction with gaseous chlorosulfonylisocyanate, and exhibited enhanced blood compatibility due to its heparin-like structure. Fixing heparin onto membrane surfaces by ionic coupling or covalent bonding has also been investigated by several researchers. Graft polymerization [Higuchi, *et al.* 2002, Chiang, *et al.* 2009) provides another method of surface modification and can give several functional groups.

Chloromethylation of the aromatic rings is a typical method of generating positively charged membranes by quaternization of the amino group (Higuchi, *et al.* 1992). The chloromethyl group can be introduced by dipping the polysulfone membrane into a reaction solution composed of hexane, chloromethyl ether and Friedel-Crafts catalysts (i.e., $AlCl_3$, $SnCl_4$, or $ZnCl_4$) for a surface reaction. Several hydrophilic groups can be introduced to the polysulfone membranes according to the reaction scheme shown in Fig. 1.

Higuchi, *et al.* (1988) reported that an interesting functional group, -$CH_2CH_2CH_2SO_3H$, was introduced on the surface of polysulfone hollow fiber ultrafiltration membranes (Fig. 1). Their report was the landmark that marked the start of surface modification of PSf membranes. After their research, many later researchers reported the surface modification of polysulfone membranes (e.g., Table 3 and 4). In their surface modification, a hydrophilic sulfonate unit was placed on the main polymer chain with a joint segment of $(-CH_2-)_n$ (Fig. 1), while sulfonation directly introduced the

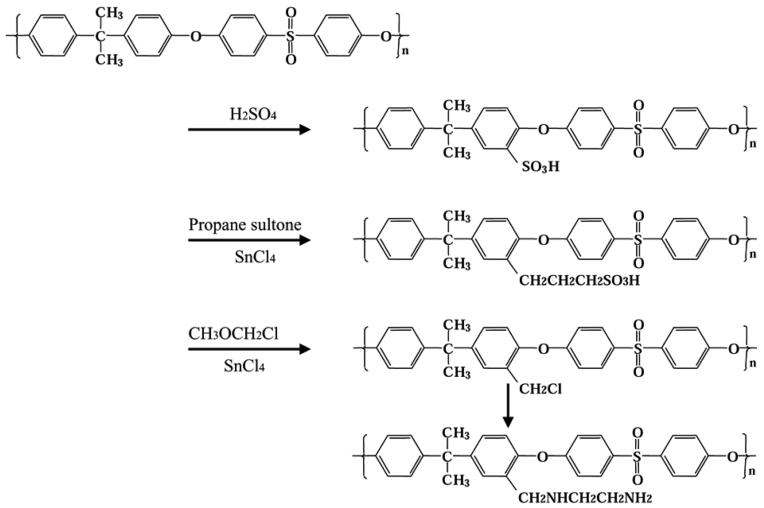

Fig. 1 Reaction scheme for the introduction of several hydrophilic groups on polysulfone membranes

sulfonate unit on the main chain (Higuchi, *et al.* 1990). The controlled reaction on one or both sides of the surfaces of polysulfone ultrafiltration membranes was performed with propane sultone and Friedel-Crafts catalysts. The molecular design of the modified segment is a long side chain that contributes to the enhanced mobility of the SO_3H moiety and decreases the pore sizes of UF membranes (Higuchi, *et al.* 1990). This could result in modified membranes with a lower molecular weight cut-off than the unmodified membranes. The original thermal stability of the unmodified membranes survived the surface reaction, and the functional groups introduced by the reaction were regarded as new modifications of heparin-active groups (e.g., - OSO_3^-, - $NHSO_3^-$, -COO^-).

Higuchi, *et al.* (2002) reported the preparation of hydrophilic polysulfone membranes (PVP-PSf) covalently conjugated with polyvinylpyrrolidone (PVP) on the surface. Polysulfone was chloromethlated on the surface through the Friedel-Crafts reaction, followed by amination with ethylene diamine. Ethylenediaminated polysulfone membranes were reacted with the active ester of *N*-succinimidylacrylate (NSA) to introduce double bonds on the PSf surface. Vinylpyrrolidone (VP) was subsequently polymerized with redox initiators (see Fig. 2). The amount of immobilized vinylpyrrolidone on the PVP-PSf membranes was controlled by the reaction time and the amount of vinylpyrrolidone monomer in the reaction solution. The PVP-PSf membranes were found to be the most hydrophilic membranes among the polysulfone and surface-modified polysulfone membranes prepared in their study (Higuchi, *et al.* 2002). This is explained by the long hydrophilic side chain of PVP on the PVP-PSf membranes, which contributes to the hydrophilic wiper on the hydrophobic PSf membranes. PVP-PSf membranes exhibited lower protein adsorption from a plasma solution than polysulfone and other surface-modified membranes in their research. This was attributed to the hydrophilic surface of the PVP-PSf membranes, because the hydrophilic surface is known to reduce protein adsorption on the membranes. The PVP-PSf membranes showed much fewer platelets adhered to the surface than polysulfone and other surface-modified membranes. It was suggested that the hydrophilic surface of the PVP-PSf membranes without ionic groups causes the suppression of platelet adhesion to the PVP-PSf membranes and that the long hydrophilic side chain of PVP on PVP-PSf membranes contributes to the hydrophilic and hemocompatible wipers (nano-brush) on the surface of the hydrophobic PSf membranes (Higuchi, *et al.* 2002).

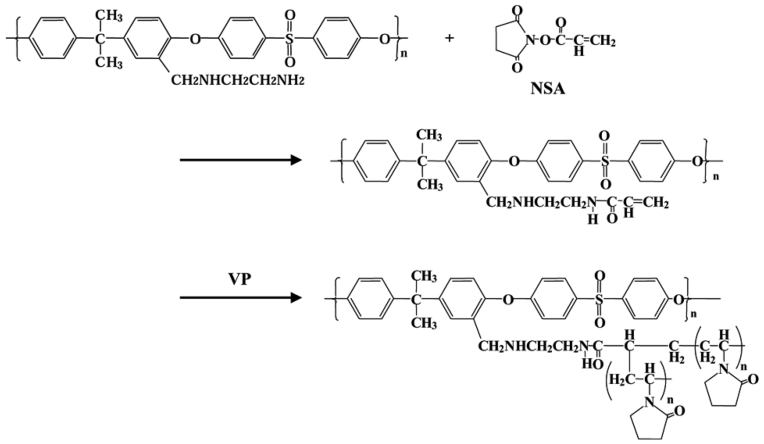

Fig. 2 Reaction scheme of polysulfone membranes grafted with polyinylpyrrolidone from ethylenediamined polysulfone membranes.

Mahta and Zydney (2008) investigated the effect on UF performance of the spacer arm length on the surface of charge-modified UF membranes. A series of charged ultrafiltration membranes that differed in spacer arm length and charge group functionality was prepared using epichlorohydrin (EPI) activation of a regenerated cellulose membrane. Hydraulic permeability and protein retention data were obtained over a range of ionic strengths, using cytochrome *c* as a model protein. They observed that the protein sieving coefficient decreased sharply with increasing spacer arm length, particularly for 30 kDa membranes (Mahta and Zydney 2008). For example, the observed sieving coefficient for cytochrome *c* through the 30 kDa membrane made with 1,10-diaminodecane (n=10) was more than an order of magnitude smaller than that for a similar membrane made using 1,2-diaminoethane (n=2), even though these membranes had very similar hydraulic permeabilities and pore size distributions (Mahta and Zydney 2008). The large reduction in protein transmission was directly related to the larger effective surface charge (i.e., apparent zeta potential), and this behavior was consistent with a shift in the p*K*a value associated with the intramolecular interactions between the two amine groups on the charged ligand. Further confirmation of this phenomenon was provided by data obtained with a membrane generated using 1-amine-6-hexanol; this membrane had only a single secondary amine (with a terminal hydroxyl), leading to significantly less protein retention than membranes with two amine groups (Mahta and Zydney 2008).

The permeability–selectivity trade-off for the charge-modified membranes clearly demonstrated that the electrostatic interactions led to much better UF performance than could be obtained with neutral membranes. The permeability–selectivity trade-off for the 30 kDa membranes improved significantly with increasing spacer arm length. The 30 kDa membrane with n=10 provided 20-fold better selectivity than the membrane with n=2, and 1000-fold better selectivity than the unmodified cellulose membrane at comparable permeabilities (Mahta and Zydney 2008). These results provide important insights into the effects of the charged ligand and, in particular, the length of the spacer arm on the performance characteristics of charge-modified UF membranes (Mahta and Zydney 2008).

Chang, *et al.* (2008b) prepared PVDF MF membranes grafted with PEGMA via surface-activated ozone treatment and thermally induced graft copolymerization. The grafting density of the polymerized PEGMA and the hydrophilicity on the surface of PVDF MF membranes increased with increasing

PEGMA macromonomer concentration in the reaction solution. The grafting distribution of PEGMA on the resulting membranes was found to form a uniform polymer hydrogel-like layer controlled by a sufficiently high content of PEGMA in the reaction solution, while their surface roughness was lower than that of the unmodified membrane (Chang, *et al.* 2008b). In the platelet adhesion test, a remarkable suppression of the platelet adhesion was observed in the PVDF MF membranes grafted with PEGMA polymer. In the water flux experiments, the PEGMA-grafted hydrophilic PVDF MF membranes exhibited excellent anti-fouling properties, substantially reducing the irreversible membrane fouling caused by platelet adhesion and plasma protein adsorption as compared with the virgin hydrophobic PVDF MF membranes (Chang, *et al.* 2008b).

Atom transfer radical polymerization (ATRP) is a living polymerization, which enables the generation of a uniform polymer chain growth and leads to low polydispersity, and utilizes a transition metal-based catalyst. In recent developments of surface reaction chemistry, ATRP has also been used for the surface modification of polymeric membranes.

Li, *et al.* (2009) developed PSf membranes grafted with polyHEMA and PEGMA using surface-initiated ATRP. A simple one-step method for the chloromethylation of PSF under mild conditions was used to introduce surface benzyl chloride groups as active ATRP initiators. Covalently tethered hydrophilic polymer brushes of PEGMA and polyHEMA and their block copolymer brushes were prepared via surface-initiated ATRP from the chloromethylated PSf surfaces (Li, *et al.* 2009). An approximately linear increase in the graft yield of the functional brushes with polymerization time indicated that the chain growth from the membrane surface was consistent with a controlled process. Protein adsorption experiments revealed that the grafted PSf membranes exhibited substantially better antifouling properties than the unmodified PSf surface (Li, *et al.* 2009).

Chiang, *et al.* (2009) prepared sulfobetaine-grafted PVDF ultrafiltration membranes, where zwitterionic sulfobetainemethacrylate (SBMA) was grafted onto the surface of a PVDF membrane via ozone surface activation and surface-initiated ATRP (Chiang, *et al.* 2009). The static adsorption of BSA and γ-globulin were investigated to test the antifouling characteristics of PVDF membranes after SBMA grafting. Albumin adsorption was not observed, and the adsorption of γ-globulin was extensively reduced in surface-modified PVDF membranes with polySBMA grafting densities of more than 0.4 mg/cm^2 (Chiang, *et al.* 2009).

Cyclic filtration evaluation was performed to investigate whether ozone surface activation along with ATRP was able to graft SBMA inside the pores of the membranes (Chiang, *et al.* 2009). The cyclic filtration evaluation for BSA through surface-modified PVDF membranes yielded an extremely low irreversible membrane fouling ratio (R_{ir}) of 13% in the first cycle, and apparently no irreversible fouling was observed in the second cycle. A more stringent test was carried out by filtering a γ-globulin solution. It was found that the unmodified PVDF membrane was continuously fouled by γ-globulin after three cyclic operations, while the polySBMA-modified membrane had an R_{ir} value as low as 4.7% in the third cycle (Chiang, *et al.* 2009). The results indicated that surface modification via ozone surface activation and ATRP could actually penetrate into the pores of a UF membrane (Chiang, *et al.* 2009). The polySBMA-grafted PVDF membrane was observed to effectively resist the plasma protein adsorption and exhibited extremely low biofouling characteristics during filtration.

4. Conclusions

This article reviews several hydrophilic segments proposed for coating or grafting onto hydrophobic

UF and MF membranes. The most typical hydrophilic segment is PEG (Chang, *et al.* 2008a, Hyun, *et al.* 2006, Li, *et al.* 2009, Susanto, *et al.* 2007). Several studies showed that PEG-based surfaces can resist protein adhesion (Chang, *et al.* 2008a, Hyun, *et al.* 2006, Li, *et al.* 2009, Susanto, *et al.* 2007). Protein adsorption on self-assembled monolayers (SAMs) of PEG, which were analyzed on smooth gold substrates under ideal conditions, also suggested that PEG immobilized surfaces lead to low-protein-binding surfaces (Herrwerth, *et al.* 2003, Vanderah, *et al.* 2009). However, the conditions that generate biofouling on actual membranes are much different from those investigated in the research of SAMs. Furthermore, the protein solution used in the research of SAMs is typically a simple protein solution, e.g., BSA. BSA has the weakest binding ability on the material surface when compared to other proteins (Feldman, *et al.* 1999, Harder, *et al.* 1998). In general, BSA is preferable for adhesion on biomaterial surfaces because BSA can prohibit non-specific adsorption of other proteins. The primary drawback limiting the usage of PEG-based surfaces in UF and MF membranes is their lack of long-term chemical stability (Branch, *et al.* 2001, Hatakeyama, *et al.* 2009, Kawai 2002). PEG-base segments on membrane surfaces are considered to be susceptible to oxidation and degradation by biological entities (Branch, *et al.* 2001, Hatakeyama, *et al.* 2009, Kawai 2002).

It was reported that oligo(ethylene glycol)-functionalized SAMs that form an all-trans alkyl chain conformation do not show protein resistance, but the same oligo(ethylene glucol)-based SAMs with a helical alkyl chain conformation do exhibit protein resistance (Feldman, *et al.* 1999, Harder, *et al.* 1998, Hatakeyama, *et al.* 2009). Furthermore, high coverage (almost 100%) of oligo(ethylene glycol) on the membrane surface exhibits high protein adsorption (Vanderah, *et al.* 2004), while moderate coverage (60%) of oligo(ethylene glycol) on the surface generates a protein-resistant surface. This should be originated from the flexibility of oligo(ethylene glycol) on the membrane surface. Hydrophobic membranes covalently conjugated with polyvinylpyrrolidone (PVP) (Higuchi, *et al.* 2002) or polysulfoalkylbetaine (Chiag, *et al.* 2009, Higuchi, *et al.* 2004) are reported to generate high flexibility of the long hydrophilic side chains, which contribute to low protein binding characteristics as well as hemocompatible wipers. Flexibility, surface concentration, the chemical structure of hydrophilic segments and the conformation of hydrophilic segments on the membrane must all be considered when designing membrane grafting segments, in order to create real protein-resistant surfaces.

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References

Barona, G.N.B., Cha, B.J. and Jung, B. (2007), "Negatively charged poly(vinylidene fluoride) microfiltration membranes by sulfonation", *J. Membrane Sci.*, **290**(1-2), 46-54.

Belfer, S., Fainchtain, R., Purinson, Y. and Kedem, O. (2000), "Surface characterization by FTIR-ATR spectroscopy of polyethersulfone membranes-unmodified, modified and protein fouled", *J. Membrane Sci.*, **172**(1-2), 113-124.

Branch, D.W., Wheeler, B.C., Brewer, G.J. and Leckband, D.E. (2001), "Long-term stability of grafted polyethylene glycol surfaces for use with microstamped substrates in neuronal cell culture", *Biomaterials*, **22**, 1035-1047.

Castilho, L.R., Deckwer, W.D. and Anspach, F.B. (2000), "Influence of matrix activation and polymer coating on the purification of human IgG with protein A affinity membranes", *J. Membrane Sci.*, **172**, 269-277.

Chang, Y., Cheng, T.Y., Shih, Y.J., Lee, K.R. and Lai, J.Y. (2008a), "Biofouling-resistance expanded poly(tetrafluoroethylene) membrane with a hydrogel-like layer of surface-immobilized poly(ethylene glycol) methacrylate for human plasma protein repulsions", *J. Membrane Sci.*, **323**, 77-84.

Chang, Y., Shih, Y.J., Ruaan, R.C., Higuchi, A., Chen, W.Y. and Lai, J.Y. (2008b), "Preparation of poly(vinylidene fluoride) microfiltration membrane with uniform surface-copolymerized poly(ethylene glycol) methacrylate and improvement of blood compatibility", *J. Membrane Sci.*, **309**, 165-174.

Chen, H. and Belfort, G. (1999), "Surface modification of poly(ether sulfone) ultrafiltration membranes by low-temperature plasma-induced graft polymerization", *J. Appl. Polym. Sci.*, **72**, 1699-1711.

Chiang, Y.C., Chang, Y., Higuchi, A., Chen, W.Y. and Ruaan, R.C. (2009), "Sulfobetaine grafted poly(vinylidene fluroride) ultrafiltration membranes exhibit excellent antifouling property", *J. Membrane Sci.*, **339(1-2)**, 151-159.

Crassous, G., Harjanto, F., Mendjel, H., Sledz, J., Schue, F., Meyer, G. and Jozefowicz, M. (1985), "A new asymmetric membrane having blood compatibility", *J. Membrane Sci.*, **22**(2-3), 269-282.

Dai, Z.W., Nie, F.Q. and Xu, Z.K. (2005), "Acrylonitrile-based copolymer membranes containing reactive groups: Fabrication dual-layer biomimetic membranes by the immobilization of biomacromolecules", *J. Membrane Sci.*, **264**(1-2), 20-26.

Dai, Z.W., Wan, L.S. and Xu, Z.K. (2008), "Surface glycosylation of polyacrylonitrile ultrafiltration membrane to improve its anti-fouling performance", *J. Membrane Sci.*, **325**, 479-485.

Fan, Z.F., Wang, Z., Sun, N., Wang, J. and Wang, S. (2008), "Performance improvement of polysulfone ultrafiltration membrane by blending with polyaniline nanofibers", *J. Membrane Sci.*, **320**(1-2), 363-371.

Fang, B.H., Ling, Q.Y., Zhao, W.F., Ma, Y., Bai, P., Wei, Q., Li, H. and Zhao, C. (2009), "Modification of polyethersulfone membrane by grafting bovine serum albumin on the surface of polyethersulfone/ poly(acrylonitrile-co-acrylic acid) blended membrane", *J. Membrane Sci.*, **329**(1-2), 46-55.

Feldman, K., Hahner, G., Spencer, N.D., Harder, P. and Grunze, M. (1999), "Probing resistance to protein adsorption of oligo(ethylene glycol)-terminated self-assembled monolayers by scanning force microscopy", *J. Am. Chem. Soc.*, **121**, 10134-10141.

Feng, W., Zhu, S., Ishihara, K. and Brush, J.L. (2005), "Adsorption of fibrinogen and lysozyme on silicon grafted with poly(2-methacryloyloxyethyl phosphorylcholine) via surface-initiated atom transfer radical polymerization", *Langmuir*, **21**, 5980-5987.

Ghosh, R. and Cui, Z.F. (1998), "Fractionation of BSA and lysozyme using ultrafiltration: effect of pH and membrane pretreatment", *J. Membrane Sci.*, **139**, 17-28.

Goda, T., Konno, T., Takai, M., Moro, T. and Ishihara, K. (2006), "Biomimetic phosphorylcholine polymer grafting from polydimethylsiloxane surface using photo-induced polymerization", *Biomaterials*, **27**(30), 5151-5160.

Gu, J.S., Yu, H.Y., Huang, L., Tang, Z.Q., Li, W., Zhou, J., Yan, M.G. and Wei, X.Y. (2009), "Chain-length dependence of the antifouling characteristics of the glycopolymer-modified polypropylene membrane in an SMBR", *J. Membrane Sci.*, **326**, 145-152.

Harder, P., Grunze, M., Dahint, R., Whitesides, G.M. and Laibinis, P.E. (1998), "Molecular conformation in oligo(ethylene glycol)-terminated self-assembled monolayers on gold and silver surfaces determines their ability to resist protein adsorption", *J. Phys. Chem. B*, **102**, 426-436.

Hatakeyama, E.S., Ju, H., Gabriel, C.J., Lohr, J.L., Bara, J.E., Noble, R.D., Freeman, B.D. and Gin, D.L. (2009), "New protein-resistant coatings for water filtration membranes based on quaternary ammonium and phosphonium polymers", *J. Membrane Sci.*, **330**, 104-116.

He, X.C., Yu, H.Y., Tang, Z.Q., Liu, L.Q., Yan, M.G., Gu, J.S. and Wei, X.W. (2009), "Reducing protein fouling

of a polypropylene microporous membrane by CO2 plasma surface modification", *Desalination*, **244**, 80-89.
Herrwerth, S., Eck, W., Reinhardt, S. and Grunze, M. (2003), "Factors that Determine the Protein Resistance of Oligoether Self-Assembled Monolayers – Internal Hydrophilicity, Terminal Hydrophilicity, and Lateral Packing Density", *J. Am. Chem. Soc*., **125**(31), 9359-9366.
Hester, J.F. and Mayes, A.M. (2002), "Design and performance of foul-resistant poly(vinylidene fluoride) membranes prepared in a single-step by surface segregation", *J. Membrane Sci*., **202**(1-2), 119-135.
Higuchi, A., Iwata, N., Tsubaki, M. and Nakagawa, T. (1988), "Surface-modified Polysulfone Hollow Fibers", *J. Appl. Polym. Sci*., **36**, 1753-1767.
Higuchi, A., Iwata, N. and Nakagawa, T. (1990), "Surface Modified Polysulfone Hollow Fibers. II. Fibers having $CH_2CH_2CH_2SO_3^-$ Segments and Immersed in HCl Solution", *J. Appl. Polym. Sci*., **40**, 709-717.
Higuchi, A., Koga, H. and Nakagawa, T. (1992), "Surface modified polysulfone hollow fibers. IV. chloromethylated fibers and their derivatives", *J. Appl. Polym. Sci*., **46**, 449-457.
Higuchi, A., Shirano, K., Harashima, M., Yoon, B.O., Hara, M., Hattori, M. and Imamura, K. (2002), "Chemically modified polysulfone hollow fibers with vinylpyrrolidone having improved blood compatibility", *Biomaterials,* **23**(13), 2659-2666.
Higuchi, A., Hashiba, H., Hayashi, R., Yoon, B.O., Hattori, M. and Hara, H. (2004a), "Chemically modified polysulfone hollow fibers with zwitterionic sulfoalkylbetaine group having improved blood compatibility", *ACS Symposium Series 876*, 2004, chp 25.
Higuchi, A., Hashiba, H., Hayashi, R., Yoon, B.O., Sakurai, M. and Hara, M. (2004b), "Serum protein and platelet adsorption on aspartic acid-immobilized polysulfone membranes", *J. Biomat. Sci., Polym. E*., **15**(8), 1051-1063.
Hilal, N., Kochkodan, V., Al-Khatib, L. and Levadna, T. (2004), "Surface modified polymeric membranes to reduce (bio)fouling: a microbiological study using E. coli", *Desalination*, **167**(1-3), 293-300.
Hu, M.X., Yang, Q. and Xu, Z.K. (2006), "Enhancing the hydrophilicity of polypropylene microporous membranes by the grafting of 2-hydroxyethyl methacrylate via a synergistic effect of photoinitiators", *J. Membrane Sci*., **285**(1-2), 196-205.
Hyun, J., Jang, H., Kim, K., Na, K. and Tak, T. (2006), "Restriction of biofouling in membrane filtration using a brush-like polymer containing oligoethylene glycol side chains", *J. Membrane Sci*., **282**(1-2), 52-59.
Ishihara, K., Fukumoto, K., Iwasaki, Y. and Nakabayashi, N. (1999a), "Modification of polysulfone with phospholipid polymer for improvement of the blood compatibility. Part 1. Surface characterization", *Biomaterials*, **20**, 1545-1551.
Ishihara, K., Fukumoto, K., Iwasaki, Y. and Nakabayashi, N. (1999b), "Modification of polysulfone with phospholipid polymer for improvement of the blood compatibility. Part 2. Protein adsorption and platelet adhension", *Biomaterials*, **20**, 1553-1559.
Ishihara, K., Iwasaki, Y., Ebihara, S., Shindo, Y. and Nakabayashi, N. (2000), "Photoinduced graft polymerization of 2-methacryloyloxyethyl phosphorylcholine on polyethylene membrane surface for obtaining blood cell adhesion resistance", *Colloid Surface B*, **18**, 325–335.
lto, Y., Kotera, S., Inabe, M., Kono, K. and Imanishi, Y. (1990), "Control of pore size of polycarbonate membrane with straight pores by poly(acrylic acid) grafts", *Polymer*, **31**, 2157-2161.
Kaeselev, B., Pieracci, J. and Belfort, G. (2001), "Photoinduced grafting of ultrafiltration membranes: comparison of poly(ether sulfone) and poly(sulfone)", *J. Membrane Sci*., **194**(2), 245-261.
Kawai, F. (2002), "Microbial degradation of polyethers", *Appl. Microbiol. Biot*., **58**, 30-38.
Kim, J.H., Kang, M.S. and Kim, C.K. (2005), "Fabrication of membranes for the liquid separation. 1. Ultrafiltration membranes prepared from novel miscible blends of polysulfone and poly(1-vinylpyrrolidone-co-acrylonitrile) copolymers", *J. Membrane Sci*., **265**(1-2), 167-175.
Kull, K.R., Steen, M.L. and Fisher, E.R. (2005), "Surface modification with nitrogen-containing plasmas to produce hydrophilic, low-fouling membranes", *J. Membrane Sci*., **246**(2), 203–215.
Li, L., Yan, G.P. and Wu, J.Y. (2009), "Modification of polysulfone membranes via surface-initiated atom transfer radical polymerization and their antifouling properties", *J. Appl. Polym. Sci*., **111**, 1942-1946.
Liu, S.X., Kim, J.T., Kim, S. and Singh, M. (2009), "The Effect of Polymer Surface Modification Via Interfacial Polymerization on Polymer-Protein Interaction", *J. Appl. Polym. Sci*., **112**(3), 1704-1715.
Liu, Z.M., Xu, Z.K., Wan, L.S., Wu, J. and Ulbricht, M. (2005), "Surface modification of polypropylene

microfiltration membranes by the immobilization of poly (N-vinyl-2-pyrrolidone): a facile plasma approach", *J. Membrane Sci*., **249**(1-2), 21-31.

Louie, J.S., Pinnau, I., Ciobanu, I., Ishida, K.P., Ng, A. and Reinhard, M. (2006), "Effects of polyether-polyamide block copolymer coating on performance and fouling of reverse osmosis membranes", *J. Membrane Sci*., **280**, 762-770.

Mehta, A. and Zydney, A.L. (2008), "Effect of spacer arm length on the performance of charge-modified ultrafiltration membranes", *J. Membrane Sci*., **313**, 304-314.

Nabe, A., Staude, E. and Belfort, G. (1997), "Surface modification of polysulfone ultrafiltration membranes and fouling by BSA solutions", *J. Membrane Sci*., **133**, 57-72.

Nie, F.Q., Xu, Z.K., Yang, Q., Wu, J. and Wan, L. (2004), "Surface modification of poly(acrylonitrile-co-maleic acid) membranes by the immobilization of poly(ethylene glycol)", *J. Membrane Sci*., **235**(1-2), 147-155.

Nunes, S.P., Sforca, M.L. and Peinemann, K.V. (1995), "Dense hydrophilic composite membranes for ultrafiltration", *J. Membrane Sci*., **106**, 49-56.

Qiu, C.Q., Nguyen, Q.T. and Ping, Z.H. (2007), "Surface modification of cardo polyetherketone ultrafiltration membrane by photo-grafted copolymers to obtain nanofiltration membranes", *J. Membrane Sci*., **295**(1-2), 88-94.

Pieracci, J., Crivello, J.V. and Belfort, G. (1999), "Photochemical modification of 10 kDa polyethersulfone ultrafiltration membranes for reduction of biofouling", *J. Membrane Sci*., **156**(2), 223-240.

Rahimpour, A., Madaeni, S.S. and Mehdipour-Ataei, S. (2008), "Synthesis of a novel poly(amide-imide) (PAI) and preparation and characterization of PAI blended polyethersulfone (PES) membranes", *J. Membrane Sci*., **311**(1-2), 349-359.

Rajam, S. and Ho, C.C. (2006), "Graft coupling of PEO to mixed cellulose esters microfiltration membranes by UV irradiation", *J. Membrane Sci*., **281**(1-2), 211-218.

Shi, Q., Su, Y.L., Zhu, S.P., Li, C., Zhao, Y. and Jiang, Z. (2007), "A facile method for synthesis of pegylated polyethersulfone and its application in fabrication of antifouling ultrafiltration membrane", *J. Membrane Sci*., **303**(1-2), 204-212.

Su, Y.L., Li, C., Zhao, W., Shi, Q., Wang, H., Jiang, Z. and Zhu, S. (2008), "Modification of polyethersulfone ultrafiltration membranes with phosphorylcholine copolymer can remarkably improve the antifouling and permeation properties", *J. Membrane Sci*., **322**, 171-177.

Susanto, H., Balakrishnan, M. and Ulbricht, M. (2007), "Via surface functionalization by photograft copolymerization to low-fouling polyethersulfone-based ultrafiltration membranes", *J. Membrane Sci*., **288**, 157-167.

Takahashi, A. and Hisatomi, H. (2009), *Hydrophilic monomers suppress the adsorption of plasma protein onto a poly(vinylidene fluoride) membrane*, Molecular Medicine Reports, **2**, 749-752.

Taniguchi, M., Kilduff, J.E. and Belfort, G. (2003), "Low fouling synthetic membranes by UV-assisted graft polymerization: monomer selection to mitigate fouling by natural organic matter", *J. Membrane Sci*., **222**(1-2), 59-70.

Tian, M., Zhong, R., Sun, S.D., Zhao, C., Huang, Z. and Yue, Y. (2007), "Comparison of two approaches to grafting hydrophilic polymer chains onto polysulfone films", *J. Membrane Sci*., **103**, 3818-3826.

Toyomoto, K. and Higuchi, A. (1992), *Microfiltration and Ultrafiltration, in Membrane Science and Technology* (Eds. Y. Osada and T. Nakagawa), Marcel Dekker Inc., New York, p289-331.

Ulbricht, M. and Belfort, G. (1996), "Surface modification of ultrafiltration membranes by low temperature plasma .2. Graft polymerization onto polyacrylonitrile and polysulfone", *J. Membrane Sci*., **111**, 193-215.

Ulbricht, M., Matuschewski, H., Oechel, A. and Hicke, H.G. (1996a), "Photo-induced graft polymerization surface modifications for the preparation of hydrophilic and low-protein-adsorbing ultrafiltration membranes", *J. Membrane Sci*., **115**(1), 31-47.

Ulbricht, M., Riedel, M. and Marx, U. (1996b), "Novel photochemical surface functionalization of polysulfone ultrafiltration membranes for covalent immobilization of biomolecules", *J. Membrane Sci*., **120**, 239-259.

Vanderah, D.J., La, H., Naff, J., Silin, V. and Rubinson, K.A. (2004), "Control of protein adsorption: molecular level structural and spatial variables", *J. Am. Chem. Soc.*, **126**, 13639-13641.

Vanderah, D.J., Vierling, R.J. and Walker, M.L. (2009), "Oligo(ethylene oxide) Self-Assembled Monolayers, with Self-Limiting Packing Densities for the Inhibition of Nonspecific Protein Adsorption", *Langmuir*, **25**, 5026-5030.

Wang, Y., Kim, J.H., Choo, K.H., Lee, Y.S. and Lee, C.H. (2000), "Hydrophilic modification of polypropylene microfiltration membranes by ozone-induced graft polymerization", *J. Membrane Sci*.,**169**(2), 269-276.

Wang, Y.Q., Su, Y.L., Ma, X.L., Sun, Q. and Jiang, Z.Y. (2006), "Pluronic polymers and polyethersulfone blend membranes with improved fouling-resistant ability and ultrafiltration performance", *J. Membrane Sci*., **283**(1-2), 440-447.

Wavhal, D.S. and Fisher, E.R. (2002), "Hydrophilic modification of polyethersulfone membranes by low temperature plasma-induced graft polymerization", *J. Membrane Sci*., **209**, 255-269.

Yu, H.Y., Liu, L.Q., Tang, Z.Q., Yan, M.G., Gu, J.S. and Wei, X.W. (2008), "Mitigated membrane fouling in an SMBR by surface modification", *J. Membrane Sci.*, **310**(1-2), 409-417.

Zhao, C.S., Liu, X.D., Rikimaru, S., Nomizu, M. and Nishi, N. (2003), "Surface characterization of polysulfone membranes modified by DNA immobilization", *J. Membrane Sci*., **214**(2), 179-189

Zhao, Y.H., Qian, Y.L., Pang, D.X., Zhu, B.K. and Xu, Y.Y. (2007), "Porous membranes modified by hyperbranched polymers II. Effect of the arm length of amphiphilic hyperbranched-star polymers on the hydrophilicity and protein resistance of poly(vinylidene fluoride) membranes", *J. Membrane Sci*., **304**(1-2), 138-147.

Zhao, Y.H., Qian, Y.L., Zhu, B.K. and Xu, Y.Y. (2008a), "Modification of porous poly(vinylidene fluoride) membrane using amphiphilic polymers with different structures in phase inversion process", *J. Membrane Sci*., **310**(1-2), 567-576.

Zhao, W., Su, Y.L., Li, C., Shi, Q., Ning, X. and Jiang, Z. (2008b), "Fabrication of antifouling polyethersulfone ultrafiltration membranes using Pluronic F127 as both surface modifier and pore-forming agent", *J. Membrane Sci*., **318**(1-2), 405-412.

Zhang, M.G., Nguyen, Q.T. and Ping, Z.H. (2009), "Hydrophilic modification of poly (vinylidene fluoride) microporous membrane", *J. Membrane Sci*., **327**, 78-86**.**

Zhou, J., Meng, S., Guo, Z., Du, Q. and Zhong, W. (2007), "Phosphorylcholine-modified poly (ethylene-co-vinyl alcohol) microporous membranes with improved protein-adsorption-resistance property", *J. Membrane Sci*., **305**(1-2), 279-286.

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