

Heparin-Mimicking Polymer Modified Polyethersulfone Membranes - A Mini Review

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Abstract: Recent studies on the modification of polyethersulfone (PES) membranes using heparin-mimicking polymers are reviewed. The general conception of heparin-mimicking polymers is defined as the synthetic polymers (including the biopolymer derivatives and synthetic sulfated artificial polymers) with similar biological functionalities as heparin, such as the anticoagulant, growth factor binding, and also disease mediation. In the review, heparin-mimicking polymers is briefly reviewed; then heparin-mimicking polymer modified PES membranes, including blended, coated, and grafted membranes are discussed respectively.

Keywords: Heparin-mimicking, polyethersulfone, blood compatibility, blending, coating.

1. INTRODUCTION

Polyethersulfone (PES) and PES-based membranes have been extensively applied in separation fields, due to their outstanding hydrolytic, thermal, and oxidative stabilities, as well as good mechanical property. One of the main application fields is in biomedical field, such as medical devices and artificial organs used for blood purification (plasma collection, plasmapheresis, hemofiltration and hemodialysis) [1-4]. However, proteins will rapidly adsorb onto the PES membrane surfaces after contacting with blood, leading to further undesirable results, such as platelet adhesion, platelet activation, aggregation and thrombus formation. As a result, hemocompatibility of the membrane is not very good, and injection of anticoagulant is crucial during the clinical application [5]. Thus, modification of PES membranes used for biomedical applications is needed.

Pinnau *et al.* [6] summarized the most universally practical modification methods for membranes, including chemical treatment (pyrolysis, crosslinking, fluorination), surface coating, solvent treatment, and annealing with heat treatment. Van der Bruggen *et al.* [7] reviewed the chemical and physicochemical methods for the modification of PSF/PES nanofiltration (NF) membranes to improve the hydrophilicity. Chemical or physical modifications after the fabrication of membrane provide more hydrophilic surfaces. Such

modification processes are (1) physical pre-adsorption of hydrophilic compounds onto the surfaces; (2) plasma treatment to introduce various functional groups onto the surfaces; and (3) grafting polymerization of hydrophilic monomers attached to the surfaces. Most recently, we reviewed the modification methods of PES membranes [8]. Two types of membranes, including hollow fiber and flat-sheet membrane types were discussed respectively. The modifications are aimed to improve the antifouling property, blood compatibility and other specific functions.

In this review, recent studies on the modification of polymeric membranes using heparin-mimicking polymer to increase the membrane blood compatibility are discussed. Firstly, heparin-mimicking polymers are briefly reviewed; then heparin-mimicking polymer modified membranes, including blended, coated, and grafted membranes, are discussed respectively.

2. HEPARIN-MIMICKING POLYMERS

Heparin, composed of repeating disaccharide units of uronic acid and glucosamine, is the first glycosaminoglycans applied in medicine. The hydroxyl and amino groups of the glucosamine units are partially sulfated. It is a highly sulfated glycosaminoglycan, and has been widely used as an injectable anticoagulant.

Heparin-mimicking polymers can be defined as the synthetic polymers (including the biopolymer derivatives and synthetic sulfated artificial polymers) with similar biological functionalities as heparin, such as the anticoagulant, growth factor binding, and also disease mediation. The heparin-mimicking polymers are ionic polymers owning ionic functional groups such as

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carboxylic acid, sulfamide, and sulfate, and it is believed that the presence of the groups [9-11] contributed to the anticoagulant activity of heparin as shown in Figure 1.

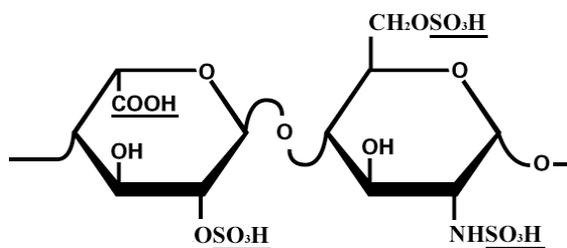


Figure 1: Molecular structure of heparin.

2.1. Natural Biomacromolecule Derived Heparin-Like Polymers

The first study on heparin-like polymers is based on the natural biomacromolecules. RGTA11, was deemed efficiently to preserve the heparin-binding growth factors FGF2 against trypsin digestion, which was a dextran derivative containing carboxymethyl, carboxymethyl benzylamide, and carboxymethyl benzylamide sulfonate groups, thus could mimic heparin [12]. The RGTA11 also presented anti-inflammatory and tissue repair activities mediated by growth factor protection, which would be benefit to digestive ulcer treatment [13]. Then, it was found that beta-cyclodextrin sulfates could also be used to mimic heparin as inhibitor on angiogenesis [14].

Since heparin can be regarded as the sulfonation of the hydroxyl and amino groups of glucosamine units, the sulfonation of other polysaccharides such as the laminarin might yield very potent new anticoagulants and express heparin-like biological activities [15]. Heparin-like oligosaccharides also showed heparin biological activities [16, 17]. Thioglycosides was also utilized to synthesize the heparin-like oligosaccharides with well-defined reactivity. The proposed one-pot synthesis method of uronic acids through the selective oxidation at C-6 after the assembly of the oligosaccharides is highly efficient [18].

Hansen *et al.* reported an efficient method to synthesize a structurally defined heparin-like dodecasaccharide [19]. The H-3 radiolabelling was utilized to provide the first example of this kind of agent for monitoring *in vivo* stability and *in vivo* tissue distribution of a structurally defined and biologically active heparin-like dodecasaccharide. Furthermore, the group also confirmed that the heparin-like oligosaccharides, such as the octa-, deca-, and

dodecasaccharides [20]. The investigation of the activity *in vitro* for these compounds against VEGF(165) and FGF2 suggested that the octa- and deca-saccharides were more effective to target FGF2 induced effects, where the cell migration was affected more obvious than the proliferation. The relationships of the structure and activity exemplified significant effect of the 6-O-sulfation in regulating the activity for angiogenic growth factors.

To mimic the anticoagulation of heparin, Pereira *et al.* designed sulfated fucans, which was composed of oligosaccharide repeating units with sulfation and also was one of the most widely studied sulfated polysaccharides of non-mammalian origin [21]. The comparison results of anticoagulant activities of the sulfated fucans from echinoderms and brown algae indicated that different structural features determined not only the anticoagulant potency but also the mechanism by which they exerted this activity. Andrade *et al.* had isolated another natural heparin-like compound from crab. From the analysis of nuclear magnetic resonance and enzymatic, it was found that the compound was rich in disulfated disaccharides, owning large quantities of the 2-O-sulfated-beta-D-glucuronic acid units [22]. This heparin-like compound showed negligible *in vitro* anticoagulant activity and low bleeding potency, thus it was a promising alternative to develop therapeutic agents which were structure-driven, heparin based and with fewer undesirable effects.

Apart from the bio-isolated heparin-like polymers, a series of synthesized biopolymer based heparin-like derivatives had been intensively reported. Yang *et al.* reported the 6-carboxylchitin derivatives with different sulfate group and N-acetyl group contents [23]. The *in vitro* anticoagulant activity results indicated that all the 6-carboxylchitin derivatives had prolonged activated partial thromboplastin times (APTTs). It confirmed that the anticoagulant activity for the heparin-like polymers strongly depended on their chemical structures. Recently, our group synthesized a sulfated chitosan derivative by sulfating the phthaloylated chitosan [24], and the novel derivative was dissolved in many organic solvents, as shown in Figure 2.

Lia *et al.* prepared the sulfated hyaluronic acid (SHA) to modify the electrically conductive polypyrrole (PPY) film. The plasma recalcification time (PRT) for the SHA modified films were obviously prolonged compared to the HA modified films. The platelet adhesion was also reduced [25]. Moreover, the

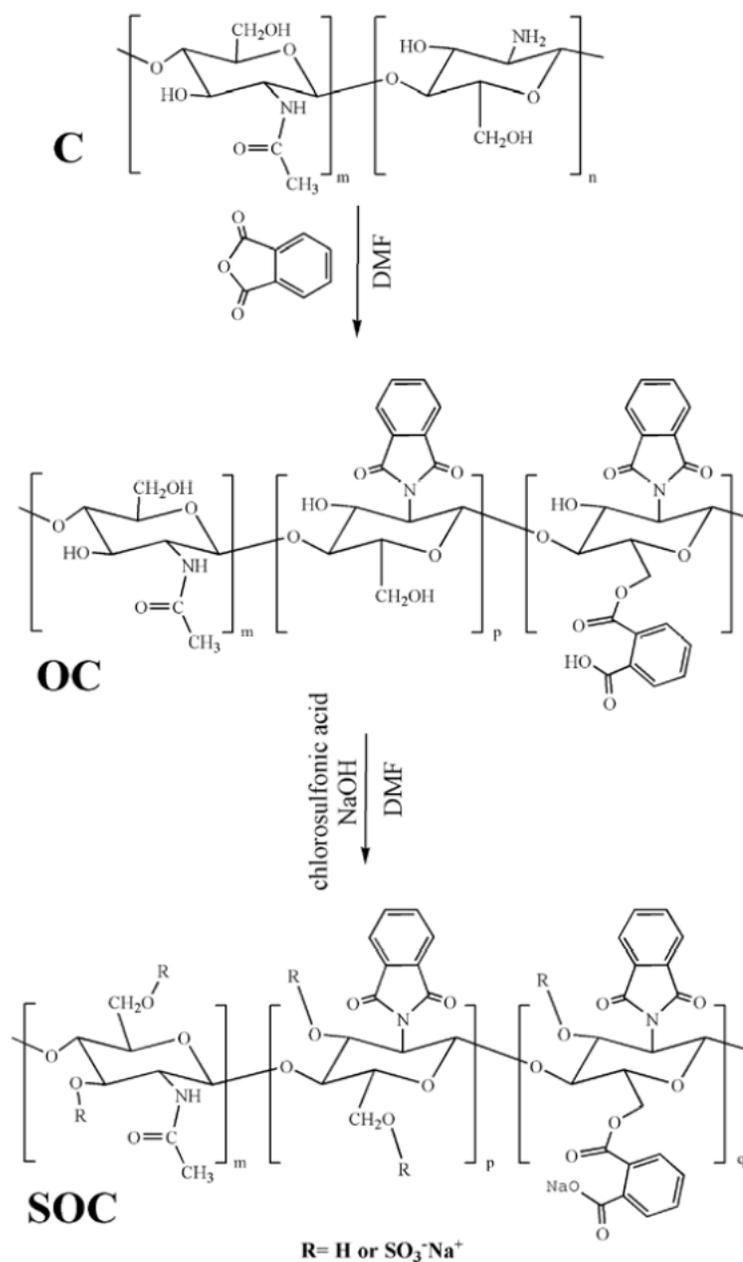


Figure 2: Synthesis of sulfated derivative of chitosan (SOC).

heparin-like polymers also showed anti-inflammatory properties by reducing the activity of the MMP-9 secreted by the human activated leukocytes and also reducing the flux of the inflammatory cells to injury site [26].

In general, many kinds of natural biomacromolecules, especially for polysaccharides, can be used to prepare heparin-mimicking polymers. However, few of the studies concerned membranes. Also, it is difficult to modify membranes using the heparin-mimicking polymers by blending method, since the polymers are water-soluble, while most of

membrane matrixes are water insoluble. Coating and grafting methods to modify membranes using the heparin-mimicking polymers may be good choices.

2.2. Synthetic Polymer Derived Heparin-Like Polymers

Thrombus formation on blood-contacting artificial surfaces is a major problem. A series of antithrombogenic heparinized surfaces had been obtained either by heparin binding, or by grafting biomacromolecules based heparin-like polymers. However, the application of these approaches is limited

by their inherent drawbacks of high cost and complex synthesis process [27]. Thus, the development of ideal antithrombogenic polymers is a primary objective in the blood-contacting fields of artificial hearts, cardiovascular prostheses, hemodialysis, and other devices. The synthesized sulfated polymers become the emerging star in the application of blood-contacting fields due to their low-cost, facile, and controllable synthetic processes.

To prepare synthetic heparin-like polymer, the mostly widely used method is the sulfonation of the present and/or synthetic polymers. Jang *et al.* [28] synthesized novel copolymers of sulfonated PEG acrylate (PEG-SO₃A/OA) and polyethylene glycol (PEG), and used as the blending and/or coating materials for biomedical applications. The copolymer modified surfaces showed decreased plasma adsorption level and decreased anti-coagulation property due to the increased reorientation characteristics and hydrophilic properties of the PEG/PEG-SO₃A chains in water phase.

Ran *et al.* [29] synthesized a polymer *via* RAFT polymerization, and a heparin-like structure was obtained after the sulfonation using the sulfonating agent of concentrated sulfuric acid, as shown in Figure 3. The clotting time of the heparin-like polymer (HLSM) was longer than that of the pure plasma using a small amount of the HLSM, and the plasma became anti-coagulate when 2 mg/100 μ L of heparin-like polymer was used.

Many kinds of polymers such as PES, polysulfone, polystyrene, and so on, can be prepared into heparin-like polymers by the sulfonation, for which the sulfonic acid groups can replace the hydrogen atoms at the ortho position on the aromatic rings [30, 31]. The sulfonating agents used in the sulfonation were sulfur trioxide (SO₃) [32, 33], trimethyl silylchlorosulfate ((CH₃)₃SiSO₃Cl) [32, 34-38], sulfuric acid (H₂SO₄) [30, 39, 40], and chlorosulfonic acid (ClSO₃H) [41-46].

Another method to prepare heparin-like polymers is a direct synthesis approach using sulfonic and/or carboxyl group contained monomers, and the most

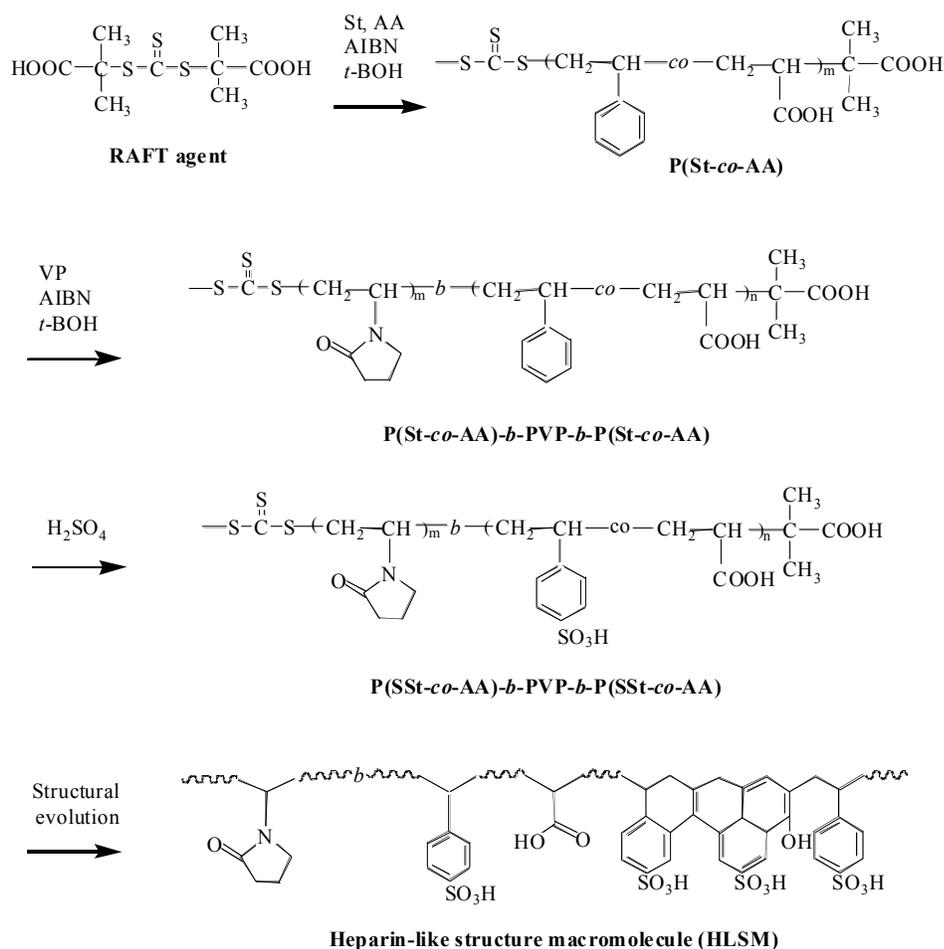


Figure 3: Synthesis of the heparin-like structure macromolecule.

widely used monomer is sodium-4-styrenesulfonate (SS). Sangaj *et al.* [47] found that the synthetic poly(sodium-4-styrenesulfonate) (PSS) could mimic the effect of heparin on the myogenic differentiation for C2C12 cell. The differentiation of C2C12 were increased with the exogenous supplementation in a dose-dependent manner, however a nonmonotonic dependence with the PSS concentration was showed for the formation of the multinucleated myotubes. It was found that the binding capacity of the PSS to bFGF was comparable to heparin by molecular docking calculations and through native PAGE. Maynard group [48] established that the heparin-like copolymer, poly(polyethylene glycol methylether methacrylate-co-sodium 4-styrenesulfonate) (p(PEGMA-co-SS)) could

stabilize bFGF by covalent conjugation. The bioactivity of the bFGF conjugate for the copolymer was retained after the synthesis, which is much better than the earlier developed PEG conjugation. The conjugate was stable to various therapeutically and environmentally stressors, such as harsh, mild and heat acidic conditions, storage and proteolytic degradation-different from the native bFGF.

In a recent report [49], two different methacrylic derivatives of anti-angiogenic monomers, 2-acrylamido-2-methylpropane sulfonic acid (AMPS) and 5-amino-2-naphthalenesulfonic acid (MANSA) were copolymerized with a hydrophobic monomer (butyl acrylate, BA) or a hydrophilic monomer (vinyl pyrrolidone, VP), then synthetic heparin-like

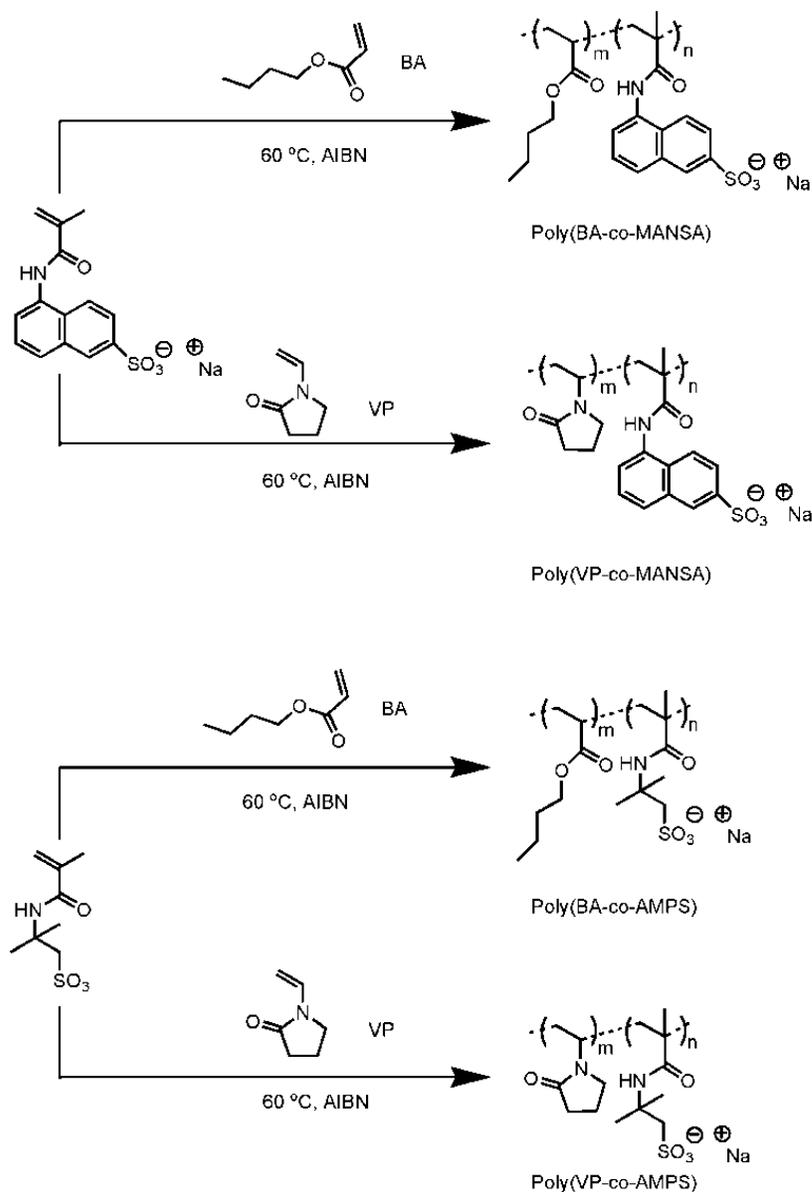


Figure 4: Synthesis of the different heparin-like macromolecules.

macromolecules were prepared, as shown in Figure 4. The macromolecules were also found to act as anti-angiogenic polymeric drugs.

Wang *et al.* [50] successfully prepared a heparin-like polymer of PES (HLPES) by the polycondensation and carboxylation reactions. The HLPES exhibited excellent heparin-like activity, and the clotting times were about 44.3% of that for heparin. Uchman *et al.* [51] synthesized a heparin-like amphiphilic terpolymer of poly((sulfamate-carboxylate)isoprene)-co-polystyrene-co-poly(ethylene oxide) (PISC-co-PS-co-PEO) to prepare heparin-like multicompartiment micelles, for which the core was consisted of discrete PISC and PS domains, and the shell was consisted of PEO. Recently, we grafted PSS onto GO through free radical polymerization [52]. The APTT was dramatically prolonged with the concentration of the PSS-g-GO from 0.5 $\mu\text{g}/100 \mu\text{L}$ to 20 $\mu\text{g}/100 \mu\text{L}$, which was resulted from the increment of the sulfonic and carboxyl groups in PSS-g-GO. The TT also prolonged to some extent.

In a word, most of the heparin-like polymers are synthesized for specific applications, such as modification of micelles and membranes. The blood compatibility for the membranes increased, which will be discussed in the following sections in detail.

3. HEPARIN-LIKE POLYMER BLENDED MEMBRANES

Methods for the modification of PES membrane usually include coating, physical blending and surface grafting. Herein, modifications of polymeric membranes using heparin-like polymers are reviewed; of course, the above methods can also be used to modify other polymeric membranes. Blending is the simplest, but most widely applied method for the modification of membranes, though sometimes the results might be not very well. Thus, heparin-like polymer blended PES membranes are discussed firstly.

Heparin-like polymers derived from natural biomacromolecules had been intensively studied as mentioned above. However, due to the water-soluble and organic solvent non-soluble properties of the polymers, few studies had been reported on the modification of PES membranes using the polymers. Most recently, our group [24] synthesized a sulfated chitosan derivative with good solubility in many common solvents. Then modified PES membranes could be prepared by blending the sulfated chitosan derivative with PES. The modified membranes possessed decreased protein adsorbed amounts and suppressed platelet adhesion (as shown in Figure 5). Moreover, the APTT of the modified membranes was

Table 1: Heparin-Like Polymers Used to Modify Membranes

Modification methods	Functional polymers	Possible applications	References
blending	sulfated chitosan derivative	plasma separation	[24]
	citric acid grafted polyurethane	plasma separation	[53]
	P(St-co-AA)-b-PVP-b-P(St-co-AA)	hemodialysis	[54]
	sulfated P(St-co-AA)-b-PVP-b-P(St-co-AA)	hemodialysis	[29]
	MPEG-P(SSNa-co-MMA)	hemofiltration	[56]
	sulfonated PES	plasma separation	[57-60]
	P(AN-AA-VP)	hemofiltration	[58]
	carboxylic PES	hemofiltration	[59]
	P(AA-NaSS-VP)	plasma separation	[61]
Coating	P(NaSS-AA), dopamine	hemofiltration	[63]
	CHI/PSS multilayer	protein separation	[64]
	PSS /protonated PAH; PSS/ PDADMAC	hemofiltration	[65]
	Ag NPs/PEI/PSS	antibacterial	[66]
Grafting	HEMA, NVP; AAG, AA; AMPS, SPMA	hemofiltration	[67, 68]
	zwitterionic copolymers	plasma separation	[70]
	P(SBMA-NaSS)	plasma separation	[71]

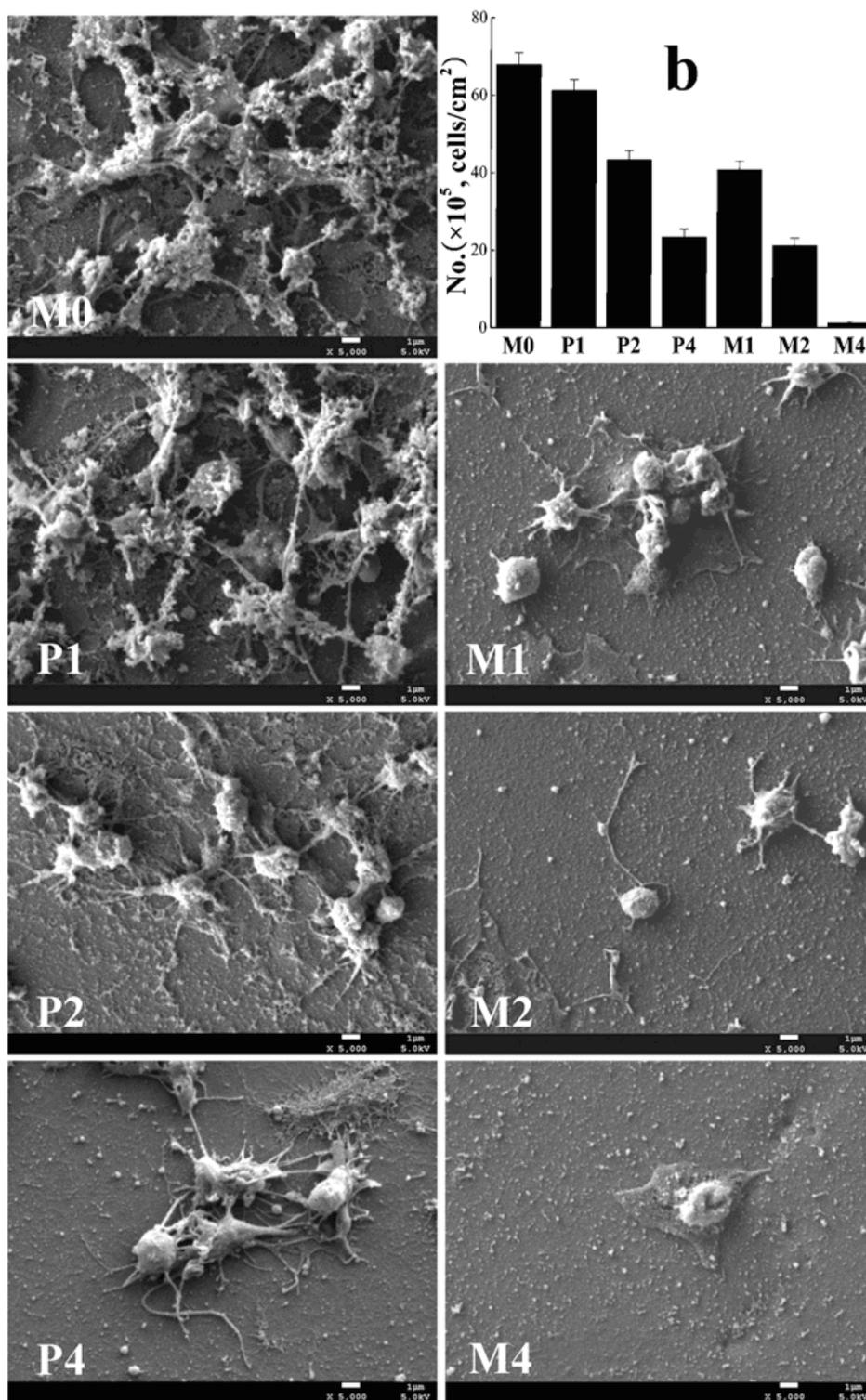


Figure 5: Typical SEM images of the platelets adhered on themembranes; magnification: 5000×. (b) Number of the adherent platelets on themembranes estimated from the SEM pictures. Note: The membranes with the PES/OC (as control samples) ratios of 16/1, 16/2, and 16/4 (wt.%) are termed P1, P2, and P4, respectively; The prepared membranes with the PES/SOC ratios of 16/0, 16/1, 16/2, and 16/4 (wt.%) are termed M0, M1, M2, andM4, respectively.

increased about 60% compared to the pristine PES membrane. The study provided a method to modify polymeric membranes using heparin-like polymers.

Citric acid is a weak organic acid, and consists of 3 carboxyl (R-COOH) groups. Though, it has no sulfonic groups, it is a widely used anticoagulant due to the carboxyl groups. Li *et al.* [53] synthesized citric acid

grafted polyurethane by a two-step polymerization. The blending solution of the synthesized polymer and PES could be prepared into PES modified membranes, which revealed decreased protein adsorption amounts and suppressed platelet adhesion. The APTT, PRT, prothrombin time (PT), and the whole blood clotting time (WBCT) of the modified membranes were significantly prolonged due to the binding ability of calcium ions in blood. Using acrylic acid as a monomer, Nie *et al.* [54] synthesized a novel triblock copolymer, poly(styrene-co-acrylic acid)-*b*-poly(vinyl pyrrolidone)-*b*-poly(styrene-co-acrylic acid) (P(St-co-AA)-*b*-PVP-*b*-P(St-co-AA)) *via* RAFT polymerization, which was then used for the modification of PES membrane by blending. The APTT for the membrane was prolonged; while the thrombin-antithrombin III (TAT) generation and platelet activation were decreased. Since there are no sulfonic groups in the polymers, the hemocompatibility for the modified membrane was not obviously improved.

To mimic the structure of heparin, a HLSM was synthesized by RAFT polymerization as mentioned above [29]. The HLSM/PES blended membranes were prepared by using a phase separation technique. The anticoagulant ability of the membranes may be improved due to the binding capacity of the anionic groups ($-\text{SO}_3\text{H}$ and $-\text{COOH}$) on the membrane surfaces. The results illustrated that the anticoagulant properties of the modified membranes were significantly enhanced, and the HLSM modified biomaterials has potential to be applied in blood purification including bioartificial liver supports and hemodialysis. Different heparin-like polymers, including poly(sulfonated styrene-co-acrylic acid-co-methyl methacrylate) (P(SS-co-AA-co-MMA)), poly(acrylic acid-co-methyl

methacrylate) (P(AA-co-MMA)), and poly(sulfonated styrene-co-methyl methacrylate) (P(SS-co-MMA)) were synthesized and then utilized to modify PES membranes [55]. The hemocompatibility of the membranes was also compared. The results indicated that the membrane using the heparin-like polymer with appropriate proportions of MMA, AA and SS showed better performance, and one possible anticoagulant mechanism of the modified membrane is summarized as in Figure 6.

Besides RAFT technique, atom transfer radical polymerization (ATRP) can also be used for the synthesis of heparin-like polymers. He *et al.* [56] synthesized a random terpolymer of MPEG-P(SSNa-co-MMA) by ATRP for the first time, which was then used as an additive for the modification of PES membranes by blending method. The results illustrated that the hydrophilicity was increased for the modified membranes, and the antifouling property of the modified membrane was improved compared to the pristine PES membrane. In addition, the modified membranes also revealed suppressed platelet adhesion and prolonged APTTs.

As mentioned above, the heparin-like polymers should contain both sulfonic groups and carboxyl groups to improve the blood compatibility of PES membranes. In the studies, it was also found that the miscibility of the PES matrix and heparin-like polymers was not very well, and phase separation occurred during the membrane preparation using the blending method.

To improve the miscibility of heparin-like polymers and PES matrix, several other polymers were

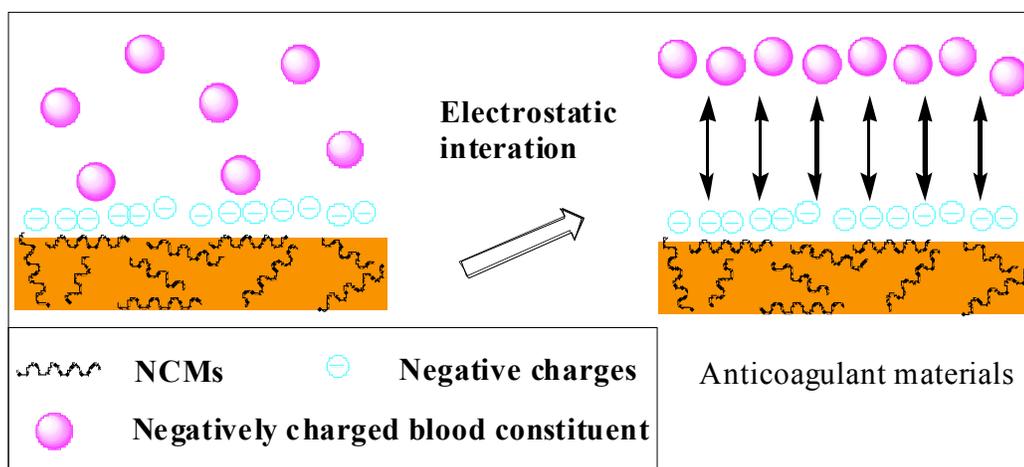


Figure 6: Schematic illustration of the interaction between the negatively charged blood constituents and the anticoagulant biomaterial surface.

synthesized. Wang *et al.* [57] synthesized a sulfonated PES (SPES) by using an electrophilic substitution reaction, and then PES/SPES blended membranes were prepared. The PES/SPES blended membrane could effectively decrease BSA adsorption and prolong the blood clotting time compared to the pristine PES membrane, thereby improving hemocompatibility. To further improve the hemocompatibility of PES membrane and construct heparin-like membrane surface, poly (acrylonitrile-co-acrylic acid-co-vinyl pyrrolidone) (P(AA-AN-VP)) and SPES, for which providing the -COOH and -SO₃H, respectively, were blended in PES membrane [58]. The P(AA-AN-VP) was prepared by a free radical polymerization. The modified membrane revealed lower protein adsorption amount and suppressed platelet adhesion. In addition, the modified membrane showed significantly decreased TAT, complement activation on C3a and C5a levels, and percentage platelets positive for CD62p expression compared to the pristine PES membrane. Due to the similar negatively charged groups as heparin, the modified membranes could effectively prolong the APTT. Furthermore, the modified membranes revealed good cytocompatibility. This study may be the first time to construct heparin-like membrane surface, and the surface modification with heparin-like structure has potential to improve the blood compatibility of biomaterials.

To further increase the miscibility, carboxylic PES (CPES) was used instead of P(AA-AN-VP) to provide carboxylic acid groups, then modified membranes with heparin-like structure were prepared by physically blending PES, CPES and SPES at rational ratios [59]. Since the SPES and CPES had the same backbone as PES, which conferred them good miscibility with PES. SPES can also be synthesized *via* a feasible way, in which sulfonic groups was introduced onto the amino-substituted PES [60]. The modified membranes could be fabricated by blending PES and the obtain SPES at any ratios. The SEM images illustrated that the structure of the modified PES membranes changed obviously after the modification. The modified membranes showed increased APTT and PRT, and also showed suppressed blood platelet adhesion.

Recently, heparin-like PES (HLPES) was synthesized as mentioned above by the polycondensation and carboxylation reactions [50]. The modified PES/HLPES membranes could be prepared by blending the HLPES and PES at any ratios, due to the similar structure of backbone. The hydrophilicity was significantly improved for the modified

membranes, while the microscopic structure was also changed. The PES/HLPES membranes showed obviously decreased leukocytes activation on CD11b levels, complement activation on C3a and C5a levels, and platelet activation on PF-4 level compared to the pure PES membrane. The enhanced hemocompatibility of the modified membranes might be due to the negatively charged groups (-SO₃Na and -COONa).

Most recently, a special blending method, termed in situ cross-linked polymerization/copolymerization was provided for the blood-compatible modification of PES membranes [61]. The monomers of AA, NaSS, and VP with the same weight ratios were used in the facile modification. The APTTs of the modified membranes were obviously increased. Furthermore, due to the heparin-like structure, the AA and NaSS modified membranes revealed significantly improved anticoagulant property. In addition, many other functional polymers owning outstanding pH-sensitivity and pH-reversibility, anticoagulant property, antifouling property, and antibacterial property could be synthesized by the in situ cross-linked polymerization/copolymerization. The method of in situ cross-linked polymerization/copolymerization opens a route for the functionalization of polymers, which leads to significant progress for the applications of polymeric materials.

Then, Qin *et al.* [62] developed a highly efficient, convenient and universal protocol for blood-compatible modification of PES membranes *via* in situ cross-linked copolymerization of 2-hydroxyethyl methacrylate (HEMA) and acrylic acid (AA) in PES solutions, as shown in Figure 7. The modified membranes showed improved hydrophilicity, good blood anticoagulant and antifouling properties after introducing HEMA and AA. Meanwhile, the modified membranes perform low contact activation and complement activation when they come in contact with blood. The effect of the HEMA/AA ratios on the blood compatibility is also investigated to identify the different roles played by PHEMA and PAA in the modification; the PHEMA could more effectively enhance the antifouling property, while the PAA could more effectively improve the anticoagulant property.

4. HEPARIN-LIKE POLYMER COATED MEMBRANES

Surface coating is an approach to modify material surface with a coating of selective thin film layer (TFL). By surface coating, porous UF/MF membranes could

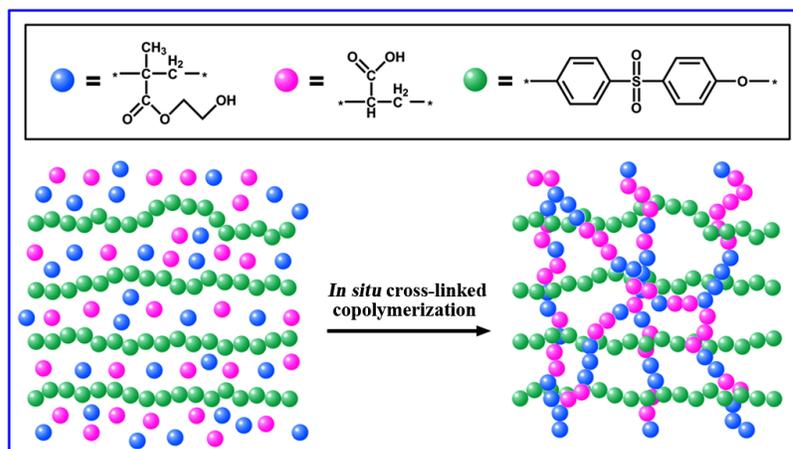


Figure 7: *In situ* cross-linked copolymerization of AA and HEMA.

be prepared into nanofiltration membrane. However, directly surface coating heparin-like polymers onto PES membranes is not a good choice, since the polymers can be easily washed away due to the water solubility; thus no study was reported on directly surface coating heparin-like polymers onto PES membranes.

Most recently, our group [63] reported a facile and green approach to prepare modified PES membranes with significant blood compatibility and cytocompatibility by multifunctional mussel-inspired coating, as shown in Figure 8. Heparin and a highly sulfonated linear heparin-like polymer (poly(sodium 4-vinylbenzenesul-

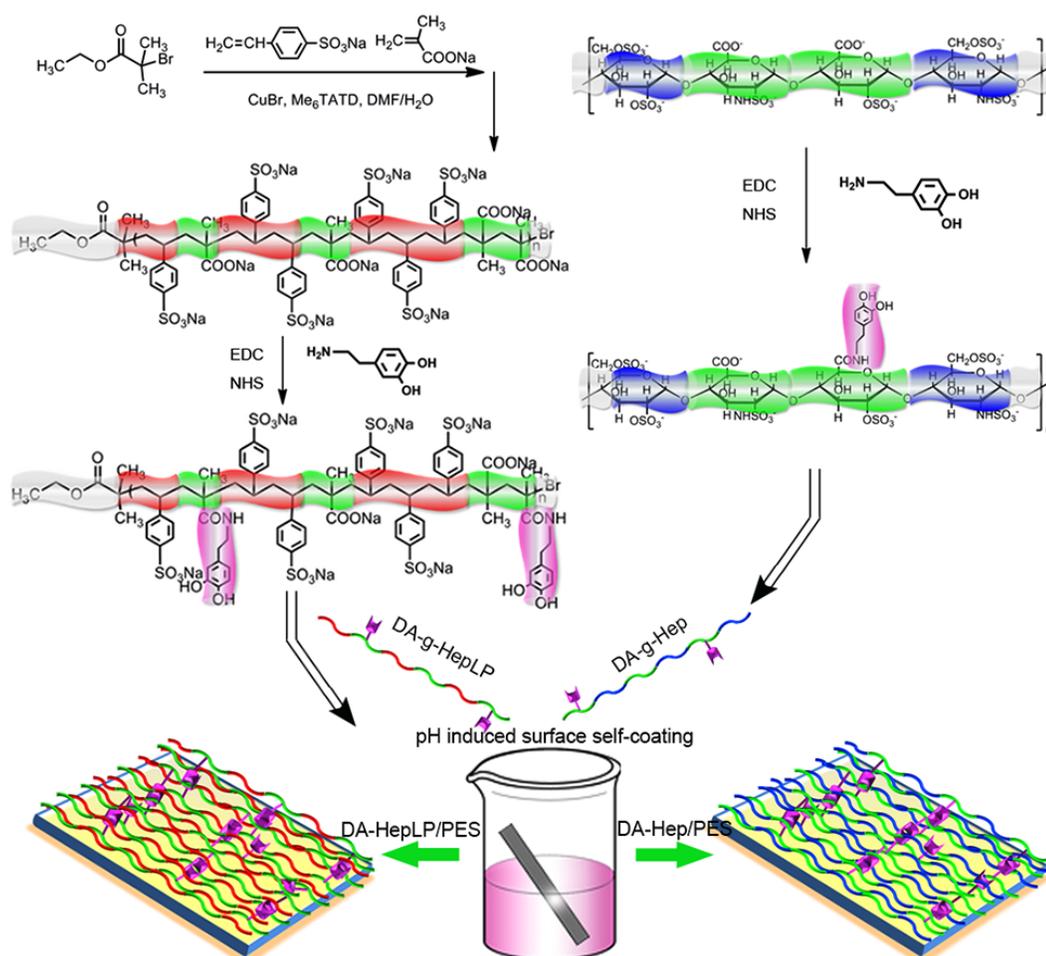


Figure 8: Schematic illustrations for the preparation of HepLP, DA-g-Hep, DA-g-HepLP, DA-Hep/PES and DA-HepLP/PES.

fonate)-co-poly(sodium methacrylate), HepLP) are chosen as the coating, respectively. Firstly, dopamine (DA) is grafted on the backbone of heparin or HepLP using the carbodiimide chemistry method. Then, the DA grafted DA-g-Hep and DA-g-HepLP were used as the coatings to modify the PES membranes. The coated membranes revealed increased electro negativity and hydrophilicity, reduced plasma protein adsorption, and suppressed platelet adhesion compared with those of the pure PES membrane. The cell morphology and MTT illustrated that the heparin-mimicking PES membranes had superior performance in morphology differentiation and endothelial cell proliferation. Furthermore, the good anticoagulation suggested that the biological activity of the DA-g-Hep (or DA-g-HepLP) coating was realized or maintained after being immobilized. Thus, the heparin-mimicking PES membranes can be widely used in many biomedical applications such as hemodialysis and tissue cultures.

To enhance the water flux and selectivity of PES membrane, a novel coating of chitosan (CHI)/polystyrene sulfonate (PSS) multilayers was deposited. The modified membranes can be applied in protein separations under ultrafiltration conditions [64]. A significant change in the protein transport behavior through the multilayers was observed, and depended on the deposited layer numbers and the solution pH values. For a 9-bilayer CHI/PSS multilayer modified membrane, the transport studies revealed 95% rejection of BSA. The ovalbumin permeability was also enhanced. The individual transport studies of lysozyme and ovalbumin exhibited that the egg white proteins might be separated using the multilayer system.

Polymeric UF membranes could be converted into NF membranes by layer-by-layer (LBL) deposition of cationic and anionic polyelectrolytes. PSS /protonated

PAH and PSS/ poly(diallyldimethyl- ammonium chloride) (PDADMAC) could be deposited onto PES UF membrane [65] as shown in Figure 9. The membrane MWCO was reduced. The pure water flux of the PSS/PAH coated membrane was increased; while the chloride/sulfate selectivity of the PSS/PDADMAC coated membrane was increased.

Xia *et al.* [66] prepared modified PES membranes with 3D multifunctional nanolayers, which was deposited by LBL self-assembly of heparin-like polymers and nanogels. Ag nanoparticle embedded nanogels were prepared and assembled onto the membrane surfaces *via* electrostatic interaction to integrate long-term antibacterial activity. The nanogel coated membranes were further deposited with heparin-like polymers to gain heparin-like surfaces. The membranes revealed increased hydrophilicity, reduced protein adsorption, prolonged clotting time, and suppressed platelet adhesion compared to the pure PES membrane. The cell observations demonstrated that the pristine membrane, nanogel assembled membrane, and heparin-mimicking membrane showed different performances in endothelial cell proliferation and adhesion. The results of antibacterial study showed that the modified membranes exhibited significant inhibition capability for *Staphylococcus aureus* and *Escherichia coli*. Thus, the surface co-assembly of nanogels and heparin-like polymers conferred the modified membranes with integrated blood compatibility, cell proliferation and antibacterial properties for multi-applications, as shown in Figure 10.

5. HEPARIN-LIKE POLYMER GRAFTED MEMBRANES

It is difficult to directly graft heparin-like polymers onto PES membranes. However, the functional groups (sulfonic and carboxyl groups) can be grafted onto PES

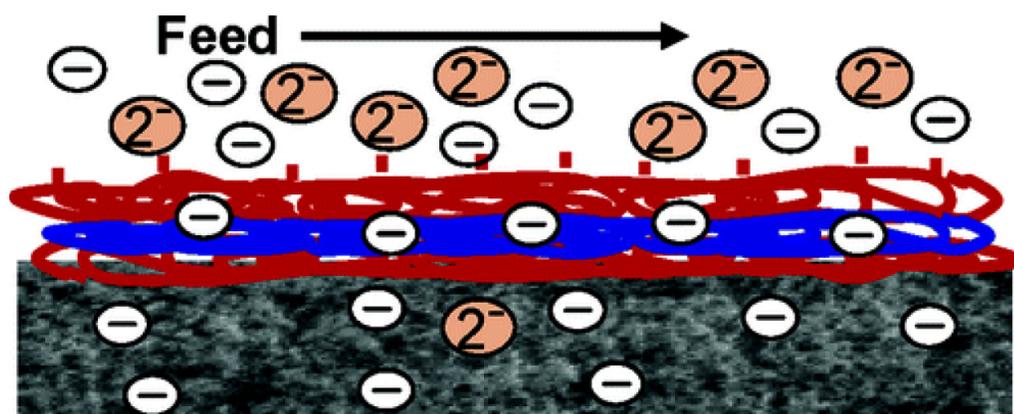


Figure 9: Layer-by-layer deposition of polyelectrolytes onto polymeric membrane.

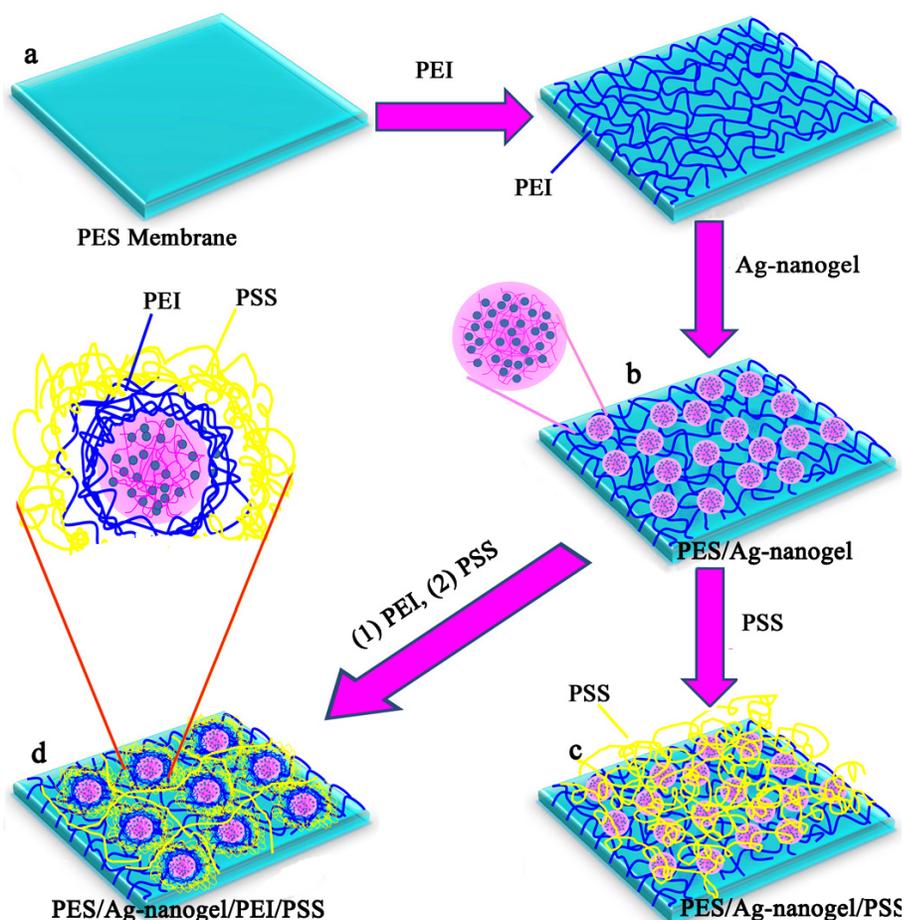


Figure 10: The fabrication processes for the 3D nanogel deposited membranes by surface engineered LBL assembly. (a) pristine PES membrane, (b) PES/Ag-nanogel, (c) PES/Ag-nanogel/PSS, and (d) PES/Ag-nanogel/PEI/PSS.

membrane surfaces. Taniguchi and Belfort [67, 68] studied the effect of different monomers on the performances of the modified membranes, and six different monomers, including 2 neutral (HEMA, NVP), 2 weak (carboxylic) acids (AAG, AA), and 2 strong (sulfonic) acids (AMPS, SPMA), were selected. Though the surface wettability of all the grafted polymers modified membranes were enhanced compared with that of the pristine PES membranes, the effect of the grafted polymers on filtration performance was various. Using the smaller pore-size PES membranes (50 kDa) for grafting, the membranes modified by NVP, AMPS and AA showed excellent performance (such as high protein solution flux, high protein retention, as well as low irreversible fouling). For larger pore-size membranes (70 and 100 kDa), however, the PES-gr-AMPS and PES-gr-AA membranes showed reasonably high BSA rejection ratios and protein solution fluxes with excellent cleaning ability (with projected high long-term performance) compared to the pure membranes. In addition, the weak acid AA modified membranes were able to reduce irreversible fouling to zero,

compared to other strongly hydrophilic monomers including HEMA and AAG, which increased irreversible fouling relative to the unmodified membrane [68].

Surface photochemical technique is an attractive method owing several advantages. Low temperature and mild reaction conditions might be applied. In addition, high selectivity is possible by choosing monomers or the reactive groups and the respective excitation wavelength; and it is easily incorporated into the end stages of a manufacturing process [69].

Xiang *et al.* [70] synthesized two kinds of zwitterionic copolymers bearing azide and alkynyl groups by ATRP and subsequent reactions, namely azide-poly(sulfobetaine methacrylate) (azide-PSBMA) and alkynyl-poly(sulfobetaine methacrylate) (alkynyl-PSBMA), which were directly used to modify azido-functionalized polysulfone (PSf-N₃) membrane through click chemistry-enabled LBL assembly, as shown in Figure 11. The alkynyl-citric acid might also be grafted onto the outermost layer of the membrane. The grafted multilayers were resistant to protein

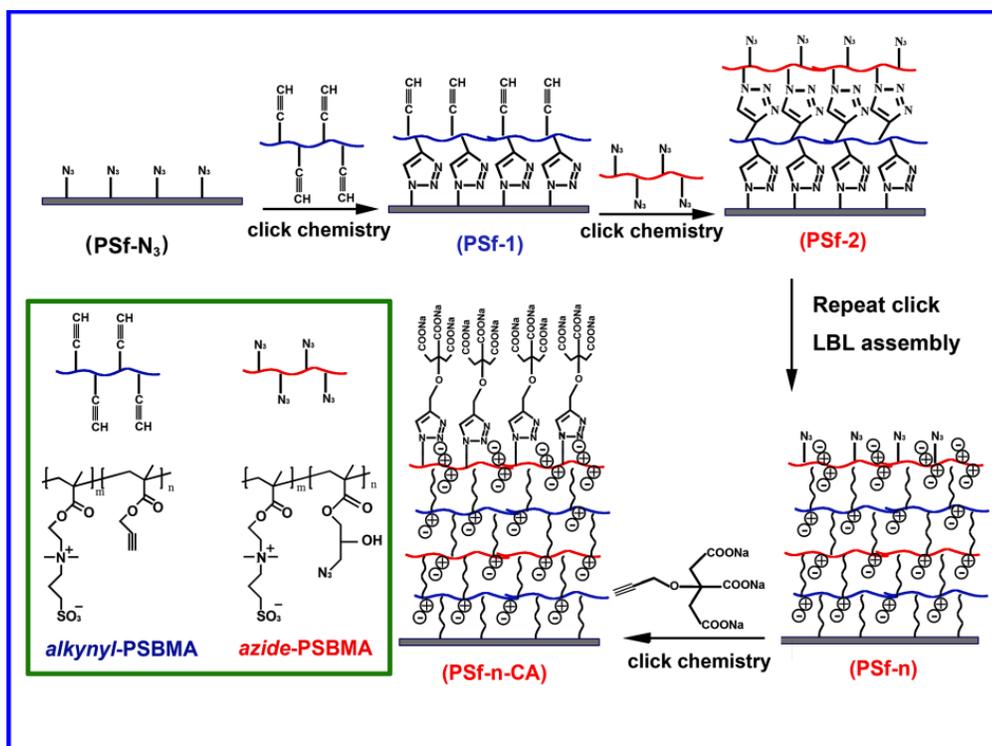


Figure 11: Scheme illustration for the preparation of zwitterionic polymer and citric acid deposited PSf membrane by click chemistry-enabled LBL assembly.

adsorption and platelet adhesion, and could prolong clotting times indicating the blood compatibility was improved. Moreover, the membrane showed further improved anticoagulant property after the outermost of the zwitterionic multilayer was deposited with alkyne-citric acid. The study provides a method to graft heparin-like polymers and other functional polymers onto membranes with reactive groups.

6. CONCLUDING REMARKS AND FUTURE PERSPECTIVE

Heparin-like polymers have been intensively studied; however, most of the studies focus on mimicking the heparin structure, i.e., the functional carboxyl and sulfonic groups, few of them pay attention on the heparin conformation. The anticoagulant property of heparin is caused by not only the functional groups but also its special conformation. Synthetic heparin-mimicking polymers have advantages such as low cost, facile, and controllable synthetic processes; natural biomacromolecules derived heparin-like polymers may show better anticoagulant property, and the polymers may be developed to instead of heparin using in clinic. In addition, the mechanism of the anticoagulant property for heparin-like polymers should be fully studied, which will guide the molecular design and characterization of heparin-like polymers.

Heparin-like polymers can be utilized to modify PES membranes *via* blending, coating, and grafting approaches. Blending method is the simplest, most widely used approach to modify PES membranes, and can be easily used for large-scale and in practice production. However, the elution of the polymers should be noted. Though surface coating heparin-like polymers onto PES substrate shows very good results of anticoagulant property, the stability of the coated polymers is very important. Few studies focus on grafting method, the emerging new methods such as RAFT and ATRP, may open the route on grafting heparin-like polymers onto membrane surfaces.

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