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Review

Protein adsorption on blood-contact membranes

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Abstract

Blood-contact membranes are crucial in almost all extracorporeal blood aphereses and purification procedures. A serious problem they frequently meet is proteins adsorption-caused fouling, which results in a progressive decline in flux and a change of membrane selectivity. Besides, such adsorption can be followed not only by the activation of different defense systems in blood, such as coagulation, complement and fibrinolysis, but also by the adhesion and activation of blood cells. This article reviews studies on the mechanism, affecting factors, and controlling strategies associated with protein adsorption.
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Keywords: Blood-contact membranes; Protein adsorption; Fouling; Affecting factor; Surface modification

1. Introduction

The medical use of membranes has been evolving since 1940s [1]. Today, microfiltration (MF) membranes and ultrafiltration (UF) membranes are widely used as blood-contact devices in blood apheresis and purification for blood collection or disease therapies, e.g. hemodialysis (artificial kidney), plasmapheresis, plasma fractionation, leukofiltration and artificial liver [1,2]. There are two basic membrane configurations used in blood purification: flat sheet and hollow fiber shapes. And most of them are made of polymeric materials [1].

Unfortunately, just like other protein-contact membranes, blood-contact membranes are faced with a problem hardly avoidable in application—a progressive decline in flux and a change of membrane selectivity. This phenomenon, known as membrane fouling, is mainly attributed to the concentration polarization and protein fouling on the membrane surface, no matter what material the membrane is made of [3–9]. Chronologically it is possible to identify three separate phases of flux decline in membrane fouling (Fig. 1) [4,10].

Concentration polarization, resulting from concentration gradient due to solute accumulation near the membrane surface, is reversible in nature, though it always exists during membrane processing due to the fundamental limitations of mass transfer and the existence of the boundary layer. The concentration polarization, independent of the physical properties of the membrane, reduces permeate flux by offering added hydraulic resistance to the flow of solvent and by causing osmotic backpressure [11]. The membrane pore size and porosity are not directly affected by concentration polarization [4]. Concentration polarization can be controlled by means of high shear on the membrane surface, if high shear can be tolerated in operation [12].

Protein adsorption or deposition on the surface or in its pores occurs rapidly within seconds to minutes

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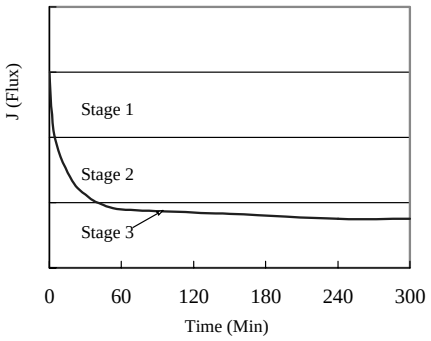

Fig. 1. Various stages of flux decline [4]. Stage 1: flux loss due to concentration polarization; stage 2: flux loss due to protein adsorption; stage 3: flux loss due to particle deposition or consolidation of the fouling material.

after the first blood-contact [3–5,7,13], which leads to a change in membrane behavior. It is irreversible in nature, because fouling is the "coupling" of the adsorbed or deposited protein to the membrane through the intermediate step of concentration polarization [4]. Apart from surface adsorption, pores plugged by adsorbed proteins may be another process affecting efficacy, especially in plasma separators and plasma fractionators with a pore size large enough to allow transmembrane crossing of proteins [14].

In addition to the disadvantage of flux decline and change of selectivity, protein adsorption can affect the biocompatibility of the membrane. For instance, plasma proteins adsorption can be followed not only by the activation of different defense systems in blood, such as coagulation, complement and fibrinolysis, but also by the adhesion and activation of blood cells [3,5,6,15].

Compared to concentration polarization, protein adsorption is more complex and is more detrimental to blood apheresis and purification. It is therefore important to investigate its mechanism and varied affecting factors in filtration so as to find the way to control. Some good reviews have been delivered on the protein adsorption in membrane filtrations [4,16], but the blood-contact membrane is not involved. So this paper focuses on proteins adsorption on the blood-contact membrane, dealing with the mechanism studies, affecting factors, and the development of control methods.

2. Adsorption-affecting factors in blood-contact membranes

Membrane protein adsorption may be affected by a series of factors [17], e.g. the surface chemistry of the membrane, adsorbed protein size, charge, shape, pH value, and so on. As for the blood-contact membrane, interest is focused on its type and morphology, its hydrophilicity, and operating conditions.

Researchers have been studying the affecting factors in membrane fouling by contacting the membrane with human blood or some protein simulation solution.

2.1. Membrane materials

Mulzer and Brash showed that the composition of adsorbed proteins would be qualitatively different with various membrane materials [18].

Fujimori et al. [15] examined the adsorption of albumin, IgG, C3a, interleukin-1β (IL-1β), interleukin-6 (IL-6), human neutrophil elastase (HNE), and tumor necrosis factor α (TNF α) on several types of membranes from dialyzers right after clinical use. They semiquantitatively graded all these membranes with confocal laser scanning fluorescence microscopy (CLSFM). Their research found that the polyacrylonitrile (PAN) membrane revealed the most abundant adsorption, especially for IL-1β, IL-6, and TNF α. Although a marked elevation of C3a in blood was observed in the cellulose triacetate membrane, considerably more adsorption took place when the polymethylmethacrylate (PMMA) and the PAN membranes were applied.

By means of radioisotope labeling technique and indirect enzyme linked immunosorbent assay, Huang examined three plasma proteins (albumin, immunoglobulin and fibrinogen) adsorption from single component protein solution or plasma of various dilutions to sulfonated polyethersulfone (SPES), polyethersulfone (PES), polysulfone (PSF), PMMA and cellulose acetate (CA) membranes [7]. She found that the binding strength of the proteins adsorbed on these membrane surfaces decreased as follows: fibrinogen > albumin > immunoglobulin, and that the extent of clotting factor activation of SPES, PES, PSF and PMMA was lower than that of CA. Sulfonation decreased the ability of PES to activate clotting factor. As these materials' ability to trigger the intrinsic

coagulation pathway had relations with Vroman effect, Huang suggested when the Vroman effect took place earlier, more fibrinogen be displaced and the chance of clotting factor to contact the material be bigger [7].

2.2. Membrane morphologies

Ho and Zydney [19] studied the effect of membrane morphologies and pore structures on protein adsorption using different track-etched, isotropic and asymmetric MF membranes. They found that the fouling occurred among straight-through pores membranes owing to the pore blockage caused by deposition of large protein aggregates on the surface. The rate of blockage was a function of membrane porosity due to the possibility of multiple pore blockages by a single protein aggregate on high porosity membranes, and membranes with interconnected pores fouled more slowly since the fluid can flow around the blocked pores through the interconnected pore structure.

There is evidence that protein is adsorbed within membrane pores, and on the surface as well [4,20]. In UF the amount of protein adsorbed within membrane pores is smaller compared with that on membrane surface [4]. On the other hand, in MF there is greater adsorption within pores, and internal fouling appears to dominate with large pores [4,20]. Numerous examples show that membrane fouling is more severe with the pore size increasing. There appears to be an optimum pore size, below which the membrane resistance restricts permeate flow, and above which severe membrane fouling decreases flux [4].

2.3. Hydrophobicity

One of the main factors enhancing the protein adsorption on the surface is hydrophobic interaction between membrane surface and protein molecules [21,22]. Matthiasson [23] studied bovine serum albumin (BSA) adsorption to CA, PSF and polyamide membranes using direct measurements of protein uptake, evaluated with ^{14}C-labeled BSA, in combination with studies of the membrane hydraulic permeability before and after adsorption. Adsorption reached the maximum on the hydrophobic PSF membranes, with a surface coverage of 2–50 mg/m^2, and got to the minimum on the hydrophilic CA membranes (approximately 0.5 mg/m^2).

2.4. Operating conditions

Operating conditions can also have an effect on the protein adsorption on membranes [8,24,25].

In their study into effects of operating conditions on selectivity of a plasma fractionator in double filtration plasmapheresis, Mineshima and et al. [24] found the ratio increase between the flow rate of the supplied plasma (Q_P) and retained plasma to be discard (Q_D) the most effective in operating conditions in terms of improving the selectivity between albumin and immunoglobulins. However, when Q_P/Q_D was increased beyond a critical value, membrane fouling could also be enhanced and the selectivity of these proteins reduced.

In Ghosh's study on membrane fouling by BSA using pulsed injection technique [25], two UF membranes were exposed to similar fluxes for similar duration. The only difference lay in the order in which the membranes underwent these different fluxes. When the membrane was exposed to fluxes from lower to higher, the fouling came to a smaller extent than it did in a reversed order.

3. Studies on adsorption mechanism

Although some explanations and models have been offered from studies on mechanism of protein adsorption on blood-contact membranes, the very nature of the surface protein adsorption is not completely clear [4,16].

Researchers suggest that a surface-formed dynamic membrane in UF produce much larger resistance than the actual membrane. As a result, the permeating flow is controlled by the dynamic membrane [4].

Le and Howell concluded that physical protein adsorption occurred first, probably in a monolayer, and then further protein build-up took place via intermolecular disulphide bonding and hydrophobic interactions [4]. Kelly and Zydney [26] also showed that BSA aggregates were formed by intermolecular disulfide bonds among albumin molecules, and these disulfide linkages have been identified in the aggregation from a wide range of proteins [27].

Nakamura and Matsumoto studied adsorption behavior of BSA in MF with porous glass membrane [28]. They suggested that the adsorption should be

irreversible and multiply, which consisted of the two types: the adsorption on clean pore surface, i.e. the primary adsorption, and that on preadsorbed pore surface, i.e. the secondary one. The adsorption rate was proportional to the feed rate of BSA, and the proportional coefficient was dependent on the adsorption process.

3.1. Mathematic models of protein fouling

Early in 1930s, Carman [29], Hermans and Bredée [30,31] introduced the cake filtration theory and the classical "blocking laws", respectively for membrane fouling. From then on, a number of different functional forms have appeared for fouling models [30–35].

In their review in 1987, Fane and Fell summarized the semi empirical fouling models for UF of proteins as follows [16]:

$$J = \frac{\Delta P}{\mu(R_\mathrm{m} + R_\mathrm{d} + R_\mathrm{bl})} \tag{1}$$

where J is permeate flux under UF, R_m represents hydraulic resistance, R_bl is the resistance due to solute in the boundary layer, R_d represents the resistance of the foulant, and can be expressed as:

$$R_\mathrm{d} = \alpha_\mathrm{d} M_\mathrm{d} \tag{2}$$

where α_d is a constant equal to the specific resistance of the deposit and M_d is the load, or mass/area, of deposit.

According to Hermia [36] and McCabe et al. [37], all the fouling processes of UF can be expounded by four theoretical kinetic models commonly employed for systems showing flux decline: completing blocking, intermediate blocking, standard filtration and cake filtration models.

The "completing blocking" assumes that each fouling particle arriving at the membrane blocks some pore or pores with no superposition of particles. It leads to:

$$J = -K_\mathrm{b} t + \ln J_0 \tag{3}$$

where t represents time, J_0 is the permeate flux per unit of area through the membrane at $t = 0$, K_b the kinetic constant for completing blocking models.

The other three models can be expressed through equation:

$$\frac{J_0}{J} = (1 + kt)^n \tag{4}$$

where k means the general kinetic constant for the fouling models. When $n = 1$, it represents the so-called "intermediate blocking" model, which presumes that each fouling particle can either settle on another particle which has already arrived and blocked some pores or it can directly block some membrane area. When $n = 2$, it represents the "standard blocking" model, which means that each particle arriving at the membrane will deposit on the internal pore walls, leading to a decrease in the pore volume. When $n = 1/2$, it represents the "cake filtration", which means that each particle will settle on another previously arrived one which has already blocked some pores, therefore cannot directly block the membrane area [38].

Similarly, Scholars [30–33] summarized that the governing equations of fouling on MF could all be conveniently written in a common mathematical form as:

$$\frac{\mathrm{d}^2 t}{\mathrm{d}V^2} = k\left(\frac{\mathrm{d}t}{\mathrm{d}V}\right)^n \tag{5}$$

or

$$\frac{\mathrm{d}J}{\mathrm{d}t} = -kJ(JA_0)^{2-n} \tag{6}$$

where t is the filtration time, V the total filtrated volume, and $J = (1/A_0)\mathrm{d}V/\mathrm{d}t$ is the filtrate flux. The exponent n characterizes the filtration model, with $n = 0$ for cake filtration, $n = 1$ for intermediate blocking, $n = 3/2$ for standard blocking, and $n = 2$ for complete pore blocking.

On the other hand, as the blocking laws regard the membrane as a collection of parallel capillary tubes of constant diameter and length [31,36], Ho and Zydney suggested that it be invalid to apply these models to the fouling of polymeric MF membranes with highly interconnected pore structures [39]. They showed that membranes with an interconnected pore structure became fouled much more slowly than those with straight-through (nonconnected) pores [19,34,39]. Moreover, they introduced some relatively more complicated models for protein fouling on membranes in MF, e.g. a combined pore blockage and cake filtration model [40,41], as well as a model for protein fouling of asymmetric and composite MF membranes [42].

However, proteins are large and complex molecules, and they may change orientation and conformation

during or after interaction with either the membrane surface or other protein molecules [4]. A layer of deposited protein on the surface cannot behave in the manner of a packed bed of inert particles. Furthermore, as the blood components are much more complicated than the protein solution used in the models (e.g. Pascual et al. indicated that the adsorbed layer formed during clinical hemodialysis was extremely complex and many proteins were degraded [43].) and there is a competitive and dynamic adsorption of proteins from blood or plasma on membrane (Vroman effect), it is more difficult to describe the mathematic model of membrane fouling in blood treatment process. Therefore, there is still considerable controversy regarding the most appropriate mechanism of protein fouling on membranes [44].

4. Control methods

Although it seems impossible to eliminate protein adsorption on membranes completely, people have been trying various ways to control the adsorption on blood-contact membranes.

4.1. Using asymmetric membrane

An asymmetric membrane consists of a very thin skin layer on a highly porous and relatively thick sublayer. The skin layer has lots of micropores. In addition to the high mass transfer rates, the asymmetric membrane has another advantage over the conventional symmetric membrane. Conventional symmetric structures act as *depth filters* and retain most particles within their internal structure. These trapped particles plug the membrane, so the fouling happens. Asymmetric membranes are *surface filters* retaining all rejected materials on the surface, where most of them could be removed by shear forces applied by the feed solution moving parallel to the membrane structure (Fig. 2) [45]. Today, the majority of commercially available membranes for blood purification have asymmetric structures [1].

4.2. Cleaning and regeneration of membranes

From mid-1970s, considering the excessive cost of clinical application of dialysis membranes, some scientists recommended the reuse of hemodialyzers for patients of end-stage renal disease. In fact, such recycle came in some countries, like the United States, even though these devices were designed for a throw-away purpose [46,47]. In 1994, 81% of dialysis patients in the United States were treated with recycled dialyzers [48].

Both physical and chemical cleaning and regeneration during and after the employment can recover the efficiency of membranes to some extent [47, 49–52].

4.2.1. Physical methods

4.2.1.1. Backflushing. Backflushing, reversed liquid permeating the membrane to clean its surface, is the simplest hydrodynamic method for cleaning and regeneration. In a lymphapheresis system invented by Babb [49], as the membrane became plugged, a reversible pump in the system was employed to backflush the membrane for it to return to a high filtration rate.

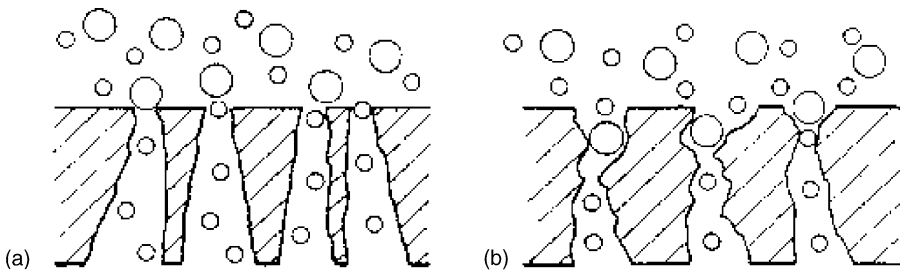

Fig. 2. Schematic diagram of the filtration behavior of (a) an asymmetric and (b) a symmetric membrane [45].

4.2.1.2. Periodic reversal of the feed stream. Ilias et al. [50] and Hargrove and Ilias [51] found that periodical reversal of the flow direction of the feed stream in the membrane module could keep the system in a hydrodynamic transient state, and prevent the formation of an undesirable stable boundary layer on the surface. Thus, the collection of particles in a gradient near membrane surface and the particle deposition on the surface would be slowed down. Therefore they invented a flux-enhanced filtration system to reduce the effect of concentration polarization and fouling [50].

Besides the hydrodynamic methods mentioned above, other physical cleaning of membrane surface includes ultrasonic (or subsonic) treatment and an electric vibration method [52].

4.2.2. Chemical cleaning

Chemical cleaning mainly refers to the membrane surface cleaning with various chemical reagents capable of removing the adsorbed proteins.

Dennis et al. [47] compared four methods of cleaning hollow fiber hemodialyzers for reuse. They found that the number of times the dialyzers could be used was more than doubled when a 0.3 M sodium hydroxide solution was the clearance agent, compared with the other three cleaning methods tested, e.g. water flush and reverse UF. Yin et al. had also found that desorption of the adsorbed human serum albumin (HSA) from membrane surface can only be achieved with NaOH [13].

Today reuse practice is permitted only for hemodialysis/diafiltration membrane modules, and only in a few countries. While the practice of reusing dialyzers has become widespread in the United States, it is less common in West European countries and Japan. Actually, it is even prohibited in some countries, such as France [46]. The difference in practice has led to claims that dialyzer reuse is a factor in the relatively high mortality reported for patients receiving dialysis in the United States [53–56]. Evidence now demonstrates that the treatment with reprocessed dialyzers is associated with elevated rates of hospitalization and death, although the mechanism underlying these associations remains unclear [46].

Cleaning and regeneration methods currently established for dialyzers in clinical use are performed off-line to permit reuse. Even though, many cleaning methods are still under way, especially the hydrodynamic cleaning in filtration [50,51].

4.3. Modification of membrane surfaces for antifouling

An effective approach against protein adsorption is the surface modification techniques that will transform the current commercial polymers membrane surface physically and/or chemically without affecting the transport properties significantly. A variety of surface modification strategies have been reported, which can be roughly grouped into four distinct categories as follows [57]:

- Introduction of negatively charged surface groups.
- Increasing hydrophilicity.
- Introduction of steric hindrance.
- Biomimetic modifications.

The above-mentioned methods and their combinations are utilized in modification of membrane surface. Actually, most of the modifications described below are still in the process of development (i.e. on lab-scale), especially the introduction of steric hindrance and biomimetic modifications.

Furthermore, most of them are used when membranes are present, while blending is used when membranes are being prepared. A basic principle is that when the membrane surfaces are modified, the desired bulk properties, including pore sizes, structures and distribution should be retained.

4.3.1. Introduction of negatively charged surface groups

Most proteins and cells are negatively charged in blood. Thus the introduction of negative charges on the membrane surface should (at least in principle) increase the electrostatic repulsion between the membrane and proteins/cells. Chen et al. [58] pretreated a UF membrane with anionic surfactants to cut the adsorption in UF of proteins. They suggested that small anionic surfactant reduce protein adsorption by altering electrostatic interactions between proteins and membrane surface. When used along with nonionic surfactants or when polyethylene oxide (PEO) segments were added to their backbone, the anionic surfactants showed significant flux improvement and fouling resistance.

Higuchi et al. [59] and Nakagawa [60] chemically modified both the inner and the outer surfaces of PSF hollow fibers with propane sultone and some Friedel-Crafts catalysts to introduce—$CH_2CH_2CH_2SO_3$—segments on the modified surfaces. Experiments suggested that the modified fibers having hydrophilic surfaces showed better results of anti-adsorption of protein than the nonmodified ones. Huang's experiment arrived at similar conclusions [7].

4.3.2. Increasing hydrophilicity

As mentioned above, hydrophilic membranes such as CA, polyvinyl alcohol (PVA), and PAN membranes have the characteristics superior to that of hydrophobic membranes, as far as less proteins adsorption is concerned. The logic behind is clear: an ordered structure of water molecules on membrane surface is formed by the hydrogen bond between the hydrophilic surface and water. For any protein or cell to be adsorbed on (or adhere to) the membrane, it must first displace the ordered water molecules associated with the surface groups on the membrane. This process consumes energy, so it will not happen automatically [14].

However, hydrophilic membranes do not usually have thermal stability and are susceptible to chemical agents, whereas some hydrophobic membranes, e.g. PSF and polyimide, have thermal stability and some chemical resistance [61]. Woffinfin and Hoenich further demonstrated that the degree of complement activation and leucopenia in blood was most marked for cellulosic membranes [62]. Thus, the surface modification of hydrophobic membranes that introduce hydrophilic segments only on their surface may be a better idea to present the advantages of both hydrophilic and hydrophobic membranes. Several studies have specifically demonstrated that increased hydrophilicity can result in a significant reduction in both protein adsorption and cell adhesion [63,64].

Considerable efforts have been made to impart the surface of traditional hydrophobic membranes with hydrophilic properties, including blending, coating and grafting techniques.

4.3.2.1. Physical coating. One of the oldest methods for modifying surface properties is to coat a membrane, which has the desired bulk properties, with an agent having the desired surface properties. This has been done to make an otherwise hydrophobic membrane function as if it is hydrophilic.

In Brink et al.' study [65], PSF UF and MF membranes were hydrophilized by preadsorption of two water-soluble polymers. Protein adsorption at the pore walls of UF membranes, resulting in the narrowing of pores, was prevented by partly sealing off the pore entrances by polymer molecules presorbed on the external membrane surface. But the pore blockage of MF membranes could not be averted by the preadsorption technique.

Kawata et al. [66] disclosed that a water solution containing polyvinyl pyrrolidone (PVP) would be applied as an internal coagulation liquid to the hollow fiber membrane in order to leave PVP, the water-soluble polymer, on the surface of the hollow fiber membrane for permeability improvement. However, the efficiency was insignificant.

To sum up, such an approach to modify surface properties has generally been found undesirable because the resulting coating tends to be temporary, and is removed as a whole or in part shortly after initial use.

4.3.2.2. Blending. Blending a hydrophilic polymer into the casting solution to form a relatively hydrophilic surface is another simple modification method. Compared with other approaches, the original pore size and its distribution of membranes are easy to keep, and the hydrophilic component is distributed evenly both on the membrane surface and into the matrix.

Ward and co-workers hydrophilized the hydrophobic PSF membrane by casting alloyed polymer membranes from solutions containing PSF and PVP in dimethylacetamide. They found that when the proportion of PVP increased, the interfacial contact angles of the modified membrane for iso-octane in water decreased. Thus the introduction of PVP could also affect the biocompatibility [67].

Kraus et al. [68] described a method to prepare hydrophilic PES membranes by forming a solution of the hydrophobic PES and adding a high molecular weight (up to 10,000 Da) polyethylene glycol (PEG) prior to casting the polymer into a membrane. The high molecular weight PEG was responsible for the initial hydrophilicity of the resulting PES membrane.

However, like physical coating, the possibility of elution of the hydrophilic component is an obvious disadvantage of the blended membrane. For instance, Kobayashi and Tanaka suggested that a defect of PSF membranes blended with a hydrophilic polymer having blood compatibility (e.g. PVP and PEG polymer) be the elution of hydrophilic polymer from the blended PSF membranes into blood, which was dangerous in clinical use [69]. Therefore, it is necessary that other methods be applied to avoid the elution of the hydrophilic component from the modified membranes.

4.3.2.3. Chemical modification. Compared with other approaches, chemical modification on the surface of hydrophobic membranes that introduces hydrophilic segments only on the surface presents the advantages of both hydrophilic and hydrophobic membranes [59,60,71,72]. The original characteristics of mechanical strength and thermal stability are kept, since only the membrane surface is modified [71,73]. In addition, the introduced hydrophilic segments are more stable and not easy to elute, for they are chemically bonded on the surface.

In the hydrophilic modification of polypropylene (PP) flat sheet MF membranes, Wang et al. introduced peroxide onto the membrane surface by ozone treatment followed by graft polymerization with hydroxyethyl methacrylate (HEMA) [70]. The graft was initiated at a mild temperature by redox decomposition of peroxide. The HEMA grafting made the surface of the PP membrane hydrophilic and less adsorbable to BSA proteins, and the protein-resistance effects depended on the ozone-treating time length.

Higuchi et al. did a series of work to introduce hydrophilic segments chemically on both the inner and outer surface of PSF hollow fibers to improve the protein-resistance capability [59,60,71,72]. Recently, they modified PSF hollow fibers by chemically bonding PVP on the surface [74]. Firstly, an aliphatic double bond was introduced on the ethylenediaminated surface of PSF membranes using *N*-succinimidylacrylate. Then, through this double bond, vinylpyrrolidone monomers were conjugated covalently on the membrane surface, and polymerized as well. The immobilized amount of vinylpyrrolidone on PVP/PSF membranes was controlled by the amount of vinylpyrrolidone monomer in the reaction solution and the reaction time. They found PVP/PSF membranes to be the most hydrophilic among the PSF and surface-modified PSF membranes prepared in their study. The PVP/PSF membranes not only exhibited lower protein adsorption from a plasma solution, but also showed a more suppressed number of adhering platelets on the surface than PSF and other surface-modified membranes. They suggested that the hydrophilic surface of the PVP/PSF membranes without ionic groups cause the suppression of platelet adhesion on the membranes, and that the long hydrophilic side chain of PVP contribute to the hydrophilic and hemocompatible wipers on the surface of the hydrophobic PSF membranes.

4.3.2.4. Photochemical modification. Photo-induced grafting is favored by some researchers [75,76]. Using benzophenone as initiator, Ulbricht et al. modified a PAN UF flat sheet membrane with various poly(ethylene glycol) methacrylates by UV irradiation-initiated graft polymerization [75]. The modified layer on the outer surface was thin ($<1\,\mu m$) even at high degree of polymerizations ($1–2\,mg/cm^2$) and the modification extended into the active layer pores of the membranes. The results of UF experiments with γ-globulins, BSA and cytochrome *c* applied as single and mixed protein solutions suggested that protein/protein UF separations become feasible because protein/polymer surface interactions were diminished.

Kaeselev et al. modified PES and PSF UF membranes by UV-assisted graft polymerization of three hydrophilic monomers, i.e. *N*-vinyl-2-pyrrolidinone, 2-acrylamidoglycolic acid monohydrate, and 2-acrylamido-2-methyl-1-propanesulfonic acid [76]. Four different modification conditions were found to provide modified UF membranes with filtration performance superior to the base-unmodified PES, the base-unmodified PSF, or a regenerated cellulose (RC) control membrane. Slightly compromised protein solution permeabilities by the graft were compensated for low fouling modified membranes that exhibited excellent cleaning characteristics. They found that low degrees of grafting ($DG < 0.53$) and intermediate wettabilities ($0.74 < \cos\theta < 0.82$) were sufficient to obtain attractive non-fouling membranes. They also suggested that PES be far more sensitive to UV-assisted graft polymerization and, hence far less energy to attain a desired degree of grafting than PSF.

However, photochemical modification can only deal with flat sheet membranes. As for hollow fibers, other methods must be tried to modify both the inner and the outer surfaces.

4.3.2.5. Irradiation. Mok et al. modified PES UF hollow fiber membranes by grafting PEG on the internal surface using γ-ray irradiation method [61]. The performance of both modified and unmodified hollow fibers in UF of porcine albumin showed the surface modification decreased the fouling of hollow fibers. However, they also found that the initial permeation rate of protein and pure water for the grafted hollow fibers was significantly lower than the unmodified one, for the grafted PEG induced by γ-ray irradiation narrowed the pores.

4.3.2.6. Plasma polymerization. Like γ-ray irradiation method, plasma polymerization of gases presented in a low temperature plasma is also a "clean" technique particularly well suited for biomedical material processing [77,78–81]. Early in 1991, Clarotti et al. studied the possibilities offered by this technique to prepare membranes with the required bio-and hemocompatibility to be implanted in an organism [80]. The deposition on PSF films from a kind of plasma containing a mixture of ethylene oxide and perfluorohexane in order to obtain very hydrophobic, less hydrophobic and intermediate coatings was studied. Their purpose is to optimize the surface properties of the treated membranes without affecting their filtering properties.

Ulbricht and Belfort [78,79] treated PAN and PSF UF membranes by low temperature helium or helium/water plasma to generate polymer peroxide on the membranes. Then graft polymerization of hydrophilic monomers such as HEMA and acrylic or methacrylic acid onto PAN and PSF UF membrane surfaces was initiated via thermal decomposition of peroxides. Hydrophilic PAN membranes, modified either by plasma treatment [78] or HEMA graft polymerization, showed significantly reduced fouling due to static protein adsorption, and improved protein UF performance. In particular, for water plasma treated PAN membranes with high initial retention, higher fluxes (up to 150%) with the same or even improved retentions were obtained. Hydrophilized PSF-*g*-HEMA membranes could provide improved performance in protein UF over unmodified PSF UF membranes. They suggested that plasma induced graft polymer modification of UF membranes could be used to adjust membrane performance by simultaneously controlling the surface hydrophilicity and permeability.

Kim et al. [82] changed the surface of PSF flat sheet UF membrane from hydrophobic to hydrophilic by means of oxygen plasma treatment, which introduced polar functional groups such as hydroxyl, carbonyl, and carboxyl group on the PSF membrane. The plasma treated membranes showed increased flow rates of pure water and gelatin solution, hence less fouling on the surface.

4.3.3. Introduction of steric hindrance

It was suggested that low grafting degrees of hydrophilic polymer and intermediate wettabilities be sufficient to obtain attractive non-fouling membranes [76]. However, as the density of hydrophilic polymers grafting onto the hydrophobic surface is high enough, their chains are obliged to stretch away from the surface, sometimes much farther than the typical unstretched size of chain. Then, the grafting polymers formed a hydrophilic "brush" on the surface [83]. In this so-called "brush regime", a high degree of protein rejection is generally observed for a variety of proteins [84–86,88–90].

Hydrophilic brushes such as PEO attached to a hydrophobic substrate can give the surface extraordinary ability to resist protein adsorption [74,84–86,88–95] and cell adhesion [96]. Early in 1980s, Nagaoka and Mori proposed the use of a hydrated dynamic surface for better blood compatibility in a study of grafting PEO onto polyvinyl chloride (PVC) [97]. They demonstrated that the excluded volume effect and the dynamic motion of the water-soluble PEO chains on the surface suppressed protein adsorption and platelet adhesion. The movement of hydrated PEO chains induces the microflow of water, and the surface adsorption is inhibited. They regarded PEO chains as "molecular cilia". Lee et al. found that pendant PEO chains on the materials surface played an important role in reducing blood proteins adsorption on the surface [98]. This property is believed to have resulted from the combination of its hydrophilicity, steric repulsion between the grafted hydrophilic polymer brushes and proteins, and unique coordination with surrounding water molecules in an aqueous medium [84].

A lot of researchers studied the mechanism of the protein-resistance character of PEO brushes, and found that the protein-resistance character of PEO was dependent on the chain length and surface density of PEO. A high surface density and long chain length of terminally attached PEO (i.e. "PEO brushes") exhibited optimal protein-resistance [85,86,91,92].

Usually, polymer brushes on solid surfaces can be prepared by (1) irreversible adsorption of diblock or triblock copolymer chains on the surface or (2) chemical graft.

4.3.3.1. Irreversible adsorption. Over the last decade, various researchers have investigated the potential use of adsorbed amphiphilic diblock and triblock copolymers on solid substrates for protein adsorption reduction [85,86].

The PEO brush can be end-tethered to the surface through irreversible adsorption of diblock or triblock copolymers of PEO and some hydrophobic component (e.g. polypropyleneoxide PPO) from solution using Langmuir–Blodgett technique [85]. The hydrophobic part of the copolymers is first adsorbed onto the substrate, with the hydrophilic end serving as the barrier for protein adsorption from aqueous solutions. Moreover, as the desorption of the hydrophobic block from the hydrophobic surface is unfavorable, the brush density on the surface remains constant under varied conditions, in contrast to hydrophilic homopolymer that can desorb [85].

Besides PEO, coatings of other nonionic polymers, such as PVP, PVA, poly(vinyl methyl ether), dextran, and methyl-cellulose, have also proven effective in reducing adsorption of certain proteins (β-lactoglobulin and BSA) onto PSF surfaces [86].

Hester and Mayes [99] prepared immersion precipitated membranes with enhanced adsorption resistance from blends of polyvinylidene difluoride (PVDF) and a free-radically synthesized amphiphilic comb polymer having a methacrylate backbone and PEO side chains. X-ray photoelectron spectroscopy (XPS) analysis indicated substantial surface segregation of comb polymer during membrane coagulation, providing an integrated near-surface coverage of up to 50 vol.% comb for a membrane containing 10 wt.%, resulting in hydrophilic surfaces with excellent stability. In addition, separation surface porosities for comb-modified membranes were up to an order of magnitude higher than PVDF controls. Thus, a membrane containing 10 wt.% comb is over 20 times as permeable as a PVDF-only membrane with equivalent separation characteristics after 3 h filtration of a foulant protein solution.

4.3.3.2. Chemical grafting. Preparation of polymer brushes can also be achieved through chemical binding of performed polymer chains [87–90,100]. In contrast to coated polymer phases, the resulting polymer phase is highly stable since polymer chains are covalently bonded to the surface. Two techniques can be employed in chemical grafting: (a) "grafting to", where the end-functionalized polymers are synthesized and reacted with appropriate groups immobilized on the substrate, (b) "grafting from", where polymer layers are formed by in situ polymerization initiated by the immobilized initiators on the surface [100].

Wang et al. coated PEO on PVDF membrane surface, including the pore surfaces [88]. The membrane was firstly dipped in a PEO/$CHCl_3$ solution. Then the pre-coated PEO was immobilized by argon plasma-induced grafting, and a high concentration of the grafted PEO polymer on the membrane surface was obtained. The PEO graft concentration was defined as the [CO]/[CF_2] ratio determined by XPS. When the [CO]/[CF_2] ratio was above 3.2, the modified membrane exhibited good anti-fouling property. According to Fig. 3, there was almost no loss in water flux due to protein adsorption for the membranes with PEO graft concentration greater than 3.2, except

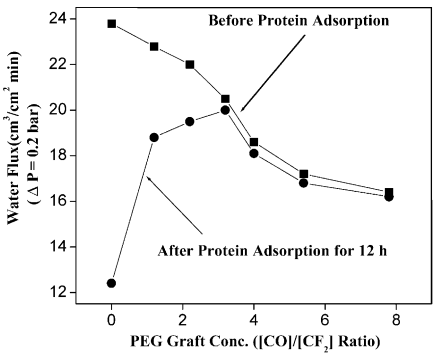

Fig. 3. Water fluxes of the pristine PVDF and the PEG-g-PVDF microporous membranes before and after protein fouling from the exposure to a buffer solution containing 10 mg/ml γ-globulins for 12 h [88].

for the inherent loss due to the presence of grafted PEO on the membrane and pore surfaces. With this "grafting to" tech, it is possible to graft monodispersed polymers onto the surface. However, since polymer molecules must diffuse to the solid surface, diffusional limitations and steric hindrance effects can severely reduce the degree of surface chain density and overall polymer graft yield.

Rovia-Bru et al. applied "grafting from" technique to graft PVP on zirconia surface to study its behavior of reducing lysozyme adsorption [89]. Firstly, they modified the –OH groups presented on the ceramic particle surface by silylation with vinyltrimethoxysilane, to generate vinyl surface sites. Then, the silylated particles were dispersed in an aqueous vinylpyrrolidone solution, and heated to the desired reaction temperature to start the PVP graft polymerization. With this kind of "grafting from" technique, diffusion limitations and steric hindrance effects are minimized owing to the much smaller size of the monomeric units diffused to react with surface chains or active surface sites. Therefore, with graft polymerization, it is possible to achieve a higher degree of surface coverage than via the "grafting to" technique, though it is not easy to get monodispersed brushes.

Witham and Johnson modified the PES membrane in both ways [90]. The modified membrane was prepared firstly by directly coating the entire surface of a hydrophobic PES membrane with an aqueous solution of PEO and at least one polyfunctional monomer. Then the monomer was polymerized over the entire surface, which could cause the PEO attach to the PES membrane so as to form a non-extractable surface that would not crack when the membrane was folded to form a pleated cartridge.

4.3.4. Biomimetic modifications

A potential technique for reducing protein adsorption for synthetic polymeric membranes is to mimic a biologic surface in nature. For example, the red blood cell plasma membrane, unlike synthetic polymer membranes, naturally resists protein fouling. This property is attributed to the unique phospholipid bilayer structure of the membrane [101].

However, the phospholipid membranes are physically and chemically unstable, because the phospholipid constituting membranes do not bond covalently and have high mobility. To improve its mechanical strength, phospholipid molecules with polymerizable group are synthesized.

Early in 1990, Ishihara et al. [102] copolymerized 2-methacryloyloxyethyl phosphorycholine (MPC) with *n*-butyl methacrylate (BMA). Then the poly(MPC-co-BMA) (PMB) was made as a hydrogel membrane by a solvent evaporation method. In addition, Chapmann [103] has demonstrated the attractiveness of this technique for the preparation of nonfouling membranes using phosphorylcholine.

From then on, Ishihara et al. have paid attention to blending MPC polymer with conventional polymeric materials used in the biomedical field [104–107]. While the mechanical strength of this blended polymer membrane does not change, the MPC polymer among it can serve as a doubly functional polymeric additive, i.e. to generate a protein-adsorption-resistant characteristic, and to render the membrane hydrophilic [106].

To improve the surface blood compatibility of PSF membranes, Ishihara et al. blended PSF with PMB and poly(MPC-co-*n*-dodecyl methacrylate) (PMD), and prepared membranes by a solvent evaporation [104,105]. The compatibility of the MPC polymer with the PSF was excellent, and the mechanical properties of the blended membranes were similar to that of the original PSF membrane. The MPC polymer was not easy to elute. Surface analysis revealed that the MPC unit in the polymer additive was concentrated there. Compared with the PSF membrane, the blended membrane significantly reduced human plasma fibrinogen (HPF) [104], albumin, γ-globulin, and platelet adsorption (Fig. 4) [105]. Moreover, the change in the morphology of adherent platelets was also suppressed by the modification with MPC polymer (Fig. 5) [105].

To obtain protein-adsorption-resistant membrane for hemodialysis, Hasegawa et al. [106] prepared a similar polymer blend composed of PSF and poly(MPC-co-2-methacryloyloxyethyl butylurethane) (PMBU). Its mechanical strength did not change compared with that of the PSF membrane. The amount of plasma protein adsorbed on the PSF membrane was reduced by addition of the MPC polymer. The permeability of low-molecular-weight protein ($M_w = 1.2 \times 10^4$) did not change even after the PSF/MPC polymer membrane was contacted with plasma protein solution for 4 h, whereas it decreased dramatically in

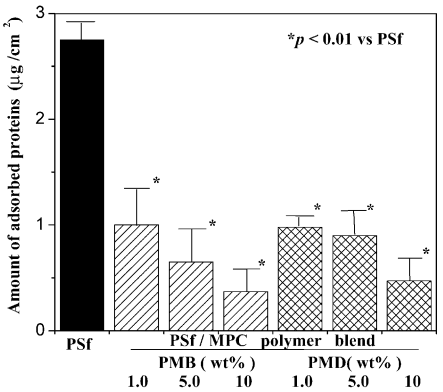

Fig. 4. Amount of total proteins adsorbed on the PSF and PSF/MPC polymer blend membranes from human plasma [105].

the case of the PSF membrane. Platelet adhesion was also effectively suppressed on the PSF/MPC polymer membrane.

Ye et al. [108] blended PMB with CA to improve the hemocompatibility of CA membranes for hemofiltration. Both the original CA and the blended membrane had an asymmetric and porous structure. The mechanical properties and solute permeability of the CA/PMB blended membrane could be controlled by preparation conditions. By blending with PMB, the membrane showed both good permeabilities of water and solute and good permselectivity in comparison with the original CA membrane. Moreover, the blended membranes had excellent blood compatibility such

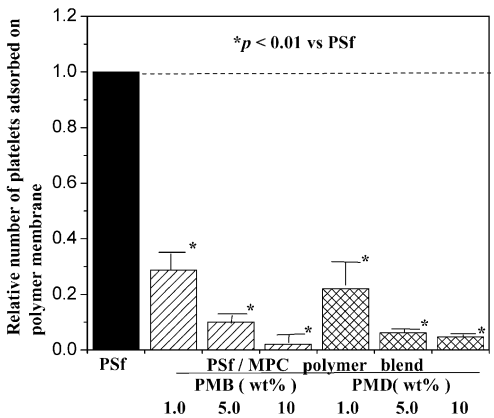

Fig. 5. Relative number of platelets adhered on PSF and PSF/MPC polymer blend membranes [105].

as protein adsorption resistance, compared to the CA membrane.

In addition to blending, other researchers took advantage of other approaches to introduce MPC polymer on the membrane. Akhtar et al. [109] treated PVDF and CA membranes by plasma etching to generate surface hydroxyl groups first, and then grafted MPC on to those membranes via a reaction initiated by ceric ammonium nitrate (CAN). During the filtration of test BSA solutions, it indicated that the MF membranes coated by grafting with MPC showed a much lower decline in flux compared to the uncoated control membranes, and in some cases a higher starting flux. Moreover, a reduction in protein fouling on the surface and within the matrix of the coated membranes was demonstrated as assesses by anionic gold staining. They concluded that the phospholipid coating was an effective treatment for both reducing protein fouling on and in membranes and improving their performance in filtration.

In their study of the membrane oxygenator, Iwasaki et al. prepared PMD skin film adhered to a PE porous membrane [110]. The results of the whole blood experiment showed that, compared with the PE surface, the adhered PMD/PE porous membrane could reduce plasma protein adsorption and platelet adhesion. And the morphology of adherent platelets on the PMD maintained native shape, which means they were preserved, could not result in further activity of other components in the blood on the surface. Moreover, the test showed that the PMD film did not detach from the PE porous membrane even after being soaked in water for more than 6 months.

Introduction of heparin is also an interesting topic. Jen et al. [111] prepared a heparin containing copolymer membrane. Initially, they grafted vinyl pyridine (VP) onto styrene–butadiene–styrene (SBS) triblock copolymer membrane by UV-radiation induced graft copolymerization to obtain the SBS-*g*-VP copolymer membrane. Subsequently, the substituted pyridine groups on the SBS-*g*-VP graft copolymer membrane were quaternized with iodomethane, and then the membrane was treated with heparin to prepare the heparin containing SBS-*g*-VP copolymer membrane (SBS-*g*-VP-HEP). Protein adsorption of fibrinogen and albumin onto the membranes was performed to evaluate the effect of graft amount and heparin content on the biocompatibility of SBS-*g*-VP and

SBS-*g*-VP-HEP membranes. The amount of the adsorption of albumin and fibrinogen decreased with increasing grafting amount and heparin content.

As blood does not coagulate in normal blood vessels whose inside surface is covered with endothelial cells, Attafuah and Hall prepared UF membranes composed of biologically derived matrices, which were derived from a bovine aorta endothelial cell line, individually crosslinked onto ceramic microfilters using glutaraldehyde, cyanuricchloride and carbodiimide as fixing agents [112]. The fouling nature and rejection properties of the matrix were examined, suggesting that the biological membrane compared very favorably with CA UF membranes.

Most of these biological modifications are hydrophilic in nature, and they may also introduce negatively charged side groups onto the membrane surface. Therefore, more researchers have paid their attention to the biomimetic modification of membranes [57].

5. Prospects

Because of the complexity of blood components and the diversity of membranes, studies on the protein adsorption fouling on blood-contact membranes are far from enough. Therefore, researches on modification methods against protein fouling are booming. The ideal blood-contact membrane is one that not only resists plasma protein adsorption fouling, but also keeps the desired bulk properties, with pore sizes, pore size distribution and pore structures included. In clinical practice of blood purification therapies, it is expected that membrane separation procedures be combined with some specific adsorption procedure that can selectively get rid of some harmful proteins from blood (e.g. β2-microglobulin, a protein which intervenes in amyloidis arthritis [113]). Consequently, it is significant to develop a novel membrane which cannot only resist the non-specific plasma protein adsorption on the surface so that the permeability and the selectivity of the membrane can be maintained, but also remove some specific harmful proteins from blood [44,114,115]. From this point of view, more attention should be paid to the development of modification on the membrane with regards to polymer brushes and biomimetic method.

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