Journal of Membrane Science & Research

journal homepage: www.msrjournal.com

Review Paper

Advances in Polysulfone-Based Membranes for Hemodialysis

I.G. Wenten*, P.T.P Aryanti, Khoiruddin, A.N. Hakim, N.F. Himma

Department of Chemical Engineering, ITB, Jl. Ganesha 10, Bandung 40132, Indonesia

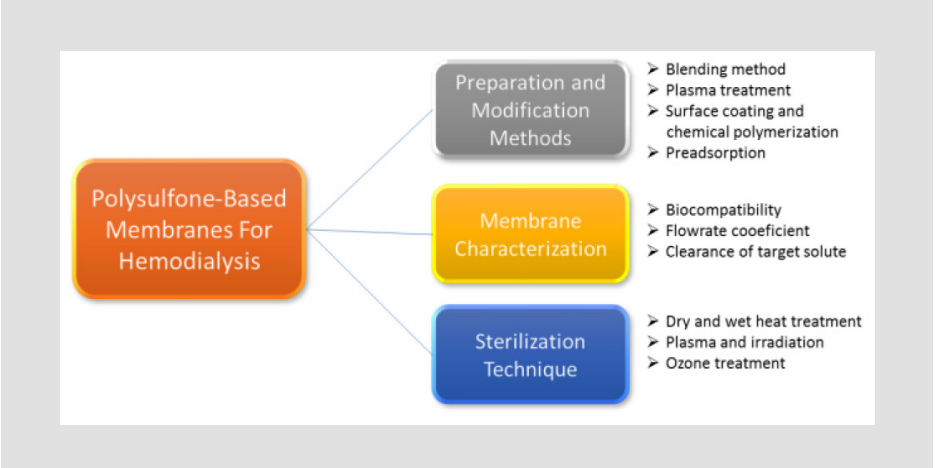
ARTICLE INFO

Received 2015-03-04
Revised 2015-04-24
Accepted 2015-05-01
Available online 2015-05-01

KEYWORDS

Hemodialysis
Polysulfone membrane
Biocompatibility
Membrane modifications

GRAPHICAL ABSTRACT



HIGHLIGHTS

- Polysulfone-based membrane for hemodialysis (HD)
- Special attention is given to preparation, characterization, and sterilization of HD membranes
- Biocompatibility, appropriate ultrafiltration rate, clearance target of solutes are parameters should be considered in membrane characterization
- Interaction between protein in blood and membrane surface is a critical point in HD membrane preparation and modifications
- Sterilization of HD membranes also becomes very important to improve membrane performances

ABSTRACT

The polysulfone-based membrane has been used in hemodialysis (HD) and it is continuously developed to maintain its sustainability on the subject of biocompatibility. During the polysulfone-based membrane development, several parameters should be considered to improve the membrane performances, such as excellent biocompatibility, appropriate ultrafiltration rate, and effective clearance of the target solute. In terms of biocompatibility, characteristics of interaction between proteins in the blood and membrane surface is a critical point of view to avoid platelet adhesion and activation that initiate the inflammatory responses. Different methods of modifications have been proposed. Most of the modification methods are focused on the increase of membrane hydrophilicity. A number of modified polysulfone-based membranes have been developed through several methods including blending materials, plasma treatment, and other surface modifications. Selectivity of the polysulfone membrane also plays an important role in avoiding endotoxin leakage and reducing albumin loss during HD treatment. On the other hand, sterilization of the HD membrane also becomes very important with regard to its effects, such as changes in physicochemical properties, biocompatibility, and performances of the membranes. In this paper, the polysulfone-based membrane for HD is reviewed comprehensively. Special attention is given to the preparation, characterization and sterilization of HD membranes.

1. Introduction

The polysulfone (PSf)-based membrane has been increasingly used in many industrial and medical fields, due to its good chemical and temperature resistance, as well as good mechanical strength and stability. In the hemodialysis (HD) application, PSf-based membranes exhibit the intrinsic biocompatibility, high permeability for low-molecular weight proteins, high endotoxin retention and high resistance during sterilization [1, 2]. In addition, the PSf membrane meets the solute and fluid removal requirement for all

* Corresponding author at: Phone: +62 818620014, fax: +62 22 2511404
E-mail address: igw@che.itb.ac.id (I.G. Wenten)

treatment modalities (low- and high-flux dialysis, online hemodiafiltration, and hemofiltration) [3].

In comparison to other membrane materials, the PSf membrane exhibits better biocompatibility [4, 5]. For example, Yamashita et al. (2009) found that the PSf membrane showed essentially no affinity to α-chymotripsinogen A (MW 25,000) and cytochrome C (MW 12,400) compared with Polymethylmethacrylate (PMMA) and polyacrylonitrile (PAN) membranes [6]. Despite these advantages, the PSf membrane faces some limitations when it is in contact with the human blood during the HD process. The HD membranes are limited with progressive flux decline and changes of membrane selectivity due to fouling. This fouling is mainly attributed to the accumulation of protein, which could be followed by the activation of different defense systems in blood [7, 8]. Therefore, further modification of the PSf membrane is required to maintain their sustainability on the subject of biocompatibility.

On the other hand, a new generation of the polyethersulfone (PES) membrane has also been developed through an advanced fabrication and modification. PES membranes are therefore known for achieving outstanding middle molecule removal with minimal albumin loss, and both their biocompatibility and endotoxin retaining characteristics adhere to the highest standards. However, similar to the PSf membrane, proteins are rapidly adsorbed onto the membrane surface. Thus, injections of anti-coagulants are required during its clinical application. Modification of the PSf membrane can be categorized into three different approaches: (1) bulk modification of PSf material, which is then used to prepare the modified membrane; (2) surface modification of prepared PSf membrane; and (3) blending, which can also be regarded as a surface modification. In this paper, development of the PSf-based membrane to overcome problems faced in HD will be reviewed comprehensively.

2. Preparation of polysulfone-based membrane for hemodialysis

The requirement of biocompatibility during HD treatment has lead to continuous development in the PSf membrane. There is an increasing demand in the new biocompatibility membrane that provides good performances during dialysis treatment, such as low blood pressure variability and low impact on oxidative stress or complications. High-performance PSf membranes have been developed to address these needs, such as the vitamin E-coated PSf membrane and PSf membrane hemodiafiltration filter [9]. Therefore, hydrophilicity, a thin active membrane skin layer, high porosity, narrow pore size distribution, surface roughness, mechanical strength, and membrane stability should also be considered in HD membrane preparation to meet the requirement. In this sub-chapter, PSf membrane modifications for HD are further described and discussed.

2.1. Blending method

Morphological characteristics of membranes depend on parameters in membrane preparation such as casting solution (the type of polymer and solvent and ratio of polymer to solvent), preparation conditions (temperature, method), and additive. Biocompatible hydrophilic polymers, such as polyethylene glycol (PEG), oiligo (ethylene glycol) (OEG) and polyvinylpirrolidone (PVP) are the most widely used blending materials to improve the hydrophilicity of the HD membrane [10]. Wang et al. [11] used PVP as additive during PES membrane preparation and found that the addition of 10% PVP reduced the water contact angle of the PES membrane from 160° to 70°. High rejection of BSA was obtained by the addition of 6% wt of PVP due to its hydrophilicity. The adsorption of BSA is effectively reduced by approximately 20% while the clotting time is prolonged. Chakrabarty [12] investigated the effect of PVP of different molecular weights (24.000, 40.000 and 360.000 Da) on the structure and permeation properties of the PSf membrane that was prepared in two solvents, i.e N-methyl-2-pyrrolidone (NMP) and dimethyl acetamide (DMAc). The DMAc is found to be more suitable than NMP, in terms of BSA rejection. The highest BSA rejection (at pH 9.3) was found when 5%wt of PVP 360.000 Da was added into the membrane solution. The increase of PVP molecular weight resulted in a dense structure with less macrovoids, higher porosity, and smoother membrane surface. The same tendency was also found when using the PEG [13-15].

Sinha et al. [16] blended polyethylene glycol methyl ether (PEGME) into PSf-Dimethyl formamide (PSf-DMF) solution. It was shown that the hydrophilicity of the modified membrane is increased by the increase of additive molecular weight (from 200 to 5000 Da) due to the entrampment of additives in the membrane matrix as well as the increase of number of pores in the membrane structure. The increase of membrane hydrophilicity reduced the total fouling resistance in the membrane structure, which could be easily cleaned by a simple method. Sinha et al. [17] also prepared a novel crosslinked pegylated functional copolymer poly(acrylicacid-co-methyl ether methacrylate) from AA (acrylic acid) and PEGMA, via precipitation polymerization. Then, the obtained copolymer was blended into PSf by using NMP as solvent. Cross sectional morphology of the membranes was changed significantly with higher concentration of the copolymer. The finger-like structures became shorter with the increase of copolymer concentration. Surface roughness was also increased due to the settlement of copolymer on the membrane surface. Contact angle and hydraulic permeability of the modified membrane were 48.7° and 0.794 L/m^2.h.kPa, respectively, by adding 7% wt of copolymer concentration into the PSf solution compared to 63.2° and 0.353 L/m^2.h.kPa for the unmodified membrane. In addition, fouling on the modified membrane surface was dominated by reversible fouling. 90% of flux recovery ratio was achieved after bovine serum albumin (BSA) separation.

Since the hydrophilic polymers can be leached from the membrane over time due to its solubility, the presence of hydrophilic polymer in the dialysis membrane surface may become a critical problem during HD. Some researchers improved the additives performance by several methods, such as cross-linking of PVP by subjecting to a thermal treatment or tailored function of the macromolecule. Miscibility of PSf with poly(1-vinylpyrrolidone-co-styrene) (P(VP-S)) copolymers containing various amounts of VP has been prepared [18, 19]. Since P(VP-S) copolymers are water insoluble, they still remain in the membrane matrix after the phase inversion process. Zhuan et al. [20] synthesized amphiphilic polysulfone–graft-poly(ethylene glycol) methyl ether methacrylate (PSf-g-POEM) through atom transfer radical polymerization (ATRP) and then used it as modifier to the PES membrane. The great hydrophilic improvement of membranes was resulted from the high coverage of PEOM segments in the surface as well as the fouling resistance. Triblock copolymer, poly(ethylene oxide)-b-poly(propylene oxide)-b-poly(ethylene oxide) (Pluronic/Plu) has been developed [21]. The water contact angle of the membrane was around 61° while rejection of dextran was 72%. Another triblock copolymer additive, 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)), was synthesized via reversible addition-fragmentation chain transfer (RAFT) polymerization to be blended with PES [22]. The presence of negative charges on the membrane surface induces electrostatic repulsion with negative charged components of blood, e.g. erythrocyte, leukocyte and platelet. The low protein adsorption, low platelet adhesion, and surface segregation of the block copolymer contributed to the prolonged coagulation time.

Sulfonation is one of the chemical modification methods that introduces hydrophilic groups onto polymer backbones using a sulfonation agent. A self-transformable sulfonated poly(ethylene glycol) acrylate diblock copolymer (PEG-SO3A/OA) has been prepared as additive to induce hydrophilicity on the PSf membrane surface [23]. The hydrophilic mobile segments served to exhibit less platelet adhesion, resulting in enhanced biocompatibility. It was found that platelet adhesion on the membrane surface was below 20%. Park et al. [24] synthesized amphiphilic graft copolymers having PSf backbones and PEG via reaction of an alkoxide formed from PEG and a base (sodium hydride) via reaction of an alkoxide formed from PEG and a base (sodium hydride) with chloromethylated PSf (C-PSf). The graft copolymer was insoluble in water and could be used as additive in the PSf membrane to improve membrane wettability, porosity, protein resistance and reduce cell attachment. Haitao et al. [25] synthesized sulfonated PES through an electrophilic substitution reaction. The sulfonated PES was used as additive to enhance PES membrane hydrophilicity and improve blood compatibility. It was found that the BSA adsorption is effectively reduced and the coagulation time is considerably prolonged.

Citric acid, which is widely used as anticoagulant, could be used as a synthesized additive by grafting it onto the polymer surface. Li et al. [26] grafted citric acid onto polyurethane and directly blended it into the polyethersulfone membrane solution. By blending 8% of the copolymer into the polyethersulfone membrane, the measured water contact angle was improved from 77° to 64°, where 60% reduction of protein adsorption (BSA dan fibrinogen) is achieved. The grafted citric acids acted as anticoagulant that suppressed platelet adhesion on the membrane surface, and effectively prolonged the activated partial thromboplastin time (APTT), prothrombin time (PT), plasma recalcification time (PRT) and the whole blood clotting time (WBCT). Similar research has been conducted to use heparin as an anticoagulant based copolymer additive which is known as heparin-mimicking polyurethane (HMPU) [27]. As a result, water contact angle is reduced from 81° to 61° by blending 8% of additive during membrane preparation. Meanwhile, flux recovery of the membrane could be increased to 92% and protein adsorption could be reduced up to 50%.

A 2-methacryloyloxyethyl phosphorylcholine (MPC) is also considered as proper additive to produce surface blood compatibility of the PSf

membrane. Ishihara et al. [28] blended 10% wt concentration of (MPC) into the PSf membrane solution which was prepared by the solvent evaporation method. The increase of MPC concentration up to 10% slightly decreased the water contact angle, but significantly reduced plasma protein and fibrinogen adsorption from 22-27 to 0,4 μg/cm^2 [29]. Hasegawa et al. (2002) prepared the PSf membrane by the wet-dry phase inversion method with the addition of 15% wt MPC concentration in the membrane solution [30]. As a result, the hydrophilicity of the membrane could be increased up to 8–13 times and inhibited platelet adhesion to the membrane surface. Zao et al. [31] blended biomaterial DNA into the polysulfone membrane solution to reduce the protein adsorption on the membrane surface. The membrane hydrophilicity was increased when DNA was blended with PSf and further improved after UV irradiation. However, the amount of adsorbed protein on the membrane surface was not significantly decreased by the increase of DNA concentration due to interaction between DNA and the proteins.

Due to its ability to improve membrane hydrophilicity and fouling-resistance ability, pluronic F127 has been used as additive to be blended into the PES membrane solution [32-34]. Below 35^o , water contact angle is measured with 94% of flux recovery and 98% rejection of BSA, when 60% of the weight ratio of Pluronic F127/PES is blended into PES membrane solution [34]. The increase of Pluronic F127/PES weight ratio to 100% increased the water flux up to 209.06 L/(m^2.h), which also has high rejection of BSA (almost 97%) but low rejection of Lysozyme (up to 50%). This may be attributed to the formation of a larger pore in the skin layer structure of the membrane. In addition, the increase of PES membrane hydrophilicity by the increase of Pluronic F127 contributes to the decrease of measured irreversible fouling which means that the modification of PES membranes with Pluronic F127 remarkably improves the antifouling property. However, the increase of membrane hydrophilicity is not always followed by the improvement of irreversible fouling. Aryanti et al. [35] found that the increase of PEG concentration up to 35% into the PSf membrane increased irreversible fouling of low molecular humic acid. This means that a high concentration of hydrophilic materials in the membrane solution reduces the antifouling properties of the membrane. However, the low fouling performance could be improved by the addition of acetone into the membrane solution [36]. Tight skin layer formation due to acetone improves membrane rejection and reduces irreversible fouling of humic substances into the membrane structure. The effect of modification methods on membrane performance are summarized in Table 1.

Recently, zwitterionic polymer modified biomaterials (such as phosphobetaine, sulfobetaine, and Carboxybetaine) have received much attention in usage as blood-contacting materials due to their excellent antifouling properties, suppressed platelet adhesion and activation [20, 37, 38]. These materials contain both cationic and anionic groups that bind water molecules strongly via electrostatically induced hydration [39, 40]. The preparation of a composite membrane that uses nanoparticle as additives is also developed [41, 42]. Although many efforts have been made to develop low fouling or functional membranes using various nanoparticles, further researches are still needed to provide better understanding on the design and operation of nanoparticle-based membranes. Incorporation of nanoparticles into polymeric membranes has some drawbacks. One of the limiting factors is the dispersion of the nanoparticles in the polymers. The aggregation or dispersion behavior control, which is the first process for the preparation of new functional materials incorporating nanoparticles, is difficult for nanoparticles with less than 100 nm in diameter due to surface interactions [43]. It should be handled carefully due to the potentially toxic properties of the nanoparticles.

2.2. *Plasma treatment method*

Surface modifications of PSf membranes have become one of the key methods in biomaterial engineering, such as plasma sputtering and etching, plasma implantation, plasma deposition, plasma polymerization, laser plasma deposition, and plasma spraying [44]. Generally, these methods can change the surface properties of a membrane by introducing some polar groups, such as hydroxyl and amino groups. However, there is still one major drawback that is sometimes called “hydrophobic recovery”. Plasma polymerization is a unique ultrathin film technology which yields polymers having completely different properties from those of the more conventional polymers [45]. Plasma polymerization and plasma-induced graft polymerization can endow a membrane surface with permanent effects and the alternative is to utilize the introduced polar groups to initiate graft polymerization on the membranes. This method has been used in the last years as a useful method to modify the surface properties of different materials in special polymers. There are several reports on modification of polymeric membrane surfaces by plasma treatment using different reagents, such as CO_2, O_2, H_2O_2, H_2O, Ar and ammonia [46-50].

Kim et al. [46] reported the modification of the PSf membrane using oxygen plasma treatment. In this method, oxygen containing polar groups were introduced to the membrane surface. Polar functional groups such as the hydroxyl, carbonyl, and carboxyl group were introduced on the PSf membrane. The results showed that the surface of the PSf membrane was changed from hydrophobic to hydrophilic (contact angle ≈30^o). This change leads to an increase of membrane flux (unmodified: 9 kg/m^2.hr, modified: 11 kg/m^2/h) and decrease in fouling. The effect of NH_3 and NH_3/Ar plasma on PSf membranes has been studied by Bryjak et al. [47]. Pure NH_3 plasma acts mildly–gradual and ablation causes cleaning of the membrane surface and enlarges the membrane pores. The addition of argon to the plasma environment increases the amount of grafted functional groups that provides more hydrophilicity of the membrane surface. However, on the other hand, this plasma is more aggressive and serious material etching is observed. The pores diameter becomes smaller than what might be an effect of redeposition of etched material on the pores wall.

Wavhal and Fisher [51] studied carbon dioxide plasma for modifying hydrophobic PSf ultrafiltration membranes to create hydrophilic surfaces throughout the membrane structure. The hydrophilicity of the membrane was achieved by implantation of hydroxyl, carbonyl, and carboxylic acid polar functional groups. The hydrophilicity was maintained during long operation. In addition, the plasma treatment reduced protein fouling and increased water flux significantly. Furthermore, the adsorbed protein layer was found to be reversible, with almost complete recovery after backflushing using water. Highly hydrophilic surfaces of acidic character were also obtained using CO_2 plasma treatment which was reported by Gancarz et al. [52]. They also found that prolonged plasma excitation causes significant damage to the membrane surface. Moreover, in the case of porous membrane, prolonged plasma excitation contributes to pore enlargement and widening of pore size distribution. This phenomena was also found when using nitrogen plasma treatment [53]. However, the longer exposition to plasma showed no further effect to membrane pores.

Zhan et al. [54] used low temperature plasma treatment to graft a positively charged monomer 2-(dimethylamino)ethyl metacrylate (DMAEMA), C_4 monomer, and acrylic acid on the membrane surface. The plasma treatment was used to initiate polymerization on the hydrophilic PSf membrane of negative surface charge. The filtration of BSA through an acrylic acid modified hydrophilic membrane showed that the enhancement of the repulsive electrostatic force was effective in reducing protein adsorption on the membrane surface. Ulbricht and Belfort [55] investigated the modification of the PSf membrane using water and water/helium plasma treatments. The plasma treatment drastically increased the hydrophilicity of the membrane surface. The PSf membrane was also modified through graft polymerization of monomers such as 2-hydroxy-ethyl methacrylate (HEMA). The results indicated that hydrophilized PSf-g-HEMA membranes can provide improved performance in protein ultrafiltration over the unmodified PSf UF membrane, higher filtrate flux (> 30%) and higher protein retention of bovine serum albumin (BSA) than the unmodified membrane.

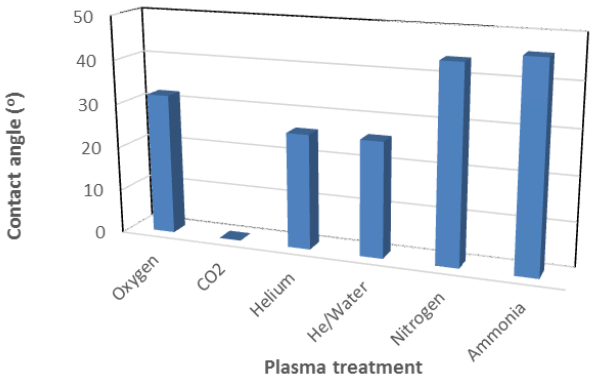


Fig. 1. Comparison of plasma treatment on contact angle of polysulfone membrane [46, 47, 51, 53, 55].

Steen et al. [56] developed a unique design of the membrane holder for rendering an asymmetric polymeric membrane by H_2O plasma treatment. The result demonstrated that the developed design could achieve permanent and complete hydrophilic modification of the PSf membrane. The low plasma powers serve to minimize pitting, etching and redeposition that may occur through interactions of energetic plasma species with membranes. This suggests that remote plasma exposure is a key to developing plasma treatments that will be effective in controlling surface properties and filtration

performance of the porous membranes. Since the chemical nature of the plasma affects the permeance of the treatment, the choice of plasma system also appears to be a controlling factor in membrane penetration. Thus, plasma treatment demonstrated by several studies holds significant promise for enhancing the general performance properties of membranes. The effects of the above plasma treatment on the hydrophilicity and characteristics of the resulted membranes are summarized in Figure 2 and Table 2.

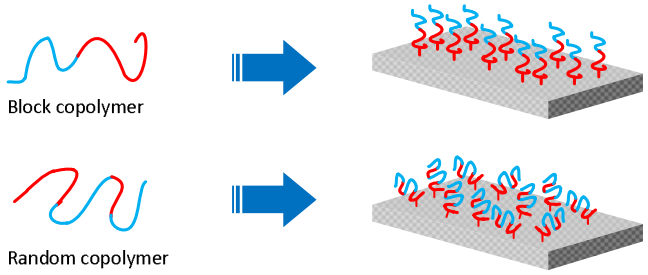


Fig. 2. Schematic of modified polysulfone membran surface by polymerization method.

2.3. Surface modification by chemical reaction and coating

The HD treatment is influenced by membrane surface characteristics, which are considered as the vital role in reducing protein fouling and plasma activation. Therefore, appropriate modifications are necessary to render membrane biocompatibility. Several surface modification methods have been proposed, such as grafting, chemical reaction, and coating. The choice of method depends on the chemical structure of the given support membrane and the desired characteristics of the surface. Most of these modifications are focused on the increase of membrane hydrophilicity to reduce the hydrophobic interaction between the biofoulant and the hydrophobic surface.

Nabe at al. (1997) modified the PSf membrane surface by two different homogeneous chemical reaction techniques to produce epoxide polysulfone (E-PSf) and sulfonated polysulfone (S-PSf) [57]. Then, the effect of modified membrane hydrophilicity on water flux, fouling, and rejection characteristics of the membrane were investigated. The highest membrane hydrophilicity was achieved by the S-PSf membrane, which exhibits the lowest flux decline related to bovine serum albumin (BSA) fouling and high flux recovery ratio after the cleaning process. Furthermore, slight improvement in BSA rejection is resulted by an increase of membrane hydrophilicity. Park et al. [58] successfully immobilized PEG on a PSf membrane surface by condensation reaction of a chain-terminal amine group of PEG with a carboxyl group of 4-azidobenzoic acid in a buffer solution and then irradiated by UV. The coated PEG chains on modified surfaces are effectively depressed of both plasma protein adsorption and cell attachment [59]. In 2003, Haguchi et al. [60] investigated the adsorption characteristic of albumin, globulin and fibrinogen on the Pluronic^{TM}-coated polysulfone membrane. They found that less than 50% reduction of albumin, globulin and fibrinogen adsorption was achieved on the coated PSf membrane compared with the unmodified membrane. The higher molecular weight and concentration of Pluronic^{TM} contributes to the increase of membrane hydrophilicity and reduction in protein adsorption.

Table 1
Characteristic of modified polysulfone membrane prepared by blending method.

Membrane type	Additives		Preparation method	Bioassay	Results						Ref.
	Type	Concentration (%wt)			Contact angle (θ)	water flux (L/m2.h)	Rejection (%)	Protein adsorption (mg/cm2)	Blood coagulation time (s)	Other results	
Poly sulfone (PSF)	MPC	10	Solvent evaporation	Human plasma fibrinogen	±80			0,4		Relative number of platelets < 0,04	[28]
	PEGME (5000)	5	Immersion precipitation	BSA	47	±198[a]	85[b] ; 60[c]	-	-	Finger-like	[16]
	PEG-SO_3A/OA	x[d]	Solvent evaporation	Human whole blood[e]	47	-	-	-	-	Platelet adhesion < 20%	[23]
	poly(AA-co-PEGMA	7	Immersion precipitation	BSA	48,7	±110[f]	±89[g] ±94[h]			FRR = 90%	[17]
Polyether sulfone (PES)	Amphipilic pluronic F127		Immersion precipitation	-	-				-		[34]
	PVP (K30)	6	Dry-wet phase separation	BSA	±70	412	99,2	±80	±20-22	Finger-like	[11]
	CA-PU	8	Spin coating and immersion precipitation	BSA BSF	64	180	-	4 (BSA) 2 (BSF)	±17	- Finger-like Low platelet adhesion	[26]
	HMPU	8	Immersion precipitation	BSA BSF PBS	61	±95	-	6,5 (BSA) 5,5 (BSF)	±52	- Finger like - Reduction of urea and creatinin were 69 and 68,5% Flux recovery ratio (FRR) was 92%	[27]

MPC = 2-methacryloyloxyethyl phosphorylcholine; PVP = poyvinylpirrolidone ; PEGME = Polyethylene glycolmethylether; PEG-SO_3A/OA = sulfonated poly(ethylene glycol) acrylate diblock copolymer; CA-PU = citric acid grafted polyurethane; HMPU = heparin-mimicking polyurethane;
BSA = Bovine serum albumina ; BSF = bovibe serum fibrinogen; PBS = phosphati buffersolution
[a] at 200 kPa ; [b] pH 4,8 ; [c] pH 7 ; [d] total PVP/copolymer/DMAC is 85% wt ; [e] treated with citric acid; [f] pH 2; [g] pH 7 ; [h] pH 2

Table 2
The effect of plasma treatment on permeability, contact angle and flux recovery.

Plasma treatment	Treatment condition	MWCO (kDa)	P_{un} (lmh/bar)	P_{mo} (lmh/bar)	CA_{un} (°)	CA_{mo} (°)	FR (%)	Ref.
Oxygen	0.3-0.9 torr, 60 W, 20 s	30	3.0	3.7	68	32	60[a]	[46]
CO_2	0.15 torr, 10 W, 60 s	100	257.3	604.2	94	0	98[b]	[51]
Helium	0.1 torr, 25 W, 30 s	10	95.0	94.0	98	26	-	[55]
Helium	0.1 torr, 25 W, 30 s	30	440.0	372.0	92	24	69[c]	[55]
He/Water	0.2 torr, 25 W, 30 s	10	95.0	185.0	98	26	57[c]	[55]
He/Water	0.2 torr, 25 W, 30 s	30	440.0	300.0	92	21	-	[55]
Nitrogen	0.3 torr, 60 W, 120 s	-	120.0	40.0	87	44	89[d]	[53]
Ammonia	0.8 torr, 60 W, 180 s	-	112.0	104.0	87	46	70[d]	[47]

P: permeability; MWCO: molecular weight cut off; CA: contact angle; FR: flux recovery; un: unmodified membrane; mo: modified membrane;
[a] Aqueous gelatin
[b] Bovine serum albumin (BSA), 5 % W/V
[c] Lysozime (1 g/L)
[d] Bovine serum albumin (BSA), 1 g/L

Surface chemical reaction of the PSf membrane with different functional groups, including hydroxyl groups (–OH), azide groups ($–N_3$), amine groups ($–NH_2$), carboxyl groups (-COOH) and sulfo groups ($–SO_3H$) have been reported [61]. It was found that the –COOH and $–SO_3H$ grafted membranes exhibited improved anticoagulant property, which is shown in Figure 2. Moreover, a hydrophilic wiper on the membrane surface could be formed by chemically reacting vinylpyrrolidone monomer on the PSf membrane, which hinders the protein adsorption onto the membrane surface and suppressed number of adhering platelets [62]. Other hydrophilic groups that have succeeded have been introduced on the PSf membrane surface by chemical reaction as $–CH_2CH_2CH_2SO_3$-, $-CH(CH_3)CH_2OH$, $-CH_2Cl$, $-CH_2N(CH_2CH_3)_3$, $-CH_2NHCH_2CH_2NH_2$, $-CH_2OH$ and N-succinimidylacrylate (NSA) [63-66]. Recently, Xu et al. [67] elaborated on the antifouling PSf membrane by grafting zwitterionic sulfobetaine (SB) followed by the click-chemistry method with the acetylenic zwitterionic SB monomer (N,N'-diethyl-N-propargyl-N- (3-sulfopropyl) ammonium (DEPAS). It was found that the water contact angle of the membrane could be reduced from 104° to 84° and resulted in 76% reduction of BSA adsorption on the membrane surface. The characteristic of the modified membrane by surface modification is shown in Table 3.

In addition to the biofouling phenomenon, oxidative stress has also frequently occurred on the HD as a result of free radical formation due to the membrane-induced complement and leukocyte activation [68, 69]. Even though the PSf membrane has been known as a good biocompatible membrane to increase the albumin level and decrease the activation of complements and leukocyte, the vitamin-E coated membranes have been reported as a novel approach to reduce the accelerated generation of reactive oxygen [70-75]. Dahe et al. [76] prepared an antioxidative polysulfone/vitamin E TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate) composite hollow fiber membrane in a single step. The KUF and urea clearance increased gradually with increasing TPGS concentration to dope solution that reduced the dialysis treatment time. Furthermore, the adsorbed quantity of albumin, α-globulin and fibrinogen gradually decreased with increasing TPGS concentration. An excellent HD membrane in terms of biocompatibility and separation performance is achieved with the addition of 20% TPCGS. In another research, Mahlici et al. [77] used Alpha-lipoic acid (ALA) as an anti-oxidant, instead of vitamin-E, to modify the PSf-based HD membrane. In vitro antioxidant activity measurements showed that ALA coated membranes were not only capable of reducing reactive oxygen species (ROS) levels in human blood, protein adsorption, and platelet activation on the membranes, but also prolonged the coagulation time.

2.4. Preadsorption method

In the preadsorption method, the functional layer is only physically fabricated on the base polymer, in which the binding strength can be increased via multiple interactions between functional groups in the macromolecular layer and on the solid surface. The surface property of the membrane could change from hydrophobic or non-biocompatible to hydrophilic and biocompatible. The advantages of the surface adsorption method are the simplicity that does not involve lengthy or complicated chemical reactions. However, the adsorption method is limited by its unstable bonding to the membrane surface. The materials absorbed on the membrane surface could be easily removed. Carroll et al. [78] developed charged and non-charged hydrophilic polymers, which were grafted as a flexible layer onto a polypropylene hollow fiber. Non-cationic and cationic hydrophilic grafts have a lower rate of flux decline than ungrafted polypropylene. Anionic hydrophilic grafts have an initial flux increase up to 140% at high graft yields due to multi-valent ions in natural water, although the pure-water flux is substantially lower than that for the ungrafted membrane.

Table 3
Characteristic of modified polysulfone HD membrane prepared by surface modification method.

Membrane Type	modification method	Contact angle (°)	Water flux (LMH)	BSA reduction (%)	Permeation coefficient $\times 10^2$ (m^2/s)	Ref.
SPSF	chemical grafting	34	534	99	-	[57]
EPSF	chemical grafting	48	696	99	-	[57]
PSF-Pluronic™	Coating through chemical reaction	24	-	50	-	[60]
PSF/SPSF-ALA	Coating through electrostatic interactions	50	-	-	Urea : ±85 Vit. B12 : ±83 Lysozyme: ±75	[77]
PSF-CLA	Grafting by adsorption	93	-	-	-	[80]
PSF-zwitterionic	Grafting by click chemistry	84	-	76	-	[67]

Note: SPSF (Sulfonated polysulfone); EPSF (Epoxide polysulfone); ALA (alpha lipoic acid); CLA (conjugated linoleic acid), LMH (L/m^2.h)

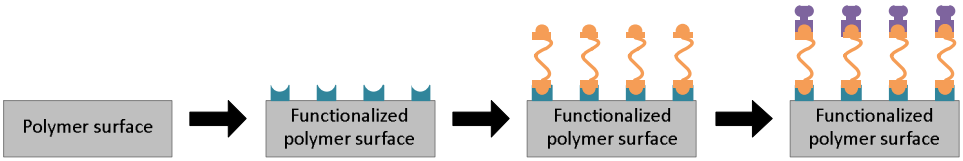


Fig. 3. General concept of biological surface modification.

Reddy et al. [79] modified the PSf membrane by adsorption of poly(sodium 4-styrenesulfonated) (PSSP). The negatively charged sulfonic acid group on the surface was obtained when aqueous solution of PSSP was permeated through the membrane. The extent and nature of surface modification by preadsorption of the polymer are strongly dependent on the size of membrane pores. Membranes with lower MWCO are primarily modified only on the top surface because the macromolecules are not able to enter the inside of the pore. While in the higher MWCO membranes, PSS permeation results in the formation of charge groups both on the surface and pore walls of the membrane.

Immobilizing a bioactive compound onto a polymeric surface is commonly prepared by adsorption methods via electrostatic interactions, ligand-receptor pairing, and covalent attachment [81], as shown in Figure 3. Pozniak et al. [82] modified the PSf membrane by immobilizing urea on the membrane surface. It was found that higher activities were achieved when the immobilization procedure was carried out at lower pH. Meanwhile, Lin et al. (2003) found that the urease immobilized dialyzer gave a faster removing rate of urea compared to a regular dialyzer, which can be further improved by increasing the dialysate velocity [83]. In another research, Zhao et al. [84] immobilized single-strand DNA onto the PSf membrane to reduce the amount of protein adsorbed on the membrane surface. It was found that the membrane hydrophilicity was increased when DNA was immobilized onto the membrane surface by UV-irradiation. Higher amounts of immobilized DNA were found on the rougher surface. This DNA-immobilized membrane was limited by the natural interaction between DNA and protein, which resulted in a slight decrease of protein adsorption although the hydrophilicity remarkably increased. To summarize, the characteristic of modified PSf by immobilizing biomaterials is shown in Table 4.

Table 4
Characteristic of modified membrane by immobilizing of biomaterials.

Membrane type	Results	Ref.
PSf-Heparin	- Hydrophilicity of the membrane is improved	[86]
	- The blood coagulation time is prolonged	
	- less platelets adhesion	
	- reduce heparin consumption during HD treatment	
PSf-Urease	- Urea removal by modified membrane could be improved, 2 times higher than the unmodified membrane	[83]
	- the urea clearance could be further improved by the increase of dialysate velocity	
PSf-DNA	- Hydrophilicity of the membrane is improved	[84]
	- limited by the natural interaction DNA and protein	

Recently, heparin has been successfully immobilized onto the PSf membrane to reduce the platelet and fibrin adhesion, which retained heparin's bioactivity and inhibited thrombosis in the blood purification system [85, 86]. Li et al. [87] found that the attachment of heparin on the membrane surface gives similar properties compared with the polysulfone membrane that blended with PVP and lipophilic domains. Up to the present time, the correlation between plasma protein adsorption to heparin-coated surfaces and the activation of the plasma is still continuously discussed and investigated [88-90].

3. Characteristics of membranes for hemodialysis

Numerous synthetic polymeric materials have been used for manufacturing the HD membrane, both in laboratory and industrial scale. The criteria of HD membrane performance include excellent biocompatibility, appropriate ultrafiltration rate, and effective clearance of target solutes. For plasma separation, the membrane should have a reasonable MWCO, a sharp cut-off curve, and a greater capacity for adsorption. In this sub-chapter, the parameters determining characteristics of the HD membrane are discussed.

3.1. Biocompatibility and low fouling characteristics

The most critical issue in material developments for the HD membrane is biocompatibility. Interaction between blood components and HD membranes plays an important role in determining membrane biocompatibility [7, 91, 92]. Fouling on the membrane surface is mainly initiated by the adsorption of proteins (such as albumin, globulin, and hemoglobin) and fibrinogen from plasma that occurs rapidly after the first blood contact [93]. The adsorbed protein layer contributes to subsequent biological reactions, i.e. platelet adhesion and activation that initiate the inflammatory responses [94, 95]. The interaction between protein and membrane surface depends on membrane characteristics (hydrophilicity, pore size and distribution, surface roughness, and charge), protein concentration, and degree of complexity including protein-protein interaction [96]. The mechanism of protein adsorption on the membrane surface is illustrated in Figure 4, which consists of diffusion of protein to the hydrophobic membrane surface, adsorption, and denaturation [97]. The adsorption of protein on the membrane surface is accompanied by the released water molecules from the interface. The water molecules could strongly bond on the hydrophilic membrane surface due to electrostatic interactions and hydrogen bonding. The interaction between the membrane surface and protein can be reversible or irreversible depending on their affinity among the molecules [15].

The blood clotting phenomenon on the membrane is another problem during the HD process. The blood clotting is initiated by platelet adhesion on the membrane surface, which is activated by coagulation factors in blood, and then stabilized by fibrin network or thrombus [98]. To prevent the blood clotting during HD, some biomolecules are used as an anticoagulant, such as linoleic acid, dextran, chitosan, and heparin [99-101]. However, the use of heparin is associated with several disadvantages. The disadvantages are bleeding risk and activation of platelets or neutrophils on the membrane surface [102, 103]. Therefore, an appropriate surface grafting or coating of the membrane is needed to render membrane compatibility.

Biocompatibility based on both lactate dehydrogenase (LDH) activity and amount of protein adsorption is greatly different among commercially available PSf hollow-fiber dialysis membranes [104]. In addition, leukocyte activation is also one of the parameters that should be considered in relation to biocompatibility that induces oxidative stress during HD.

3.2. Flowrate coefficient of membrane during Hemodialysis

HD membranes are classified according to water flux (or permeability) that is well-defined as ultrafiltration coefficient (K_{UF}: mL.h^{-1}.mmHg^{-1}). The KUF value of the membrane regulates the rate and amount of fluid flow across the dialyzer membrane, which is related to the transmembrane pressure (TMP) [105]. Based on the water permeability characteristic, the HD membranes are often categorized as low flux and high flux. The United States Food and Drug Administration recognized that low and high flux HD membranes have K_{UF} values of less and over 8 mLh^{-1}mmHg^{-1}, respectively [106]. Several studies have been conducted to investigate the effect of low and high flux during dialysis treatment [107-110]. Although these studies have suggested that high-flux membranes improve outcomes for patients compared with low-flux dialyzers [111-115], this observation is still discussed up to the present time. The major progress in dialysis membranes to meet the biocompatibility is optimized both in low-and high-flux dialysis [116].

The main features of convective treatments of high-flux membranes are characterized by high water permeability, selective to low and middle molecular weight solutes (particularly in the range of 1,000 to 12,000 Daltons), and biocompatibility [117]. The amount of albumin loss due to the larger pore size in the high-flux membrane is also a critical parameter to prevent hypoalbuminaemia and malnutrition [118]. It has been reported in the literature that the molecular size of the albumin is around 66.000 Da [119, 120]. Therefore, optimization between maximum removal of large-molecular-

weight toxin and minimum albumin losses should be considered in further development of the high flux HD membrane. On the other hand, counter-current flow of the blood and dialysate should be kept at a constant pressure. Some dialysis manufacturers have added the setting option of the dialysate flow rate at a fixed ratio of 1.5 or 2.0 times the blood flowrate. Typical blood flowrate during HD treatment is around 300–400 mL/min. Meanwhile, the standard dialysate flow rate is around 500–800 mL/min [121].

3.3. Clearance target of solutes

Solute clearance is defined as the mass removal rate divided by the concentration of the solute in the blood (milliliters/minute). Theoretical investigations of solute transport in dialysis membranes have generally focused on the effective solute diffusion coefficient [122]. The solute removal in the HD membrane depends on the concentration gradient of the unbound solute across the membrane, membrane permeability to the specific solute, membrane or solute characteristics, and the length of dialysis [123]. There are three major categories of solutes which are known as uremic toxins in the HD field based on the physicochemical properties [121], i.e. (1) small water soluble compounds (such as urea and creatinine) with a molecular weight less than 500 Da, (2) middle molecules with a molecular size between 500 Da and 15.000 Da (such as β-2 microglobulin (β-2M), leptin, complement protein, advanced glycation end products, proinflammatory cytokines, factor D, and granulocyte-inhibiting protein), and (3) protein-bond molecules.

Solute removal in the HD membrane is commonly driven by two mechanisms of solute transport, i.e. diffusion and convection, but in some cases it could be driven by adsorption [124]. The transport of small water soluble molecules and middle molecules through the membrane is driven by diffusion. Meanwhile, protein bond uremic toxins are generally driven by convective transport. However, the middle molecule could be driven through the membrane by increasing the ultrafiltration rate, such as hemofiltration and hemodiafiltration treatment [125, 126]. There are several terms used to identify the solute clearance characteristic of the HD membrane. The clearance of urea could be identified by the hemodialyzer mass transfer-area coefficient (KoA), Kt/V (where K is the dialyzer clearance of urea, t is the dialysis time and V is the volume of distribution of urea), and urea reduction ratio (URR) [127-131]. As stated in several literatures, the target of URR is more than 65% and a single pole Kt/V ≥ 1.2 for the dialysis patient who has treatment three times a week [132-134].

The diffusion and rejection of solutes in the porous membrane are determined by pore size and its distribution in the membrane structure, both in the membrane skin layer and sub-layer. Contact with plasma had little effect on the clearance of urea and vitamin B_{12}. However, it has a magnitude reduction in clearance for solutes with molecular weights > 10,000. These results provide important insights into the effects of contact with plasma on solute clearance during HD [135].

4. Sterilization of hemodialysis polysulfone-based membrane

Sterilization is an important process in the manufacture of the HD membrane. The sterilization of the hemodialyzer should mean the destruction of all forms of pathogens [136], so it can be safe for patient use. In the past, hemodialyzers were assembled and washed with alcohol solution before clinical use [137]. After disposable models became commercially available, they were sterilized in the production procedure. Gas sterilization was commonly used until the late 1980s. At the present time, many sterilization techniques are available and these include the traditional methods of autoclaving, ethylene oxide (EO) and gamma irradiation, and the more recently introduced systems involving low-temperature gas plasma and vapor phase sterilants [138]. When selecting a sterilization method, it is necessary to analyze the compatibility of the polymer membrane with the process parameters of the sterilization method and the chemical used [138]. PSf hemodialyzers are widely used due to excellent membrane formation ability, high thermal resistance (150-170 °C), chemical resistance on the entire pH range, resistance in the oxidative medium (hypochlorite 5-7%, hydrogen peroxide 3-5%), and high mechanical resistance of the films (fracture, flexure, torsion), which make it one of the few biomaterials that can withstand sterilization techniques [76, 139].

The differences of sterilization techniques may be a reason for different grades of hemocompatibility of membranes. Erlenkötter et al. [140] described an in vitro assessment of the hemocompatibility pattern of different polymers with their different modes of sterilization. Their study revealed that the Gamma-sterilized polysulfone had worse overall hemocompatibility than the steam-sterilized polysulfone. A total hemocompatibility score (THS) is calculated by measuring five hemocompatibility parameters, i.e. the plasmatic immune system, cell activation, coagulation activation, platelet factor 4 and platelet count. The THS of the steam-sterilized PSf membrane (Helixone) was found to be 19.6. The THS of the Gamma-sterilized PSf membrane (Toraysulfone) was found to be 32. Madsen et al. [141] demonstrated significant changes in the fiber physicochemical properties with different methods of sterilization. Commercial PSf hollow fibers containing PVP were subjected to standard ethylene oxide (EO), sodium hypochlorite (bleach), and electron-beam (e-beam) sterilization techniques. E-beam sterilization rendered more hydrophilic fibers compared to the ETO- and bleach-treated fibers. The e-beam-sterilized and bleach-treated membranes both had larger outside surface roughness compared to the ETO-sterilized membrane. Also, the e-beam fiber had the highest evaporation rate.

Hayama et al. [104] used γ-ray or autoclave (AC) methods to sterilize the PSf hollow-fiber membrane which was prepared by spinning the mixture of PS, hydrophilic agents, and water-soluble solvents via the dry/wet method. The gamma-ray sterilization method promotes cross-linking between PS and PVP. Hence, the AC method is capable of achieving high biocompatibility with PS membranes having a small amount of PVP and lower regularity of polymer particle structure. Yamashita et al. [137] used autoclave sterilization (AC), gamma ray sterilization (G-ray), combination of these two and no sterilization (NS) as the sterilization method, and then investigated the effect of sterilization on solute transport performances of super high-flux PSf dialyzers. A dialyzer with NS showed the lowest clearances compared with the sterilized dialyzers. Therefore, the sterilization increases the solute transfer performances. The sterilization increases the solute clearance even in so-called superhigh-flux dialyzers and the effect of sterilization may be greater in larger solutes. Each sterilization method has different effects of enhancement on the rate of mass transfer, and AC have greater effects on solute transport than γ-ray irradiation.

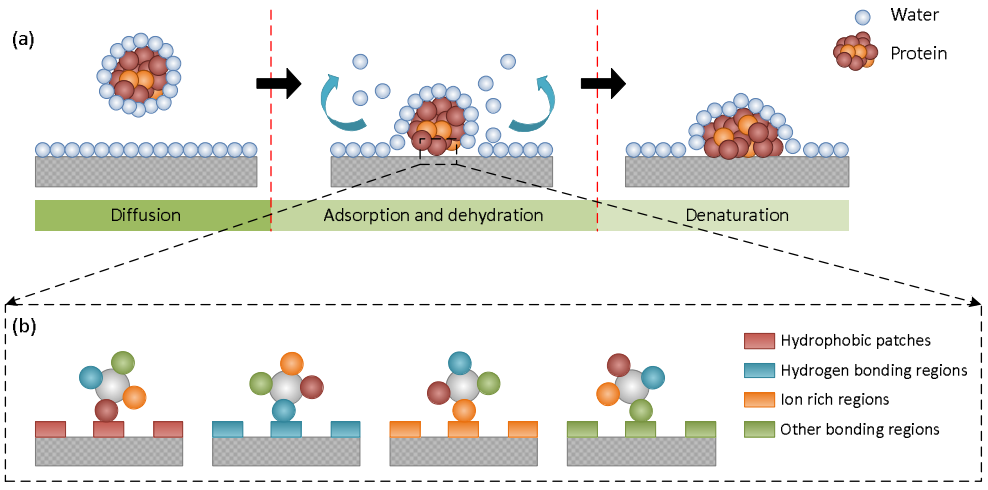


Fig. 4. Adsorption of protein onto the polymeric membrane surface : (a) mechanism of adsorption and (b) various possibilities of physico-chemical adsorption.

Table 5
Sterilization techniques and its compatibility for hemodialysis membranes.

Sterilization technique	Compatibility	References
Dry heat sterilization	- High temperature sterilization (up to 215°C) - Additional moisture removal is required when dry heat sterilization is conducted below 100°C	[144]
Ethylene oxide technique	- Compatible - Low temperature sterilization process (<60°C),rapid activity, nontoxicity and cost effectiveness - Toxic residues control is needed to minimize the potential undesirable effect on patient health	[144, 145]
Hydrogen peroxide (with plasma) technique	- Excellent - Offers a short cycle, low temperature and humidity, no aeration requirement, no chemical residues.	[144, 146]
Ozone sterilization technique	- Good - Number of cycles polymer may be compatible: Slight surface change and loss of gloss. No significant change after > 100 cycles	[144]
Steam sterilization	- Compatible - Usually employ prevacuum high-temperature steam at 121°C for 20 min	[147]
Gamma Irradiation technique	- Compatible - Increase hydraulic permeability under wet condition - Reduce membrane permeability under dry condition and vitamin B12 clearance - Promotes cross-linking between PSF and hydrophlizing agent	[104, 148]

Broek et al. [142] characterized the pore size distribution and performance of hollow fiber HD membranes. The sterilization decreases the membrane porosity. The sample sterilized with ethylene oxide (EO) had a volume porosity of 18% which was due to a decrease of the pore volume of the smallest pores. Meanwhile, the applied dry steam sterilization treatment resulted in a drastic collapse of the large pores and smaller pores were formed in which calculated porosity was only 10%. The effect of EO sterilization on the membrane performance is relatively insignificant. The effect of steam sterilization is more significant, especially for the vitamin B_{12} clearance rate and the ultrafiltration capacity (UFR). The UFR for non-sterilized, EO sterilized, and steam sterilized membranes are about 725, 680, and 77 ml/hr, respectively.

When using a sterilization method, it is necessary to analyze the reactions that may occur in patients. Marshall et al. [143] studied the reactions during HD caused by allergy to EO gas sterilization. They have examined the presence of IgE-dependent sensitization to EO gas, which is used for sterilization of disposable medical products including dialyzers. Their results demonstrate a close relationship between the presence of IgE antibodies to EO and HD-related allergic reactions in this patient population. The compatibilities of PSf to some sterilization techniques are shown in Table 5.

From the explanations above, it is claimed that the selection of sterilization method becomes very important with regard to their effects, such as changes in physicochemical properties, biocompatibility, and performances of the membranes. Further membrane development is still needed to enhance membrane resistance and stability during the sterilization process.

5. Commercial polysulfone membrane for hemodialysis

In 2013, the global market of the HD membrane value is at $61.60 billion and is expected to grow at a CAGR of 6.2% in the next five years [149], where predicted worldwide dialysis patients may reach 3.8 million in 2020 (Figure 5). The demographic factor is considered as one of the main reasons for the continued growth of dialysis markets, including the aging population and the mounting incidence of diabetes and hypertension as the two diseases that often precede end stage renal disease. In addition, the life expectancy of dialysis patients is increasing primarily due to ongoing improvements in the quality of treatment and higher standards of living, even in developing countries. Growth in the number of dialysis facilities developed as well as developing in markets, increase in private investments, and venture funding to support new product development are a few of the other key factors that contribute to the growth of the global market. However, a reduction in medicare reimbursements to dialysis centers, high costs of treatment, and low awareness of kidney related diseases and their treatment modalities are factors restraining the growth of the market.

Nowadays, the global products and services of the HD membrane market are dominated by Fresenius Medical Care AG & Co. KGaA (Germany), DaVita Healthcare Partners, Inc. (U.S.), Gambro AB (Sweden), Baxter International, Inc. (U.S.), B. Braun Melsungen AG (Germany), Membrana GmbH (Germany), Nipro Corporation (Japan), Diaverum Deutschland GmbH (Germany), Medical Components, Inc. (U.S.), Covidien (Ireland), and NxStage Medical, Inc. (U.S.) [150]. Among these HD membrane manufacturers, a major commercial product of PSf hollow fiber hemodialyzer is produced by Fresenius (Germany), which was widely acknowledged as providing an optimal biocompatibility in terms of good solute removal and low-complement activation. The other manufacturers are Toray (Japan), Asahi Kasei medical (Japan), and Bad Homburg (Germany). The market share for hemodialysis in the last few years is shown in Figure 6.

Asahi Kasei Medical Co., Ltd. produced several types of PSf-based membranes for HD such as APS series, ViE series and Rexeed series, which were claimed has having high flux and excellent biocompatibility [155]. On the other hand, Toray Medical Co. Ltd. develops two series hemodialyzers, “Filtryzer” and “Toraysulfone”. Both are hollow-fiber type dialyzers with synthetic membranes and γ-ray sterilizer. Filtryzer” using the PMMA (Polymethylmethacrylate) membrane originally developed by Toray provides excellent biocompatibility and well-balanced removal capability of small and middle molecular substances, while “Toraysulfone” is a PSf-based haemodialysis membrane with optimum structure and special design to obtain uniform flow of dialysate, thus achieving remarkable performance [156].

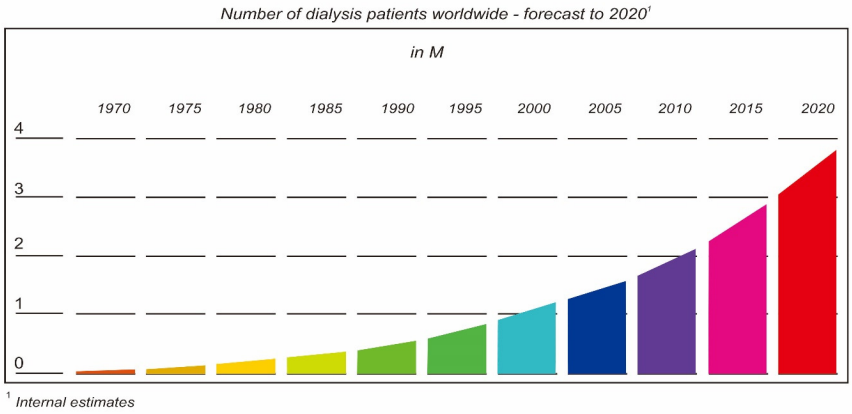


Fig. 5. Number of dialysis patients worldwide [150].

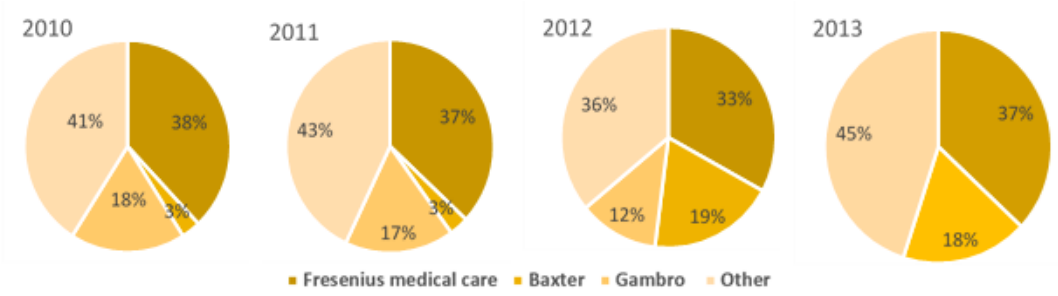


Fig. 6. Hemodialysis market share from 2010 to 2013 [151-154].

Table 6
Membrane characteristics of commercial HD membrane.

	High-flux polyethersulfone			High-flux polysulfone	
	PUREMA® H	**Diapes® HF800**	**Helixone®**	**Toraysulfone (TS-S/U series)**	**Asahi Polysulfone (APS)**
Membrane material	PES-PVP blend	PES-PVP blend	PSU-PVP blend	Crosslinked PSU- PVP	Polysulfone
Wall structure	Asymmetric	Asymmetric	Asymmetric	Asymmetric	Asymmetric
Fibre diameter (μm)	200	200	185	200	200
Wall thickness (μm)	30	30	35	40	45
Cytochrome c	0.95 ± 0.04	0.60 ± 0.05[a]	0.61 ± 0.07[a]	-	-
Albumin	0.001 ± 0.001[b]	0.005 ± 0.002	0.001 ± 0.001[b]	-	-
Ultrafiltration coefficient (ml/h m^2.mmHg)	85.3 ± 11.7[c]	82.6 ± 11.5[c]	62.2 ± 12.5	-	69
Sterilization	Gamma-ray	Gamma-ray	Inline steam	-	Gamma-ray
Ref.	[159]	[158]	[158]	[161]	[162]

[a]$P < 0.001$ vs PUREMA® H; [b]$P < 0.001$ vs Diapes® HF800; [c]$P < 0.01$ vs Helixone®

Table 7
Instantaneous plasma clearances of HD membranes.

HD Membrane	Base material	Blood/dialysate flow rate (ml/min)	Treatment time (min)	Instantaneous LMW protein plasma water clearances (ml/min)							Ref.
				Urea	Creatinine	PO_4	b2m	cysc	myo	rbp	
PUREMA® H (1.7 m^2)	PES	300/500	30	225 ± 8	209 ± 8	195 ± 7	69 ± 8[a]	67 ± 6[b]	30 ± 9[a]	-6 ± 7	[158]
			240	217 ± 6	197 ± 7[c]	189 ± 6[c]	63 ± 5[b,d]	57 ± 3[b,c]	21 ± 5[b,d]	-6 ± 5	[162]
PUREMA® H (1.9 m^2)	PES	378±33/500±0	30	266 ± 12		223 ± 16	63 ± 10	69 ± 8	24 ± 10	2 ± 9	[162]
			180	264 ± 18		226 ± 27	59 ± 9	58 ± 9	19 ± 9	4 ± 8	[162]
PUREMA® H+ (1.9 m^2)	PES	378±33/500±0	30	257 ± 19		214 ± 24	60 ± 9	64 ± 8	25 ± 8	8 ± 9	[162]
			180	256 ± 18		219 ± 24	62 ± 7	62 ± 9	25 ± 7	7 ± 9	[162]
Helixone® (1.8 m^2)	PSU	300/500	30	226 ± 5	209 ± 7	197 ± 4	58 ± 3	44 ± 3	9 ± 7	-13 ± 9	[158]
			240	217 ± 5[c]	197 ± 8[c]	190 ± 5[c]	50 ± 3[c]	36 ± 5[c]	8 ± 6	-4 ± 6	[158]
Toraysulfone (1.3 – 2.1 m^2)	PSU	200/500	-	195 ±3	192 ± 5	187 ± 8	-	-	-	-	[160]
APS-550 (1,1 m^2)	PSU	300/500	-	226	210	180					[161]

Note: Urea (60 Da); creatinine (113 Da); PO_4, phosphate (96 Da); B_2m, beta$_2$-microglobulin (11 800 Da); cysc, cystatin c (13 400 Da); myo, myoglobulin (17 800 Da); rbp, retinol-binding protein (21 200 Da); [a]$P < 0.01$ vs Helixone® (1.8 m^2); [b]$P < 0.001$ vs Helixone® (1.8 m^2); [c]$P < 0.01$ vs 30 min; [d]$P < 0.05$ vs 30 min; [e]$P < 0.001$ vs 30 min.

6. Conclusion

Fresenius Medical Care is continuing to set the standard for novel dialysis products by launching a new class of dialyzers, the FX-class. These dialyzers combine an innovative housing design with an advanced dialysis membrane, the Helixone membrane, which employs a new process of membrane preparation called Nano Controlled Spinning (NCS) Technology. Membrana GmbH developed PUREMA® H, an innovative polyelectrolyte additive-modified synthetic high-flux dialysis membrane that was prepared from PES/PVP blend [157, 158]. PUREMA® H (Membrana GmbH) was introduced in 2007 as a further development of Diapes® HF800 (Membrana GmbH, Wuppertal, Germany) [159]. The performance of PUREMA® H during HD is often compared with the high-flux polysulfone membrane (Helixone®). The efficacy of the PUREMA® H in HD determined by measuring instantaneous plasma clearances compared to the other commercial membranes is shown in Table 6. Meanwhile, the in vitro characteristics of the high-flux polyethersulfone (PUREMA® H and Diapes® HF800) and high-flux polysulfone (Helixone®) are shown in Table 7.

Advances in the development of polysulfone membranes for HD have been reviewed. Most of the unmodified polysulfone membranes were hydrophobic due to its natural polymer property, which exhibits the intrinsic

bio-incompatibility, high permeability for low-molecular weight proteins, high endotoxin retention capabilities, and high resistance during sterilization. Indeed, these characteristics are not suitable for HD treatment and should be modified to maintain their sustainability in the HD field. Several factors should be considered during polysulfone membrane development, including excellent biocompatibility, appropriate ultrafiltration rate, and effective clearance of the target solute.

Different methods of polysulfone membrane modifications have been proposed. Most of the modification methods are focused on the increase of membrane hydrophilicity to reduce the adsorption of protein and minimize platelet adhesion and complement activation that initiate the inflammatory responses. Selectivity of the polysulfone membrane also plays an important role to avoid endotoxin leakage and reduce albumin loss during HD treatment. On the other hand, sterilization of the HD membrane also becomes very important with regard to their effects, such as changes in physicochemical properties, biocompatibility, and performances of the membranes.

7. References

[1] B.-H. Su, Y. Shi, P. Fu, Y. Tao, S. Nie, C.-S. Zhao, Clinical evaluation of polyethersulfone high-flux hemodialysis membrane compared to other membranes, J. Appl. Polym. Sci. 124(S1) (2012) E91-E98.

[2] S.K. Bowry, Dialysis membranes today, Int. J. Artif. Organs 25 (2002) 447-460.

[3] S.K. Bowry, E. Gatti, J. Vienken, Contribution of polysulfone membranes to the success of convective dialysis therapies, Contrib. Nephrol. 173 (2011) 110-118.

[4] L. Kubala, M. Ciz, V. Soska, J. Cerny, A. Lojek, Influence of polysulfone and hemophan hemodialysis membranes on phagocytes, Gen. Physiol. Biophys. 21 (2002) 367-380.

[5] L. Lucchi, S. Bergamini, B. Botti, R. Rapana, A. Ciuffreda, P. Ruggiero, M. Ballestri, A. Tomasi, A. Albertazzi, Influence of different hemodialysis membranes on red blood cell susceptibility to oxidative stress, Artif. Organs, 24 (2000) 1-6.

[6] A.C. Yamashita, N. Tomisawa, Importance of membrane materials for blood purification devices in critical care, Transfus. Apher. Sci. 40 (2009) 23-31.

[7] S. Sun, Y. Yue, X. Huang, D. Meng, Protein adsorption on blood-contact membranes, J. Membr. Sci. 222 (2003) 3-18.

[8] B.D. Ratner, Biomaterials science: an introduction to materials in medicine, Academic press, 2004.

[9] T. Sanaka, M. Koremoto, Selection guidelines for high-performance membrane, Contrib. Nephrol. 173 (2011) 30-35.

[10] E. Ostuni, R.G. Chapman, R.E. Holmlin, S. Takayama, G. M. Whitesides, A survey of structure−property relationships of surfaces that resist the adsorption of protein, Langmuir 17 (2001) 5605-5620.

[11] H. Wang, T. Yu, C. Zhao, Q. Du, Improvement of hydrophilicity and blood compatibility on polyethersulfone membrane by adding polyvinylpyrrolidone, Fiber. Polym. 10 (2009) 1-5.

[12] B. Chakrabarty, A. Ghoshal, M. Purkait, Preparation, characterization and performance studies of polysulfone membranes using PVP as an additive, J. Membr. Sci. 315 (2008) 36-47.

[13] J.-H. Kim, K.-H. Lee, Effect of PEG additive on membrane formation by phase inversion, J. Membr. Sci. 138 (1998) 153-163.

[14] W.-L. Chou, D.-G. Yu, M.-C. Yang, C.-H. Jou, Effect of molecular weight and concentration of PEG additives on morphology and permeation performance of cellulose acetate hollow fibers, Sep. Purif. Technol. 57 (2007) 209-219.

[15] Y. Ma, F. Shi, J. Ma, M. Wu, J. Zhang, C. Gao, Effect of PEG additive on the morphology and performance of polysulfone ultrafiltration membranes, Desalination 272 (2011) 51-58.

[16] M. Sinha, M. Purkait, Increase in hydrophilicity of polysulfone membrane using polyethylene glycol methyl ether, J. Membr. Sc. 437 (2013) 7-16.

[17] M. K. Sinha, M.K. Purkait, Preparation and characterization of novel pegylated hydrophilic pH responsive polysulfone ultrafiltration membrane, J. Membr. Sci. 464 (2014) 20-32.

[18] J. Yoo, J. Kim, Y. Kim, C. Kim, Novel ultrafiltration membranes prepared from the new miscible blends of polysulfone with poly (1-vinylpyrrolidone-co-styrene) copolymers, J. Membr. Sci. 216 (2003) 95-106.

[19] J. Kim, C. Kim, Ultrafiltration membranes prepared from blends of polyethersulfone and poly (1-vinylpyrrolidone-co-styrene) copolymers, J. Membr. Sci. 262 (2005) 60-68.

[20] Z. Yi, L.-P. Zhu, Y.-Y. Xu, Y.-F. Zhao, X.-T. Ma, B.-K. Zhu, Polysulfone-based amphiphilic polymer for hydrophilicity and fouling-resistant modification of polyethersulfone membranes, J. Membr. Sci. 365 (2010) 25-33.

[21] H. Susanto, M. Ulbricht, Characteristics, performance and stability of polyethersulfone ultrafiltration membranes prepared by phase separation method using different macromolecular additives, J. Membr. Sci. 327 (2009) 125-135.

[22] S. Nie, J. Xue, Y. Lu, Y. Liu, D. Wang, S. Sun, F. Ran, C. Zhao, Improved blood compatibility of polyethersulfone membrane with a hydrophilic and anionic surface, Colloids Surf. B Biointerfaces 100 (2012) 116-125.

[23] Y.-W. Kim, W. Shick Ahn, J.-J. Kim, Y. Ha Kim, In situ fabrication of self-transformable and hydrophilic poly (ethylene glycol) derivative-modified polysulfone membranes, Biomaterials 26 (2005) 2867-2875.

[24] J.Y. Park, M.H. Acar, A. Akthakul, W. Kuhlman, A.M. Mayes, Polysulfone-graft-poly (ethylene glycol) graft copolymers for surface modification of polysulfone membranes, Biomaterials 27 (2006) 856-865.

[25] W. Haitao, Y. Liu, Z. Xuehui, Y. Tian, D. Qiyun, Improvement of hydrophilicity and blood compatibility on polyethersulfone membrane by blending sulfonated polyethersulfone, Chinese J. Chem. Eng. 17 (2009) 324-329.

[26] L. Li, C. Cheng, T. Xiang, M. Tang, W. Zhao, S. Sun, C. Zhao, Modification of polyethersulfone hemodialysis membrane by blending citric acid grafted polyurethane and its anticoagulant activity, J. Membr. Sci. 405 (2012) 261-274.

[27] L. Ma, B. Su, C. Cheng, Z. Yin, H. Qin, J. Zhao, S. Sun, C. Zhao, Toward highly blood compatible hemodialysis membranes via blending with heparin-mimicking polyurethane: Study in vitro and in vivo, J. Membr. Sci. 470 (2014) 90-101.

[28] K. Ishihara, K. Fukumoto, Y. Iwasaki, N. Nakabayashi, Modification of polysulfone with phospholipid polymer for improvement of the blood compatibility. Part 1. Surface characterization, Biomaterials 20 (1999) 1545-1551.

[29] K. Ishihara, K. Fukumoto, Y. Iwasaki, N. Nakabayashi, Modification of polysulfone with phospholipid polymer for improvement of the blood compatibility. Part 2. Protein adsorption and platelet adhesion, Biomaterials 20 (1999) 1553-1559.

[30] T. Hasegawa, Y. Iwasaki, K. Ishihara, Preparation of blood-compatible hollow fibers from a polymer alloy composed of polysulfone and 2-methacryloyloxyethyl phosphorylcholine polymer, J. Biomed. Mater. Res. 63 (2002) 333-341.

[31] C. Zhao, X. Liu, M. Nomizu, N. Nishi, Blood compatible aspects of DNA-modified polysulfone membrane-protein adsorption and platelet adhesion, Biomaterials 24 (2003) 3747-3755.

[32] Y. Wang, Y. Su, Q. Sun, X. Ma, X. Ma, Z. Jiang, Improved permeation performance of Pluronic F127–polyethersulfone blend ultrafiltration membranes, J. Membr. Sci. 282 (2006) 44-51.

[33] Y.-q. Wang, T. Wang, Y.-l. Su, F.-b. Peng, H. Wu, Z.-Y. Jiang, Remarkable reduction of irreversible fouling and improvement of the permeation properties of poly (ether sulfone) ultrafiltration membranes by blending with pluronic F127, Langmuir 21 (2005) 11856-11862.

[34] W. Zhao, Y. Su, C. Li, Q. Shi, X. Ning, Z. Jiang, Fabrication of antifouling polyethersulfone ultrafiltration membranes using Pluronic F127 as both surface modifier and pore-forming agent, J. Membr. Sci. 318 (2008) 405-412.

[35] P.T.P. Aryanti, S. Subagjo, D. Ariono, I.G. Wenten, Fouling and rejection characteristic of humic substances in polysulfone ultrafiltration membrane, J. Membr. Sci. Res. (2014), In Press.

[36] P.T.P. Aryanti, I. Khoiruddin, Influence of additives on polysulfone-based ultrafiltration membrane performance during peat water filtration, J. Water Sustain. 3 (2013) 85-96.

[37] S. Jiang, Z. Cao, Ultralow-fouling, functionalizable, and hydrolyzable zwitterionic materials and their derivatives for biological applications, Adv. Mater. 22 (2010) 920-932.

[38] T. Xiang, C.-D. Luo, R. Wang, Z.-Y. Han, S.-D. Sun, C.-S. Zhao, Ionic-strength-sensitive polyethersulfone membrane with improved anti-fouling property modified by zwitterionic polymer via in situ cross-linked polymerization, J. Membr. Sci. 476 (2015) 234-242.

[39] Y. He, J. Hower, S. Chen, M.T. Bernards, Y. Chang, S. Jiang, Molecular simulation studies of protein interactions with zwitterionic phosphorylcholine self-assembled monolayers in the presence of water, Langmuir 24 (2008) 10358-10364.

[40] Q. Li, Q.-Y. Bi, B. Zhou, X.-L. Wang, Zwitterionic sulfobetaine-grafted poly(vinylidene fluoride) membrane surface with stably anti-protein-fouling performance via a two-step surface polymerization, Appl. Surf. Sci. 258 (2012) 4707-4717.

[41] D.-G. Yu, W.-C. Lin, M.-C. Yang, Surface modification of poly (L-lactic acid) membrane via layer-by-layer assembly of silver nanoparticle-embedded polyelectrolyte multilayer, Bioconjug. Chem. 18 (2007) 1521-1529.

[42] M. Irfan, A. Idris, N.M. Yusof, N.F.M. Khairuddin, H. Akhmal, Surface modification and performance enhancement of nano-hybrid f-MWCNT/PVP90/PES hemodialysis membranes, J. Membr. Sci. 467 (2014) 73-84.

[43] L.Y. Ng, A.W. Mohammad, C.P. Leo, N. Hilal, Polymeric membranes incorporated with metal/metal oxide nanoparticles: a comprehensive review, Desalination 308 (2013) 15-33.

[44] Y. Chang, Y.-J. Shih, C.-Y. Ko, J.-F. Jhong, Y.-L. Liu, T.-C. Wei, Hemocompatibility of poly (vinylidene fluoride) membrane grafted with network-like and brush-like antifouling layer controlled via plasma-induced surface PEGylation, Langmuir 27 (2011) 5445-5455.

[45] H. Yasuda, Plasma polymerization for protective coatings and composite membranes, J. Membr. Sci. 18 (1984) 273-284.

[46] K. Kim, K. Lee, K. Cho, C. Park, Surface modification of polysulfone ultrafiltration membrane by oxygen plasma treatment, J. Membr. Sci. 199 (2002) 135-145.

[47] M. Bryjak, I. Gancarz, G. Poźniak, W. Tylus, Modification of polysulfone membranes 4. Ammonia plasma treatment, Eur. Polym. J. 38 (2002) 717-726.

[48] D.S. Wavhal, E.R. Fisher, Modification of polysulfone ultrafiltration membranes by CO_2 plasma treatment, Desalination 172 (2005) 189-205.

[49] P. Krakow, Modification of polysulfone by means of UV irradiation and H_2O_2 plasma treatment, Eur. Cell. Mater. 7 (2004) 59.

[50] E. Castro Vidaurre, C. Achete, F. Gallo, D. Garcia, R. Simão, A. Habert, Surface modification of polymeric materials by plasma treatment, Mater. Res. 5 (2002) 37-41.

[51] D.S. Wavhal, E.R. Fisher, Modification of polysulfone ultrafiltration membranes by CO_2 plasma treatment, Desalination 172 (2005) 189-205.

[52] I. Gancarz, G. Poźniak and M. Bryjak, Modification of polysulfone membranes 1. CO_2 plasma treatment, Eur. Polym. J. 35 (1999) 1419-1428.

[53] I. Gancarz, G. Poźniak, M. Bryjak, Modification of polysulfone membranes: 3. Effect of nitrogen plasma, Eur. Polym. J. 36 (2000) 1563-1569.

[54] J. Zhan, Z. Liu, B. Wang, F. Ding, Modification of a membrane surface charge by a low temperature plasma induced grafting reaction and its application to reduce membrane fouling, Sep. Sci. Technol. 39 (2004) 2977-2995.

[55] M. Ulbricht, G. Belfort, Surface modification of ultrafiltration membranes by low temperature plasma II. Graft polymerization onto polyacrylonitrile and polysulfone, J. Membr. Sci. 111 (1996) 193-215.

[56] M.L. Steen, A.C. Jordan, E.R. Fisher, Hydrophilic modification of polymeric membranes by low temperature H_2O plasma treatment, J. Membr. Sci. 204 (2002) 341-357.
[57] A. Nabe, E. Staude, G. Belfort, Surface modification of polysulfone ultrafiltration membranes and fouling by BSA solutions, J. Membr. Sci. 133 (1997) 57-72.
[58] Y.S. Park, J. Won, Y.S. Kang, Preparation of poly (ethylene glycol) brushes on polysulfone membranes for olefin/paraffin separation, Langmuir 16 (2000) 9662-9665.
[59] M. Zhang, T. Desai, M. Ferrari, Proteins and cells on PEG immobilized silicon surfaces, Biomaterials 19 (1998) 953-960.
[60] A. Higuchi, K. Sugiyama, B.O. Yoon, M. Sakurai, M. Hara, M. Sumita, S.-I. Sugawara, T. Shirai, Serum protein adsorption and platelet adhesion on pluronic™-adsorbed polysulfone membranes, Biomaterials 24 (2003) 3235-3245.
[61] T. Xiang, Y. Xie, R. Wang, M.-B. Wu, S.-D. Sun, C.-S. Zhao, Facile chemical modification of polysulfone membrane with improved hydrophilicity and blood compatibility, Mater. Lett. 137 (2014) 192-195.
[62] A. Higuchi, K. Shirano, M. Harashima, B.O. Yoon, M. Hara, M. Hattori, K. Imamura, Chemically modified polysulfone hollow fibers with vinylpyrrolidone having improved blood compatibility, Biomaterials 23 (2002) 2659-2666.
[63] A. Higuchi, N. Iwata, T. Nakagawa, Surface-modified polysulfone hollow fibers. II. Fibers having $CH_2CH_2CH_2SO_3$– segments and immersed in HCI solution, J. Appl. Polym. Sci. 40 (1990) 709-717.
[64] A. Higuchi, T. Nakagawa, Surface modified polysulfone hollow fibers. III. Fibers having a hydroxide group, J. Appl. Polym. Sci. 41 (1990) 1973-1979.
[65] A. Higuchi, H. Koga, T. Nakagawa, Surface-modified polysulfone hollow fibers. IV. Chloromethylated fibers and their derivatives, J. Appl. Polym. Sci. 46 (1992) 449-457.
[66] T. Miyata, N. Asami, T. Uragami, A reversibly antigen-responsive hydrogel, Nature 399 (1999) 766-769.
[67] C. Xu, S. Gu, J. Huang, W. Xu, H. Xia, J. Du, H. Liu, H. Yang, Y. Zhou, Z. Bai, Modification of polysulfones by click chemistry: Zwitterionic graft complex and their antiprotein fouling property, J. Appl. Polym. Sci. 132 (2015) DOI: 10.1002/app.41327.
[68] D. Bonnefont-Rousselot, E. Lehmann, M. C. Jaudon, J. Delattre, B. Perrone, J.P. Rechke, Blood oxidative stress and lipoprotein oxidizability in haemodialysis patients: effect of the use of a vitamin E-coated dialysis membrane, Nephrol. Dial. Transplant. 15 (2000) 2020-2028.
[69] M. Satoh, Y. Yamasaki, Y. Nagake, J. Kasahara, M. Hashimoto, N. Nakanishi, H. Makino, Oxidative stress is reduced by the long-term use of vitamin E-coated dialysis filters, Kidney Int. 59 (2001) 1943-1950.
[70] M. Piroddi, F. Pilolli, M. Aritomi, F. Galli, Vitamin E as a functional and biocompatibility modifier of synthetic hemodialyzer membranes: an overview of the literature on vitamin E-modified hemodialyzer membranes, Am. J. Nephrol. 35 (2012) 559-572.
[71] A.-S. Bargnoux, J.-P. Cristol, I. Jaussent, L. Chalabi, P. Bories, J.-J. Dion, P. Henri, M. Delage, A.-M. Dupuy, S. Badiou, Vitamin E-coated polysulfone membrane improved red blood cell antioxidant status in hemodialysis patients, J. Nephrol. 26 (2013) 556-563.
[72] V. Panichi, A. Rosati, S. Paoletti, P. Ferrandello, M. Migliori, S. Beati, G. Bernabini, R. Daini, A. Casani, D. Angelini, A vitamin E-coated polysulfone membrane reduces serum levels of inflammatory markers and resistance to erythropoietin-stimulating agents in hemodialysis patients: results of a randomized cross-over multicenter trial, Blood Purif. 32 (2011) 7-14.
[73] G. Kolb, C. Nolting, I. Eckle, T. Müller, H. Lange, K. Havemann, The role of membrane contact in hemodialysis-induced granulocyte activation, Nephron 57 (1991) 64-68.
[74] J.S. Tayeb, R. Provenzano, M. El-Ghoroury, K. Bellovich, Q. Khairullah, D. Pieper, L. Morrison, Y. Calleja, Effect of biocompatibility of hemodialysis membranes on serum albumin levels, Am. J. Kidney Dis. 35 (2000) 606-610.
[75] M. Aritomi, F. Galli, Review of the effectiveness of cellulose–and polysulfone-based vitamin E-bonded dialysis membranes, Hemodialysis. InTech, Open Access Publisher, 2011.
[76] G.J. Dahe, R.S. Teotia, S.S. Kadam, J.R. Bellare, The biocompatibility and separation performance of antioxidative polysulfone/vitamin E TPGS composite hollow fiber membranes, Biomaterials 32 (2011) 352-365.
[77] F.Y. Mahlicli, S.A. Altinkaya, Immobilization of alpha lipoic acid onto polysulfone membranes to suppress hemodialysis induced oxidative stress, J. Membr. Sci. 449 (2014) 27-37.
[78] T. Carroll, N. Booker, J. Meier-Haack, Polyelectrolyte-grafted microfiltration membranes to control fouling by natural organic matter in drinking water, J. Membr. Sci. 203 (2002) 3-13.
[79] A. Reddy, D.J. Mohan, A. Bhattacharya, V. Shah, P. Ghosh, Surface modification of ultrafiltration membranes by preadsorption of a negatively charged polymer: I. Permeation of water soluble polymers and inorganic salt solutions and fouling resistance properties, J. Membr. Sci. 214 (2003) 211-221.
[80] F.-C. Kung, M.-C. Yang, The effect of covalently bonded conjugated linoleic acid on the reduction of oxidative stress and blood coagulation for polysulfone hemodialyzer membrane, Int. J. Biol. Macromol. 38 (2006) 157-164.
[81] J.M. Goddard, J. Hotchkiss, Polymer surface modification for the attachment of bioactive compounds, Prog. Polym. Sci. 32 (2007) 698-725.
[82] G. Poźniak, B. Krajewska, W. Trochimczuk, Urease immobilized on modified polysulphone membrane: Preparation and properties, Biomaterials 16 (1995) 129-134.
[83] C.-C. Lin, M.-C. Yang, Urea permeation and hydrolysis through hollow fiber dialyzer immobilized with urease: storage and operation properties, Biomaterials 24 (2003) 1989-1994.
[84] C. Zhao, X. Liu, S. Rikimaru, M. Nomizu, N. Nishi, Surface characterization of polysulfone membranes modified by DNA immobilization, J. Membr. Sci. 214 (2003) 179-189.
[85] X.J. Huang, D. Guduru, Z.K. Xu, J. Vienken, T. Groth, Blood compatibility and permeability of heparin-modified polysulfone as potential membrane for simultaneous hemodialysis and LDL removal, Macromol. Biosci. 11 (2011) 131-140.
[86] X. Ren, L. Xu, J. Xu, P. Zhu, L. Zuo, S. Wei, Immobilized heparin and its anti-coagulation effect on polysulfone membrane surface, J. Biomat. Sci. Polym. E. 24 (2013) 1707-1720.
[87] J. Li, X.J. Huang, J. Ji, P. Lan, J. Vienken, T. Groth, Z.K. Xu, Covalent heparin modification of a polysulfone flat sheet membrane for selective removal of low-density lipoproteins: A simple and versatile method, Macromol. Biosci. 11 (2011) 1218-1226.
[88] S. Gore, J. Andersson, R. Biran, C. Underwood, J. Riesenfeld, Heparin surfaces: Impact of immobilization chemistry on hemocompatibility and protein adsorption, J. Biomed. Mater. Res. Part B Appl. Biomater. 102 (2014) 1817-1824.
[89] J. Jin, W. Jiang, Q. Shi, J. Zhao, J. Yin, P. Stagnaro, Fabrication of PP-g-PEGMA-g-heparin and its hemocompatibility: From protein adsorption to anticoagulant tendency, Appl. Surf. Sci. 258 (2012) 5841-5849.
[90] M. Kessler, C. Gangemi, A. Gutierrez Martones, J.-L. Lacombe, M.-J. Krier-Coudert, R. Galland, J.T. Kielstein, F. Moureau, N. Loughraieb, Heparin-grafted dialysis membrane allows minimal systemic anticoagulation in regular hemodialysis patients: A prospective proof-of-concept study, Hemodial. Int. 17 (2013) 282-293.
[91] R. Deppisch, M. Storr, R. Buck, H. Göhl, Blood material interactions at the surfaces of membranes in medical applications, Sep. Purif. Technol. 14 (1998) 241-254.
[92] N. Hoenich, S. Stamp, Clinical investigation of the role of membrane structure on blood contact and solute transport characteristics of a cellulose membrane, Biomaterials 21 (2000) 317-324.
[93] H.T. Spijker, R. Graaff, P.W. Boonstra, H.J. Busscher, W. van Oeveren, On the influence of flow conditions and wettability on blood material interactions, Biomaterials, 24 (2003) 4717-4727.
[94] J.M. Anderson, Biological responses to materials, Annu. Rev. Mater. Res. 31 (2001) 81-110.
[95] H. Chen, L. Yuan, W. Song, Z. Wu, D. Li, Biocompatible polymer materials: Role of protein–surface interactions, Prog. Polym. Sci. 33 (2008) 1059-1087.
[96] P. Warkentin, B. Wälivaara, I. Lundström, P. Tengvall, Differential surface binding of albumin, immunoglobulin G and fibrinogen, Biomaterials 15 (1994) 786-795.
[97] F. Poncin-Epaillard, T. Vrlinic, D. Debarnot, M. Mozetic, A. Coudreuse, G. Legeay, B. El Moualij, W. Zorzi, Surface treatment of polymeric materials controlling the adhesion of biomolecules, J. Func. Biomater. 3 (2012) 528-543.
[98] M.C. Yang, W.C. Lin, Protein adsorption and platelet adhesion of polysulfone membrane immobilized with chitosan and heparin conjugate, Polym. Adv. Technol. 14 (2003) 103-113.
[99] F.-C. Kung, M.-C. Yang, Effect of conjugated linoleic acid immobilization on the hemocompatibility of cellulose acetate membrane, Colloid. Surf. B Biointer. 47 (2006) 36-42.
[100] F. Ziai, T. Benesch, K. Kodras, I. Neumann, L. Dimopoulos-Xicki, M. Haas, The effect of oral anticoagulation on clotting during hemodialysis, Kidney Int. 68 (2005) 862-866.
[101] W.-C. Lin, T.-Y. Liu and M.-C. Yang, Hemocompatibility of polyacrylonitrile dialysis membrane immobilized with chitosan and heparin conjugate, Biomaterials 25 (2004) 1947-1957.
[102] R. Hofbauer, D. Moser, M. Frass, R. Oberbauer, A.D. Kaye, O. Wagner, S. Kapiotis, W. Druml, Effect of anticoagulation on blood membrane interactions during hemodialysis, Kidney Int. 56 (1999) 1578-1583.
[103] J. Chanard, S. Lavaud, C. Randoux, P. Rieu, New insights in dialysis membrane biocompatibility: relevance of adsorption properties and heparin binding, Nephrol. Dial. Transplant. 18 (2003) 252-257.
[104] M. Hayama, K.-I. Yamamoto, F. Kohori, K. Sakai, How polysulfone dialysis membranes containing polyvinylpyrrolidone achieve excellent biocompatibility?, J. Membr. Sci. 234 (2004) 41-49.
[105] A. Ficheux, P.G. Kerr, P. Brunet, À. Argilés, The ultrafiltration coefficient of a dialyser (KUF) is not a fixed value, and it follows a parabolic function: the new concept of KUF max, Nephrol. Dial. Transplant. 26 (2011) 636-640.
[106] G. Belfort, R. Davis, A. Zydney, M. Cheryan, L. Zeman, Dialysis in medical separations, Academic Press, 2000.
[107] K. Opatrný, T. Reischig, J. Vienken, J. Eiselt, L. Vít, S. Opatrná, F. Šefrna, J. Racek, G.S. Brown, Does treatment modality have an impact on anemia in patients with chronic renal failure? Effect of low-and high-flux biocompatible dialysis, Artif. Organs 26 (2002) 181-188.
[108] A.A. House, G.A. Wells, J.G. Donnelly, S.P. Nadler, P.C. Hébert, Randomized trial of high-flux vs low-flux haemodialysis: effects on homocysteine and lipids, Nephrol. Dial. Transplant. 15 (2000) 1029-1034.
[109] P.-L. Chu, Y.-L. Chiu, J.-W. Lin, S. Chen, K.-D. Wu, Effects of low-and high-flux dialyzers on oxidative stress and insulin resistance, Blood Purif. 26 (2008) 213-220.
[110] M. Traut, C.C. Haufe, U. Eismann, R.M. Deppisch, G. Stein, G. Wolf, Increased binding of beta-2-microglobulin to blood cells in dialysis patients treated with high-flux dialyzers compared with low-flux membranes contributed to reduced beta-2-microglobulin concentrations, Blood Purif. 25 (2007) 432-440.
[111] H.F. Woods, M. Nandakumar, Improved outcome for haemodialysis patients treated with high-flux membranes, Nephrol. Dial. Transplant. 15 (2000) 36-42.
[112] C. Küchle, H. Fricke, E. Held, H. Schiffl, High-flux hemodialysis postpones clinical manifestation of dialysis-related amyloidosis, Am. J. Nephrol. 16 (1996) 484-488.
[113] J. Wong, E. Vilar, K. Farrington. Endotoxemia in end-stage kidney disease. in Seminars in Dialysis 28 (2015) 59-67.
[114] F. Locatelli, A. Martin-Malo, T. Hannedouche, A. Loureiro, M. Papadimitriou, V. Wizemann, S.H. Jacobson, S. Czekalski, C. Ronco, R. Vanholder, Effect of membrane permeability on survival of hemodialysis patients, J. Am. Soc. Nephrol.

20 (2009) 645-654.
[115] H. Woods, M. Nandakumar, Improved outcome for haemodialysis patients treated with high-flux membranes, Nephrol. Dial. Transplant. 15 (2000) 36-42.
[116] F. Locatelli, C. Manzoni, S. Di Filippo, The importance of convective transport, Kidney Int. 61 (2002) S115-S120.
[117] J. Cerdá, C. Ronco. The clinical application of CRRT-current status: modalities of continuous renal replacement therapy: technical and clinical considerations. in Seminars in Dialysis 22 (2009) 114-122.
[118] D.H. Krieter, B. Canaud, High permeability of dialysis membranes: what is the limit of albumin loss?, Nephrol. Dial. Transplant. 18 (2003) 651-654.
[119] X. Hu, Z. Deng, Y. Wang, Y. Yin, Study on the interaction between bovine serum albumin and terbium complex containing polymer, Soft Mater. 12 (2014) 277-283.
[120] N. Seedher, Mechanism of interaction of some antimicrobial agents with bovine serum albumin, J. Glob. Pharma Technol. 2 (2010) 975-8542.
[121] N.N. Li, A.G. Fane, W.S. Winston Ho, T. Matsuura, Advanced membrane technology and applications, John Wiley & Sons, Ltd, 2011.
[122] L.J. Langsdorf, A.L. Zydney, Diffusive and convective solute transport through hemodialysis membranes: A hydrodynamic analysis, J. Biomed. Mater. Res. 28 (1994) 573-582.
[123] A. Pierratos, New approaches to hemodialysis, Annu. Rev. Med. 55 (2004) 179-189.
[124] W.R. Clark, R.J. Hamburger, M.J. Lysaght, Effect of membrane composition and structure on solute removal and biocompatibility in hemodialysis, Kidney Int. 56 (1999) 2005-2015.
[125] C. Colton, L. Henderson, C.A. Ford, M. Lysaght, Kinetics of hemodiafiltration. I. In vitro transport characteristics of a hollow-fiber blood ultrafilter, J. Lab. Clinic. Med. 85 (1975) 355-371.
[126] I. Ledebo, Principles and practice of hemofiltration and hemodiafiltration, Artif. Organs 22 (1998) 20-25.
[127] A. Alayoud, M. Benyahia, D. Montassir, A. Hamzi, Y. Zajjari, A. Bahadi, D. El Kabbaj, O. Maoujoud, T. Aatif, K. Hassani, A model to predict optimal dialysate flow, Ther. Apher. Dial. 16 (2012) 152-158.
[128] O. Marsenic, L. Zhang, A. Zuppa, J.S. Barrett, M. Pfister, Application of individualized Bayesian urea kinetic modeling to pediatric hemodialysis, ASAIO J. 56 (2010) 246-253.
[129] A.T. Azar, A novel system for haemodialysis efficiency monitoring, Int. J. Healthcare Technol. Manage. 12 (2011) 132-167.
[130] J.T. Daugirdas, T.A. Depner, T. Greene, N.W. Levin, G.M. Chertow, M.V. Rocco, Standard Kt/Vurea: a method of calculation that includes effects of fluid removal and residual kidney clearance, Kidney Int. 77 (2010) 637-644.
[131] J.E. Flythe, G.C. Curhan, S.M. Brunelli, Shorter length dialysis sessions are associated with increased mortality, independent of body weight, Kidney Int. 83 (2012) 104-113.
[132] C. Shaw, R. Steenkamp, A. Davenport, UK renal registry 16th annual report: chapter 9 adequacy of haemodialysis in UK adult patients in 2012: National and centre-specific analyses, Nephr. Clin. Prac. 125 (2014) 171-181.
[133] H. Adas, N.J. Rowa'Al-Ramahi, R. Badran, Renal data from the arab world, Saudi J. Kidney Dis. Transpl.25 (2014) 438-442.
[134] N. Dunne, M. Campbell, M. Fitzpatrick, P. Callery, Comparison of Kt/V and urea reduction ratio in measuring dialysis adequacy in paediatric haemodialysis in England, J. Renal Care 40 (2014) 117-124.
[135] S.M. Morti, A.L. Zydney, Protein-membrane interactions during hemodialysis: effects on solute transport, ASAIO J. 44 (1998) 319-326.
[136] S. Lerouge, Introduction to sterilization: definitions and challenges, in: S. Lerouge, A. Simmons (Eds.), Sterilisation of biomaterials and medical devices, Woodhead Publishing Series in Biomaterials, 2012, pp. 1-19.
[137] A.C. Yamashita, R. Fujita, N. Hosoi, Effect of sterilization on solute transport performances of super high-flux dialyzers, Hemodial. Int. 16 (2012) S10-S14.
[138] A. Simmons, 11- Future trends for the sterilisation of biomaterials and medical devices, in: S. Lerouge, A. Simmons (Eds.), Sterilisation of biomaterials and medical devices, Woodhead Publishing Series in Biomaterials, 2012, pp. 310-320.
[139] G. Nechifor, S.I. Voicu, A.C. Nechifor, S. Garea, Nanostructured hybrid membrane polysulfone-carbon nanotubes for hemodialysis, Desalination 241 (2009) 342-348.
[140] A. Erlenkötter, P. Endres, B. Nederlof, C. Hornig, J. Vienken, Score model for the evaluation of dialysis membrane hemocompatibility, Artif. Organs 32 (2008) 962-969.
[141] B. Madsen, D.W. Britt, F. Griffiths, E. McKenna, C.H. Ho, Effect of sterilization techniques on the physicochemical properties of polysulfone hollow fibers, J. Appl. Polym. Sci. 119 (2011) 3429-3436.
[142] A.P. Broek, H.A. Teunis, D. Bargeman, E.D. Sprengers, C.A. Smolders, Characterization of hollow fiber hemodialysis membranes: pore size distribution and performance, J. Membr. Sci. 73 (1992) 143-152.
[143] C.P. Marshall, F.C. Pearson, M.A. Sagona, W. Lee, R.L. Wathen, R.A. Ward, J. Dolovich, Reactions during hemodialysis caused by allergy to ethylene oxide gas sterilization, J. Allergy Clin. Immunol. 75 (1985) 563-567.
[144] S. Lerouge, A. Simmons, Sterilisation of biomaterials and medical devices, Elsevier, 2012.
[145] G.C. Mendes, T. R. Brandao, C.L. Silva, Ethylene oxide sterilization of medical devices: a review, Am. J. Infect. Control 35 (2007) 574-581.
[146] L.A. Feldman, H.K. Hui, Compatibility of medical devices and materials with low-temperature hydrogen peroxide gas plasma, Med. Device Diagn. Ind. 19 (1997) 57-63.
[147] C. Ronco, G. La Greca, Hemodialysis technology, Vol. 137, Karger Medical and Scientific Publishers, 2002.
[148] S. Takesawa, S. Ohmi, Y. Konno, M. Sekiguchi, S. Shitaokoshi, T. Takahashi, H. Hidai, K. Sakai, Varying methods of sterilisation, and their effects on the structure and permeability of dialysis membranes, Nephrol. Dial. Transplant. 1 (1987) 254-257.
[149] D. TX Market Research Company and Consulting Firm. Dialysis market. Available from: www.marketsandmarkets.com/Market-Reports/dialysis-market-1279.html.
[150] F.M. Care, Outlook business. 2012, Available from: reports.fmc-ag.com/reports/fmc/annual/2012/gb/English/5060/outlook.html.
[151] F.M. Care, Annual report 2012, 2012, Available from: reports.fmc-ag.com/reports/fmc/annual/2012/gb/English/5060/outlook.html.
[152] F.M. Care, Annual report 2010, 2010, Available from: www.fmc-ag.com/files/GB2010_en.pdf.
[153] F.M. Care, Annual report 2011, 2011, Available from: www.fresenius.com/documents/F_GB11_2011_e_Internet.pdf.
[154] F.M. Care. Annual report 2013, 2013, Available from: www.fresenius.com/documents/F_GB13_Gesamt_PDF_e.pdf.
[155] L. Asahi Kasei Medical Co. Dialysis Membrane, Available from: www.asahi-kasei.co.jp/medical/en/dialysis/.
[156] L. Toray Medical Co. Toray Hemodialyzers, Available from: www.toray-medical.com/en/medical/ketsueki_t/index.html.
[157] D.H. Krieter, H.D. Lemke, C. Wanner, A new synthetic dialyzer with advanced permselectivity for enhanced low-molecular weight protein removal, Artif. Organs 32 (2008) 547-554.
[158] D.H. Krieter, A. Morgenroth, A. Barasinski, H.-D. Lemke, O. Schuster, B. von Harten, C. Wanner, Effects of a polyelectrolyte additive on the selective dialysis membrane permeability for low-molecular-weight proteins, Nephrol. Dial. Transplant. 22 (2007) 491-499.
[159] D. K. H.-D. Lemkeb, Polyethersulfone as a high-performance membrane, High-Performance Membrane Dialyzers, 173 (2011) 130-136.
[160] L. Toray Medical Co. Hollow Fiber Dialyzer - Toraysulfone TS-S/Y Series, 2015, Available from: www.toray-medical.com/en/medical/ketsueki_t/pdf/TS.pdf.
[161] A.K. Medical, APS Hemodialyzer, Available from: http://www.asahi-kasei.co.jp/medical/en/dialysis/product/aps/spec.html
[162] D.H. Krieter, A. Hackl, A. Rodriguez, L. Chenine, H.L. Moragues, H.-D. Lemke, C. Wanner, B. Canaud, Protein-bound uraemic toxin removal in haemodialysis and post-dilution haemodiafiltration, Nephrol. Dial. Transplant. 25 (2010) 212-218.