PREPARATION AND CHARACTERISATION OF BIOCOMPATIBLE POLYETHERSULFONE-BASED HOLLOW FIBRE MEMBRANE FOR HAEMODIALYSIS APPLICATION

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Specially for my mom and dad
and for the ummah

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"We act as though comfort and luxury were the chief requirements of life, when all that we need to make us happy is something to be enthusiastic about." Albert Einstein

ABSTRACT

In Malaysia, the number of dialysis patient keeps increasing every year with an estimation of 5,000 new cases of end-stage kidney failure (ESRD) each year. Thus, the development of an efficient haemodialyser is crucial to meet this demand. The objective of this research is to develop a biocompatible asymmetric, ultrafiltration hollow fibre membrane (HFM) for haemodialysis application. Polyethersulfone (PES) was chosen as the main polymer in the fabrication of the haemodialysis HFM due to its outstanding oxidative, thermal and hydrolytic stability as well as good mechanical and film-forming properties. Polyurethane (PU) heparin like structure (range of 0-5wt%) was used as additive in the PES HFM to improve blood compatibility of PES HFM. The HFM of blended PES/PU was fabricated using a dry/wet inversion phase spinning technique and its properties was characterised using a number of physico-chemical analyses and in-vitro blood compatibility tests. For the physico-chemical analyses, each of the membrane fabricated showed the desired asymmetry structure, dense area in the inner surface near the lumen and finger-like structure near the end of the outer membrane. The pore size of the membrane is in good agreement with the morphology and the surface roughness of the membrane. A high amount of PU in the membrane resulted in more porous finger-like pore structure, smoother surface, higher hydrophilicity and higher pore size. Based on the in-vitro biocompatibility analysis of the membrane, it is proposed that the membrane incorporated with PU has better anticoagulant properties compared to the control sample. PU incorporation prolonged the clotting time, decreased the formation of thrombin, decreased soluble C3a generation and suppressed platelet adhesion and aggregation. The anionic groups on the membrane surface might bind to coagulation factors (antithrombin) and thus improve anticoagulant ability. Based on both physico-chemical and in-vitro results, 4% loading of PU is the optimum loading for incorporation with PES HFM. The results suggested that the blended PES-PU membranes with good haemocompatibility should be applied in the field of blood purification during haemodialysis process.

ABSTRAK

Di Malaysia, bilangan pesakit yang mengalami kegagalan buah pinggang peringkat akhir (ESRD) semakin meningkat dengan anggaran 5000 pesakit yang didiagnosis positif ESRD setiap tahun. Justeru, pembangunan membran dialisis yang efisien adalah sangat kritikal untuk menampung permintaan ini. Objektif kajian ini adalah untuk membangunkan membran gentian geronggang tidak simetri kultra turasan untuk aplikasi hemodialisis. Polietersulfon (PES) telah dipilih untuk menjadi bahan polimer yang utama dalam pembentukan membran hemodialisis kerana mempunyai ciri oksidatif yang unggul, haba dan hidrolitik yang stabil serta mempunyai ciri mekanikal yang baik dan mampu menghasilkan lapisan nipis. Poliuritan (PU) yang mempunyai ciri-ciri seperti heparin akan disintesis dalam lingkungan 0-5wt% telah digunakan sebagai bahan tambahan dalam PES HFM untuk meningkatkan keserasian darah PES HFM Membran gentian geronggang PES/PU telah dihasilkan melalui proses pembentukan kaedah pemintalan kering/basah dan sifat-sifatnya dicirikan dengan menggunakan beberapa analisis fiziko-kimia dan in-vitro ujian keserasian darah. Bagi analisis fiziko-kimia, setiap membran yang terhasil menunjukkan ciri-ciri yang dikehendaki iaitu, struktur tidak simetri, kawasan padat di permukaan yang berdekatan lumen dan struktur jejari di bahagian luar membran. Saiz liang membran juga sekata dengan morfologi dan permukaan kasar membran. Kandungan PU yang lebih tinggi di dalam membran menghasilkan struktur membran yang mempunyai lebih banyak liang, permukaan yang lebih licin dan lebih hidrofilik dan saiz liang yang lebih besar. Berdasarkan keputusan dari keserasian membran dengan darah secara in-vitro, membran yang telah diubahsuai dengan PU mempunyai ciri-ciri penggumpalan yang lebih baik berbanding dengan sampel kawalan. PU ini juga mempunyai masa pembekuan yang lebih lama, mengurangkan pembentukan trombin, mengurangkan generasi C3a, dan menghalang lekatan platelet. Kumpulan anionik di permukaan membran mungkin mengikat kepada faktor-faktor pembekuan (antithrombin) dan dengan itu meningkatkan keupayaan antikoagulan. Berdasarkan keputusan fiziko-kimia dan keserasian membran dengan darah secara in-vitro, 4wt% kandungan PU yang dicampurkan dengan PES adalah campuran yang paling ideal. Dapatan kajian menunjukkan bahawa campuran membran PES-PU dengan *haemocompatibility* mempunyai sifat keserasian yang baik dan seterusnya membenarkan permohonan praktikal dalam bidang pembersihan darah semasa proses hemodialisis.

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LIST OF SYMBOLS

γ	-	Gamma
δt	-	Solubility coefficient ($MPa^{1/2}$)
Δx	-	thickness selectivity of the membrane (µm)
L	-	thickness of the support layer (µm)
K_{uf}	-	ultrafiltration coefficient of the membrane (mL/h/mmHg)
K_d	-	Dialyser clearance (mL/min)
M_w	-	Molecular weight (g/mol)
T_g	-	Glassy temperature (°C)
C	-	Carbon
H	-	Hydrogen
N	-	Nitrogen
O	-	Oxygen
R	-	Extrusion ratio
A_o	-	Initial cross-sectional area of the spinneret
A_f	-	final cross-sectional area of the spinneret
V	-	volume of permeation (L)

A	-	total area of the hollow fibres (m^2)
t	-	time taken (h).
C_P	-	permeate concentrations (wt%)
C_F	-	feed concentrations (wt%)
R_a	-	mean surface roughness
DER	-	Dope extrusion rate (cm^3/min)
BFFR	-	Bore fluid flow rate (cm^3/min)
LER	-	Linear extrusion rate (cm^3/min)
CD	-	Collection drum (Hz)
$CaCl_2$	-	Calcium chloride
C3a	-	Complement 3a
C5a	-	Complement 5a
C5b-9	-	Complement 5b, 6, 7, 8, 9 (complement membrane attack complex)

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CHAPTER 1

INTRODUCTION

1.1 Research Background

In recent years, there has been a crucial rise of kidney failure notably chronic kidney disease (CKD) caused by disease or condition impairs kidney function, causing kidney damage to worsen over several months or years as reported by National Kidney Foundation Malaysia (Yam et al., 2016). The recent statistic from National Kidney Foundation Malaysia reveals worrying figures where the total number of haemodialysis patients increases from 12,182 patients in year 2005 to 31,497 patients in year 2014 (Table 1.1). Renal patients need to undergo this treatment for 3 to 4 hours at least three times a week (Hakim et al., 2016). This treatment could be burden in term of finance especially to the people from middle class and poor background. Resulting in the urge to search for better and more efficient and low cost ultrafiltration system.

Table 1.1 Stock and flow of renal replacement therapy in Malaysia from year 2005-2014 (Yam et al., 2016)

Year	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
New dialysis patients	3,167	3,709	4,103	4,640	4,952	5,305	6,073	6,690	6,985	7,055
New transplants	172	151	112	131	141	128	127	107	98	81
Dialysis deaths	1,515	1,820	1,987	2,191	2,601	3,047	3,292	3,645	4,001	4,015
Transplant deaths	49	58	47	59	49	48	55	64	56	45
Dialysing at 31st December	13,356	15,080	17,084	19,388	21,590	23,709	26,328	29,223	32,026	34,767
Functioning transplant at 31st December	1,716	1,771	1,788	1,808	1,852	1,881	1,907	1,891	1,870	1,844

Haemodialysis is one of the prominent treatments for chronic kidney disease (CKD) and end stage renal disease (ESRD). Haemodialysis helps to filtrate out low and middle molecular weight uremic toxins from the blood and helps to balance the pH value in the body. Barzin et al. (2004) stated that uremic toxins such as urea and creatinine range from size 10,000-55,000 Da needs to be excreted out from the blood, while, proteins such as albumin (66,000 Da) need to be retained. In order for these secretion and retention to be worked, the design of the membrane needs to fulfil certain criteria. The membrane produced is preferred to be high flux, asymmetric, micro porous ultrafiltration hollow fibre membrane.

One of the most important components in blood purification application that need to be considered thoroughly is the membrane of the haemodialysis. The membrane of the haemodialysis is potted inside a module and is known as haemodialyser, which is the heart of the haemodialysis system. The implementation of membrane technology in blood purification applications has proven vital. In hollow fibre ultrafiltration system, blood purification is achieved by regulating impure blood flow through the lumen of hollow fibre membrane as the dialysate flows counter-currently outside the lumen (Dahe et al., 2011). Uremic toxins like urea, creatinine etc. are filtered out from the blood through the porous structure of the membrane. The membrane facilitates the filtration without the loss of important blood proteins such as albumin (Dahe et al., 2011). Desirable characteristics of such hollow fibre membranes include high flux, selectivity and biocompatibility (Clark et al., 2002). However, clinical complications such as neutropenia, hypersensitivity reactions, oxidative stress, contact and complement activation, have repeatedly associated with the commercially available and widely used polysulfone haemodialysis membrane (Urbani et al., 2012). This causes the decrease in quality of life, life expectancy and mortality of haemodialysis patients and has limited the success rates of such membranes. Thus, the selection of membrane used for haemodialysis needs to be chosen wisely in order to prevent any bio-incompatibility due to the interaction between blood and the new haemodialysis membranes.

Functionalisation of polymer membranes has been studied as one of the methods to improve polymer properties. The surface of membranes has been modified

and grafted using several of functional groups like hydroxyl, ketone and carboxylic acid groups. The chemical bonding between substrates and adhesives is able to be improved by adding functional groups to the polymer. Through functionalisation method, properties such as hydrophilicity, hydrophobicity, biocompatibility, anti-fouling, and antibacterial properties etc. can be enhanced, while some of membrane native properties and its core structure are still remained (Dahe et al., 2011).

1.2 Problem Statement

Currently, polysulfone (PSf) and polyethersulfone (PES) are among the most available and commercial haemodialysis membranes that have been used as the main polymer in the fabrication of asymmetric hollow fibre haemodialysis membrane. However, these membranes have been associated with numerous of clinical complications which include hypersensitivity reactions, neutropenia, oxidative stress, and complement activation.

Hydrophobic property of PES membrane is the main disadvantage of this polymer. Many studies have concluded that the material hydrophobicity is the causes of membrane fouling. Membrane fouling happens when protein adsorbs on the surface of the membrane (Khulbe et al., 2010). However, Zhao et al. (2013) has been reported the opposite findings. He stated that the adsorption of nonpolar solutes, hydrophobic particles or bacteria is the cause of membrane fouling. Membrane fouling is a serious problem in membrane filtration, resulting in a higher energy demand, shorter membrane lifetime, and unpredictable separation performance (Agenson et al., 2007; Su et al, 2011). The most desirable property of a biomaterial is the biocompatibility of the material towards body. Biologically compatible means that in contact of foreign material with human body mechanism will not produce a toxic, injurious and immunological response in living tissues or blood (Dahe et al., 2011). The most commonly accepted mode of improving hollow fibre membranes biocompatibility is the modification of surface chemistry. Thus, in order to improve the hydrophilicity of

PES hollow fibre membrane used in haemodialysis, PES is modified by hydrophilic polymers.

Polyurethane (PU) has been reported to be used in blood-contacting application due to its excellent mechanical properties and relatively good blood compatibility (Agenson et al., 2007; Li et al, 2012). Meanwhile, PU, with a Hansen solubility coefficient δt = 20.5 $MPa^{1/2}$, showed good miscibility with PES (δt = 21.3 $MPa^{1/2}$), the miscibility has also been proved by using the cloud point measurements, and all of these showed similar results (Yin et al., 2014). The excellent miscibility ensured a homogeneous blend between the PU and the PES, and inhibited the macro phase separation. Therefore, the blending of PU would not affect the morphology and the surface roughness of the PES membrane significantly.

However, limited number of research works has been done on the grafting functional group or functional molecules to PU, such as hydroxyl group, carboxyl group, and sulphonic group. Therefore, in this study, PU polymerisation and sulphonation will be tested, which it is expected that the modified PU could minimise protein adsorption and prolong blood coagulation time. The aim of this study is to introduce hydroxyl, carboxyl and sulphonic groups onto the molecular chains of PU and to synthesize a polyurethane with good blood compatibility, which later on will be used for the modification of PES haemodialysis membrane. Positive result will not only give benefits to the university but also to the biomaterial field of research.

1.3 Research Objectives

The general aim of this proposed project is to fabricate a haemocompatible PES based hollow fibre membrane for haemodialysis. The specific objectives of this study are:

1) To synthesise and functionalise hydrophilic PU heparin like structure as biocompatible additive for haemodialysis membrane.
2) To fabricate and characterise physico-chemical properties of the asymmetric PES/PU hollow fibre membrane.
3) To study the blood compatibility of PES hollow fibre membrane that incorporated with modified PU in haemodialysis application.

1.4 Scopes of Study

In order to achieve the objective of this research, the following scopes are outlined: -

1) Modifying PU molecular structure by first synthesising it from methylene diphenyl diisocynate (MDI) and dimethylolpropionic acid (DMPA) at temperature 80°C for 6 hours and then functionalising it by sulphonating with concentrated H_2SO_4 for 16 hours.
2) Determining PU characterisation by analysing the attenuated total reflectance-fourier transform infrared (ATR-FTIR), nuclear matrix resonance (NMR) and matrix assisted laser desorption ionisation time of flight (MALDI-TOF) analysis.
3) Investigating suitable spinning conditions (air gap distance, dope extrusion rate, bore fluid flow rate and the take-up speed) to produce an asymmetric, micro porous ultrafiltration hollow fibre specifically for haemodialysis membrane.
4) Preparing a dope solution that, made of different loadings of PU (0-5%wt) in PES blended with polyvinylpyrrolidone (PVP) solution.

5) Fabricating polymeric hollow fibre membrane via dry/wet spinning technique using the preliminary identified spinning parameters (50 cm air gap, 3 cm^3/min of dope extrusion rate, and 1 cm^3/min bore fluid flow rate) and PVP as the pore modifier.
6) Observing the hollow fibre membrane morphology, membrane molecular orientation, membrane hydrophobicity/hydrophilicity, membrane porosity and thermal transition and stability using scanning electron microscopy (SEM), ATR-FTIR, contact angle measurement, zeta-potential and thermagravimetric analysis (TGA) test respectively.
7) Evaluating PES/PU membrane haemocompatibility by assessment in protein adsorption, platelet adhesion, thrombogenic properties, coagulation and complement activation.

1.4 Significant of the Study

Over the past 15 years, the figure of patients experiencing chronic kidney diseases has increased dramatically. Such kidney diseases render the incapable of kidney to filter and remove body waste from the bloodstream. The most widely accepted extracorporeal treatment used to filter and purify blood is haemodialysis. According to Malaysia's National Renal Registry, it has been reported that the total number of people underwent haemodialysis had risen from 6689 in 2000 to 21159 in 2009. The number did not stop there. The latest report dated March 2013 mentioned the increase of dialysis patients to 26159 people (Yam et al., 2016).

The main component of haemodialysis machine is the dialyser, where a semi-permeable membrane is used as the filter. As the paramount component for haemodialysis system, the development of membrane continues to attain the best of it. Due to bio-incompatibility and low performance of cellulose-based membranes, fully synthetic membrane was introduced and became favourable until very recent times. These synthetic membranes are made up of a variety of hydrophobic polymers as the main component to serve as hosts. The rationale and significance of this current

research are to explore the formation and development of modified PES hollow fibre membranes blended with hydrophilic addictive PU for haemodialysis application. Physicochemical properties of PU have been proven to be reliable blood compatible biomaterials. Thus the blending of PU with PES is expected to enhance the haemocompatibility of the fabricated membrane when contacting with blood.

In Malaysia, very few researches on haemodialysis membranes have been conducted. There is no large-scale initiative to utilise local expertise in membrane for haemodialysis application. Until now, Malaysia is still depending on imported dialysers for haemodialysis treatments in either government or private hospitals. The information constraint in this field is the main cause of this problem. The impact of this matter includes unnecessary expenditure due to high cost of dialysers. Therefore, this research's long-term target is to develop a locally made dialyser equipped with a highly efficient membrane in order to sustain current demand especially in Malaysia. Furthermore, this research study may lead to a new finding that can possibly be a basis for the next move in fabricating high performance haemodialysis membrane. Positive result can benefit to the membrane field of research especially in membrane technology for haemodialysis application.

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