PREPARATION, CHARACTERIZATION AND BIOCOMPATIBILTY EVALUATION OF POLY(DIOL CITRATE) BLEND POLYETHERSULFONE HEMODIALYSIS MEMBRANES

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To my beloved mother and father

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ABSTRACT

Hemodialysis is one of the applied membrane technologies that is regarded as a life-saving therapy for patients with impaired kidneys. It purifies blood toxins outside of the patient's body using a dialyzer as a kidney replacement. Synthetic materials such as polyethersulfone (PES) polymer are currently being used to fabricate the dialyzer membrane for hemodialysis. However, the blood compatibility or hemocompatibility of these materials are still inadequate and administration of an anticoagulant (heparin) is required throughout the dialysis procedure to avoid blood clotting. Therefore this study aimed at developing a biocompatibility membrane for hemodialysis application. In this study, poly (1,8-octanediol citrate) (POC) that synthesized through a simple polycondesation method was used to enhance membrane biocompatibility. Different compositions of POC (0-3%) were added into polyethersulfone (PES) dope solutions to fabricate modified biocompatible PES membranes via the phase-inversion technique. The biocompatibility of the modified PES membranes was evaluated by human serum fibrinogen (FBG) protein adsorption, platelet adhesion, activated partial thromboplastin time (APTT) and prothrombin time (PT), thrombin–antithrombin III (TAT), complement (C3a and C5a) activation and Ca^{2+} absorption on membrane. Results showed that higher POC wt.% caused a 31% reduction of FBG adsorption, less platelets adhesion, prolonged APTT (11.1 seconds) and PT (2.5 seconds), lower TAT activation, suppressed C5a and C3a activation and absorbed 35% more Ca^{2+} ion compared to pristine PES membrane. These results indicated that modified PES blended POC has good biocompatibility properties, suggesting potential application in the field of blood purification, especially in hemodialysis.

ABSTRAK

Hemodialisis merupakan antara aplikasi dalam teknologi membran yang dapat menyelamatkan nyawa pesakit yang mengalami masalah buah pinggang. Ia membersihkan toksin darah diluar badan pesakit menggunakan dialiser sebagai pengganti kepada buah pinggang. Bahan sintetik seperti polimer polietersulfon (PES) digunakan sebagai bahan utama untuk membuat membran dialiser untuk hemodialisis. Walau bagaimanapun, keserasian antara darah dan bahan sintetik ini masih tidak mencukupi dan anti-beku darah (heparin) diperlukan sepanjang prosedur dialisis untuk mengelakkan pembekuan darah berlaku. Objektif kajian ini adalah bertujuan untuk membangunkan satu membran bioserasi yang baru bagi digunakan dalam aplikasi hemodialisis. Dalam kajian ini, poli(1,8-octanediol citrate) (POC) yang disintesis melalui kaedah polikondensasi mudah telah digunakan untuk meningkatkan bioserasian dengan membran. Komposisi POC yang berbeza (0-3%) telah ditambah pada larutan polimer PES untuk membuat membran PES yang diubahsuai melalui teknik fasa penyongsangan. Keserasian-bio membran PES yang diubahsuai telah dinilai dengan penjerapan protein fibrinogen serum (FBG), kebolelekatan platelet, masa separa-aktif tromboplastin (APTT) dan masa prothrombin (PT), pengaktifan thrombin-antithrombin III (TAT), pengaktifan komplimen (C3a dan C5a) dan penyerapan Ca^{2+} ion pada membran. Hasil kajian menunjukkan bahawa dengan wt.% POC yang tinggi, telah mengurangkan 31% penjerapan FBG, mengurangkan platelet melekat, memanjangkan masa APTT (11.2 saat) dan PT (2.5 saat) lebih lama, pengaktifan TAT yang rendah, mengurangkan pengaktifan C5a dan C3a dan menyerap lebih 35% ion Ca^{2+} berbanding membrane asal. Dapatan kajian ini menunjukkan bahawa membran yang diubahsuai dengan campuran POC mempunyai kebioserasian yang lebih baik bagi menyediakan aplikasi membran yang lebih praktikal dalam bidang pembersihan darah, terutamanya bagi aplikasi hemodialisis.

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LIST OF SYMBOLS

γ	-	Gamma
α	-	Alpha
β	-	Beta
µm	-	micrometer
µL	-	microliter
Q_b	-	Blood flow rate
Q_d	-	Dialysate flow rate
IgG	-	Immunoglobulin G (antibody G)
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)
KoA	-	Clearance efficiency
M_w	-	Molecular weight (g/mol)/Da
Da	-	Dalton
C	-	Carbon
H	-	Hydrogen
N	-	Nitrogen
O	-	Oxygen
t	-	Time taken (h).

R_a	-	mean surface roughness
M_1	-	Dry membrane mass
M_2	-	Wet membrane mass
ε	-	Porosity
A	-	Effective membrane area
p	-	water density (998 kg/m3
μ	-	water viscosity at 25 ^{o}C (8.9×10^{-4} Pa.s)
ΔP	-	pressure (Pascal)
r_m	-	pore size radius
Q	-	flow rate of permeated water (m^3/s)
J	-	Water flux
V	-	volume of water permeated (L)
Δt	-	permeation time
Cp	-	Permeate concentration
Cf	-	Feed concentration
$CaCl_2$	-	Calcium chloride
C3a	-	Complement 3a
C5a	-	Complement 5a
CL	-	Clearance
C_i	-	initial concentration
C_s	-	sample concentration

LIST OF ABBREVIATION

PES	-	Polyethersulfone
POC	-	Poly(1,8-octane citrate)
CABE	-	Citric acid based elastomer
HD	-	Hemodialysis
HF	-	Hemofiltration
RRT	-	Renal replacement therapy
PSf	-	Polysulfone
PMMA	-	Poly(methyl methacrylate)
PAN	-	Polyacrylonitrile
ATR-FTIR	-	Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy
^{1}H NMR	-	Proton Nucleus Magnetic Resonance
MALDI-TOF	-	Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry
SEM	-	Scanning electron microscopy
TF	-	Tissue factor
vWF	-	von Willebrand factor
ACE	-	Angitensin converting enzyme
HIT	-	Heparin-induced thrombocytopenia
POC-HA	-	Poly (1,8-octanediol citrates)-hydroxyapatite
CUPE	-	Crosslinked urethane-doped polyester
TGA	-	Thermogravimetric analysis

BSA	-	Bovine serum albumin
FBG	-	Fibrinogen
APTT	-	Activated partial thromboplastin time
PT	-	Prothrombin time
TAT	-	Thombin anti-thrombin III
C3a	-	Complement 3a
C5a	-	Complement 5a
MAC	-	Membrane attack complex

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CHAPTER 1

INTRODUCTION

1.1 Background of Research

Since the breakthrough in 1978 by french cleric, J. Abbé Nollet, membrane technology was only being studied by scientist in 1960s for its commercialization in industrial application (Fane et al., 2011). In 1960s, Loeb and Sourirajan developed asymmetric membrane for industrial applications (Kołtuniewicz, 2005). Then in 1980s, techniques such as reverse osmosis, ultrafiltration, microfiltration and electrodialysis resulted in worldwide membrane commercialize applications in large scale plants (Baker, 2012; Fane et al., 2011). After years of rapid development of the membrane technology, the applications of membranes was used in the development of membranes for medical separation processes, in particular, the artificial kidney (hemodialysis) (Baker, 2012).

Kidney is a vital organ in human composed of millions unit of filter which remove excess waste products and fluid out of the body. This function is essential for normal homeostasis in maintaining body fluid and chemical composition inside the body. Damage to the kidney may lead to the reduction in its performance. Subsequently, the damage result in build-up of toxins and excess fluid that may affect health. A therapy called renal replacement therapy (RRT) or commonly known as hemodialysis is required to overcome the problem.

Hemodialysis is highly successful lifesaving and life sustaining therapy for renal failure patient (Vilar & Farrington, 2011). In 2012, there were 28,590 patients receiving dialysis in Malaysia, and vast majority (92%) of these patients are on

hemodialysis (Lim et al., 2013). According to Datuk Seri Dr. Hasan Abdul Rahman Malaysian Health director-general, every year a patient in average had to spend about RM 33,000.00 for dialysis treatment and more than RM 700 million for total dialysis patients (Arukesamy, 2011). However, 60% of the cost was government subsidized. Therefore, Malaysian government spent almost RM 420 million for dialysis operational cost only (include staff salaries, consumables e.g., dialyser reuse 3 times, blood lines, CAPD system and dialysate), equipment maintenance and utilities) which do not include associate medical cost (RM 270/patient), capital cost and general hospital cost (RM 360/patient) (Lim et al., 1999).

In general, the process of dialysis involve two way movement of molecules across a semipermeable membrane. Clinically, this movement takes place in and out of blood, across a semipermeable membrane. The blood is exposed to an artificial membrane outside of the body, the process is called hemodialysis (HD) or hemofiltration (HF) (Ahmad, 2009). The dialyzer made of dialysis membrane is the most critical and important part of dialysis set up form separate adjacent paths for blood and dialysate, which flow on opposite sides of the membrane in opposite directions to maximize diffusion gradients. According to Malaysian Hemodilaysis Quality and Standard (2012) published by Ministry of Health Malaysia a dialyzers should be made from biocompatible membrane and approved by regulatory authorities in USA, Europe, Japan or local equivalent.

In selecting the material for hemodialysis, benchmarks such as biocompatibility towards white blood cell and complement system, impermeability toward dialysate impurities, adsorption capacity and pore size must be considered (Boure, 2004). The success of hemodialysis is highly dependent on the membrane used (Gautham et al., 2013). The earlier type of material used in the making of dialysis membrane was the cellulose based membrane (e.g.; cuprophane). Later, due to certain undesired effect such as immunological reaction, the cellulose was substituted by other material like mixed-cellulosic synthetic membrane (e.g.; Hemophan). Currently, the synthetic membrane (e.g; polyethersulfone (PES), polysulfone (PS), polyacrylonitrile (PAN), polycarbonate, polymethylmethacrylate (PMMA), and polyamide) is the latest type of material commonly used to produce dialysis membrane (Ahmad, 2009). Moreover, aside from having better performance in removing middle molecule (500-

15000 Da) and β2-microglobulin, the synthetic membranes also comprise higher biocompatibility properties (Kerr & Huang, 2010; Macleod et al., 2005).

Here, in this study PES is used as a material to fabricate dialysis membrane. The PES membranes are widely employed in biomedical fields such as artificial organs and medical devices used for blood purification, e.g., hemodialysis, hemodiafiltration, hemofiltration, plasmapheresis and plasma collection (Su et al., 2011). In order to achieve the production of high biocompatibility dialysis membrane a citric acid derived biodegradable elastomers (CABEs) was added as additive. This new class of biomaterials is all synthesized with non-toxic monomers using simple and cost effective procedures. These materials share one common monomer named citric acid, which is a non-toxic metabolic product of the Krebs cycle. In addition to the sodium form of citric acid, sodium citrate, is an anticoagulant currently used in hospitals. Thus, CABEs may also possess suitable hemocompatibility for blood contacting applications (Tran et al., 2009).

A novel biodegradable elastomer, poly (1, 8-octanediol-co-citrate) (POC) is synthesized and used as biocompatible additives to produce biocompatible modified PES flat-sheet membranes. The fabricated membranes are characterized for its physical and chemical properties. The dialysis performance of the modified membrane also been evaluated. The biocompatibility of the modified membranes are analyzed by studying the membrane blood compatible properties.

1.2 Problem Statement

In blood-contacting membrane application such as hemodialysis, the protein adsorption on the membrane surface cause some serious problem to membrane performance. The adsorption of protein on membrane surface eventually lead to membrane fouling resulting in flux declining and reduction of membrane selectivity. Furthermore, the adsorbed proteins plugged membrane pores affecting efficacy, by decreasing the pore size of the membrane and prevent transmembrane crossing for waste and solutes. Membrane protein adsorption may be caused by few factors such

as the membrane surface chemistry, morphology, hydrophilicity and also the adsorbed protein size, charge, shape, pH value, and so on. Besides causing membrane fouling that affect membrane performance, adsorption of protein also leads to membrane biocompatibility problems (Sun et al., 2003).

Biocompatibility of the membrane is one of the important aspect in developing a membrane for hemodialysis. It is the biological reaction between dialysis membrane and the blood. Exposure of dialysis membrane to blood leads to normal physiological response of blood components such as activation of platelets, inflammatory response, complement blood cells, and complement cascade (Ahmad, 2009; Gawaz et al., 1999) which may cause adverse effect to the dialysis patient. Activation and adhesion of the platelet on the membrane surface cause coagulation of blood (Sperling et al., 2009). Therefore, to avoid coagulation an anticoagulant such as heparin is used in the dialysis system. Yet, the usage of heparin causes several complication to dialysis patient like heparin-induced thrombocytopenia (HIT) Type II and bleeding that might lead to severe morbidity and mortality (Suranyi & Chow, 2010). Therefore, effective membrane with higher biocompatibility to perform sufficient hemodialysis is an important key to cope with the rising demands from kidney failure patient.

1.3 Objectives of Study

Based on the problem statement, the aim of this study was to reduce the incidence of membrane compatible reaction and membrane fouling in the dialyzer. Therefore, this study sought to produce a new biocompatible synthetic polymer membrane to perform sufficient hemodialysis and to cope with the rising demands from kidney failure patient in Malaysia. The objectives of this research are:

1. To synthesize poly(1,8-octanediol citrate) (POC) as additive to improve PES membrane biocompatibility

2. To fabricate and characterize physical and chemical properties of the modified PES flat-sheet membrane with different POC wt.% loading (0-3%).

3. To evaluate the biocompatibility of the modified PES/POC flat-sheet membranes different POC wt.% loading (0-3%) for hemodialysis applications.

1.4 Scope of Study

1. Preparation of poly(1,8-octane citrate) (POC) via simple polycondensation method.
2. Characterization of the POC with Attenuated Total Reflectance-Fourier Transform Infrared Spectroscopy (ATR-FTIR), proton Nucleus Magnetic Resonance (^{1}H NMR), Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF).
3. Dope preparation for different wt.% loading (0-3%) concentration of POC blend PES membranes.
4. Fabrication of modified PES membranes via liquid-liquid phase inversion method.
5. Characterization of modified PES membranes by ATR-FTIR, scanning electron microscope (SEM), atomic-force microscopy (AFM), Thermogravimetric Analysis (TGA), zeta-potential, membrane wettability, membrane porosity and pore size.
6. Evaluation of the modified membranes' performance for pure water flux, solute rejection and uremic toxins clearance.
7. Evaluation of the modified membranes biocompatibility through protein adsorption, platelet adhesion, plasma coagulation time, calcium ion absorption and coagulation and complement activation.

1.5 Significance of Study

The number of dialysis patient in Malaysia is rapidly increasing each and every year. Data from 22nd Report of the Malaysian Dialysis 2015 and Transplant Registry by the National Renal Registry showed the number of dialysis patient in Malaysia was steeply increase for the last 10 years from 13000 in 2004 and at least 35000 people in 2015. Each year the amount of new dialysis patient increase with 6107 new people need dialysis in 2014 (Goh & Ong, 2015). Herein Malaysia, there are few researchers that currently doing research on dialysis membrane but not to be commercialize. None of them focuses on improving biocompatibility of hemodialysis membrane and only study on membrane performances. Nowadays, local dialysis center and hospital still use an imported dialyzer which can be costly. Therefore, this study aims to produce locally produced high performance biocompatible hemodialysis membrane which eventually can reduce current dialyzer cost in Malaysia.

Dialyzer or artificial kidney is the heart of the dialysis which contain a semi-permeable membrane that function as kidney replacement. Nowadays, synthetic polymer such as polyethersulfone (PES) is being used to make dialysis membrane due to excellent physical and chemical properties. However, the hydrophobic nature of the polymer tends to adsorb protein and cause membrane bio-incompatibility that lead to thrombosis. Several modification have been made to improve membrane biocompatibility with anti-coagulant properties, for example by using a heparin (anti-coagulant) to modified membrane through coating (AN69ST) or grafting it on membrane surface (Morena et al., 2010; Tang et al., 2012). These modified membrane allows heparin-free dialysis which can reduce adverse events from prolong usage of heparin such as heparin induced thrombocytopenia (HIT).

The significance of this current research is by studying the development of modified PES dialysis membranes that blended with POC to improve it biocompatibility. Previous study had found that POC exhibit a biocompatible properties for blood contacting application, hence modification of the PES dialysis membrane with POC can improve biocompatibility of membrane and prevent

thrombosis formation on membrane surface. Therefore, by using this PES blend POC dialysis membrane, an anticoagulant free dialysis can be perform.

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