

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

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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.

## TABLE OF CONTENTS

<b>CHAPTER</b>	<b>TITLE</b>	<b>PAGE</b>
	<b>DECLARATION</b>	ii
	<b>DEDICATION</b>	iii
	<b>ACKNOWLEDGEMENTS</b>	iv
	<b>ABSTRACT</b>	v
	<b>ABSTRAK</b>	vi
	<b>TABLE OF CONTENTS</b>	vii
	<b>LIST OF TABLES</b>	xiii
	<b>LIST OF FIGURES</b>	xvi
	<b>LIST OF SYMBOLS</b>	xxii
	<b>LIST OF APPENDICES</b>	xxiv
<b>1</b>	<b>INTRODUCTION</b>	<b>1</b>
	1.1 Research Background	1
	1.2 Problem Statement	3
	1.3 Research Objectives	5
	1.4 Scopes of Study	5
	1.5 Significant of the Study	6
<b>2</b>	<b>LITERATURE REVIEWS</b>	<b>8</b>
	2.1 Renal Failures	8
	2.2 Haemodialysis	10
	2.3 Haemodialyser	12
	2.4 Concept or Principle in Haemodialyser	13
	2.4.1 Blood Compartment	15
	2.4.2 Dialysate Compartment	16
	2.5 Chemical Structures of Dialysis Membrane	17

2.5.1	Main Material of the Membrane	18
2.5.2	Hydrophilic Agent/Addictive	19
2.6	Physical Structure of Dialysis Membrane	20
2.6.1	Homogeneous and Asymmetry Membrane	20
2.6.2	High Flux and Low Flux Membrane	22
2.7	Chemical Structures of Dialysis Membrane	24
2.7.1	Contact Phase System and Coagulation System Activation	26
2.7.2	Complement System Activation	27
2.7.3	Platelets Activation and Aggregation	28
2.8	Chemical Structures of Dialysis Membrane	29
2.8.1	Improvement of Biocompatibility of the Regenerated Cellulose Membrane	29
2.8.2	Improvement of Biocompatibility of the Synthetic Polymeric Membrane	31
2.9	Polyethersulfone (PES)	34
2.10	PES Modification to Improve Membrane Biocompatibility	35
2.11	Polyurethane	37
<b>3</b>	<b>RESEARCH METHODOLOGY</b>	<b>39</b>
3.1	Research Design	39
3.2	Polymer and Solvent Selection	41
3.3	Polymerisation and Sulphonation of PU	44
3.3.1	Monomers for PU synthesis	44
3.3.2	PU Synthesis and Polymerisation	46
3.3.3	Sulphonation of Polyurethane	48
3.4	Characterisation of PU	49
3.4.1	Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR)	49
3.4.2	Nuclear Matrix Resonance (NMR)	49



3.4.3	Matrix Assisted Laser Desorption Ionization Time of Flight (MALDI- TOF) Mass Spectrometry	49
3.5	Selection of Suitable Spinning Parameter for Hollow Fibre Membranes Fabrication	50
3.5.1	Hollow Fibre Membrane Fabrication	50
3.5.2	Hydrophilic/Hydrophobic Property Analysis	54
3.5.3	ATR-FTIR	54
3.5.4	Adsorption/Desorption Experiment	54
3.5.5	Pure Water Flux	55
3.5.6	Rejection of the Bovine Serum Albumin (BSA)	55
3.5.7	Scanning Electron Microscopy (SEM)	56
3.5.8	Atomic Force Microscopic (AFM) Observation	57
3.6	Preparation of PES Membrane Incorporation with PU	57
3.6.1	Hollow Fibre Membrane Fabrication	58
3.6.2	Flat-sheet Membrane Fabrication	59
3.7	Characterisation of Hollow Fibre Membranes	60
3.7.1	Thermogravimetric Analysis (TGA)	60
3.8	Characterisation of Flat-sheet Membranes	61
3.8.1	Zeta-potential	61
3.9	Membrane Haemocompatibility: Materials and Reagent Preparation	62
3.9.1	Materials	62
3.9.2	Reagent Preparation	64
3.9.2.1	Phosphate Buffered Saline (PBS) Solution	64
3.9.2.2	Sodium Dodecyl sulphate (SDS) Solution	64
3.9.2.3	Glutaraldehyde	64

3.9.2.4	C3a Standard Solution	64
3.9.2.6	Human TAT Complex Standard Solution	65
3.9.2.7	Bovine Serum Albumin (BSA) Standard Solution	66
3.9.2.8	Fibrinogen (FBG) Standard Solution	67
3.9.2.9	Micro BCA™ Protein Working Reagent (WR)	67
3.10	Haemocompatibility Analysis of the Membrane	68
3.10.1	Protein Adsorption	68
3.10.2	Clotting Time	69
3.10.3	Thrombogenic Properties	71
3.10.4	Complement Activation	72
3.10.5	Platelet Adhesion	73
<b>4</b>	<b>RESULTS AND DISCUSSIONS</b>	<b>75</b>
4.1	Characterisation of Synthesised PU	75
4.1.1	ATR-FTIR Analysis of Synthesised PU	77
4.1.2	<sup>1</sup> H NMR Analysis of Synthesised and sulphonated PU	79
4.1.3	MALDI-TOF Analysis	80
4.2	Effect of Spinning Conditions on the Properties of Hollow Fibre Membrane for Haemodialysis Application	81
4.2.1	Characterisation of Membrane Spun at Different Air Gap	81
4.2.2	Pure Water Flux and BSA Rejection	84
4.2.3	Morphology	85
4.3	Characterisation of PES/PVP with different percentage of PU Composite Membranes	93
4.3.1	ATR-FTIR Analysis	93

4.3.2	Morphology of Composite PES/PVP/PU Membranes	95
4.3.3	AFM Analysis	103
4.3.4	Membrane Hydrophilicity/Hydrophobicity and Surface Charge Analysis	104
4.3.5	Membrane Thermal Stability	108
4.4	Haemocompatibility of Developed PES/PVP with Different Percentage of PU Composite Hollow Fibre Membranes via the In-vitro Analysis	110
4.4.1	Protein Adsorption	110
4.4.2	Platelet Adhesion and Aggregation	111
4.4.3	Thrombogenic Properties	113
4.4.4	Clotting Time	114
4.4.5	Complement Activation	116
<b>5</b>	<b>CONCLUSIONS AND RECOMMENDATIONS</b>	<b>117</b>
5.1	Conclusions	117
5.2	Recommendations	119
	<b>REFERENCES</b>	<b>120</b>
	Appendices A-J	129-147

**LIST OF TABLES**

<b>TABLE NO.</b>	<b>TITLE</b>	<b>PAGE</b>
1.1	Stock and flow of renal replacement therapy in Malaysia from year 2005-2014	1
2.1	Stages of kidney disease and condition of the kidney function based on the estimated glomerular rate (eGFR) reading	13
2.2	Waste product and component inside blood that enter hemodialyser	16
2.3	The normal composition of a dialysate fluid.	17
2.4	Classification of dialysers based on dialysis membrane permeability	24
2.5	Cellulose based membranes that are commonly used during the early invention of the haemodialysis	31
2.6	Synthetic membranes that are used for haemodialysis application	33
2.7	Some examples of PES modification for haemodialysis application and its method of modification	36
3.1	The chemical and physical properties of PES	42
3.2	The chemical and physical properties of PVP	43

3.3	Physical properties of DMAc	44
3.4	The chemical and physical properties of MDI	45
3.5	The chemical and physical properties of DMPA	46
3.6	Spinning parameters for different air gap distance, different dope extrusion rate (DER), bore fluid flow rate (BFFR) and speed during membrane collection (CD)	53
3.7	Composition of each component in the dope solution	58
3.8	Spinning parameter for HFMs fabrication	59
3.9	Reagents list and its manufacturer	62
3.10	Kits list and its manufacturer	62
3.11	Instruments list and its manufacturer	63
3.12	Consumables list and its manufacturer	63
3.13	List of two-fold dilution series for Human TAT complex standard solution	66
3.14	List of two-fold dilution series for BSA standard solution	66
3.15	List of two-fold dilution series for FBG standard solution	67
3.16	Normal range of APTT and PT test	70
4.1	Physical properties of the membranes spun at different air gap distance	84
4.2	Water permeability and protein rejection of the hollow fibre membrane	85

4.3	The OD and ID of the membrane with different air gap lengths	86
4.4	The OD and ID of the membrane with different dope extrusion rate (DER) and bore fluid flow rate (BFFR)	89
4.5	Surface roughness of the hollow fibre membrane	93
4.6	Surface roughness of the hollow fibre membrane	103

**LIST OF FIGURES**

<b>TABLE NO.</b>	<b>TITLE</b>	<b>PAGE</b>
2.1	The gross anatomy of normal kidney and chronic renal failure kidneys	9
2.2	Simplified haemodialysis circuit	10
2.3	Mechanism of blood and dialysate flow through semipermeable membrane	12
2.4	Graphic illustration of water and solute movement across the semipermeable membrane	14
2.5	Chemical structure of natural (cellulose) and synthetic polymer membrane	18
2.6	Types of membrane. (a) homogeneous membrane, (b) asymmetric membrane-porous structure, (c) asymmetric membrane-finger-like structure	20
2.7	Movement of uremic toxins, albumin and water molecules across asymmetric membrane	21
2.8	Comparison of homogeneous and heterogeneous membrane	22
2.9	Haemodialysis and haemofiltration principles	23
2.10	The effect of protein adsorption and its activation cascade	25

2.11	Blood purification across the glomerular	26
2.12	The contact pathway activation mechanism induces by negatively charged material	27
2.13	Three pathway of complement system	28
2.14	SEM images of platelet adhesion during resting state, non-thrombotic state (R), and 4 different stages of platelet spreading or pseudopodia formation; dendritic (D), spread-dendritic (SD), spread (S) and fully spread (FS)	29
2.15	The SEM findings of cross-sectional structure of cellulose triacetate (CTA)	30
2.16	The structural formulas of PES and PSf	34
2.17	The SEM findings of cross-sectional structural of PES	35
3.1	Experimental stages flow chart of this research study	40
3.2	The molecular structure of (a)heparin and (b)modified polyurethane	41
3.3	Chemical structure of PES, Veradel® A-301 (n = number of unit)	41
3.4	Chemical structure of PVP, K90	42
3.5	Chemical structure of MDI, Sigma-aldrich	45
3.6	The schematic diagram of PU polymerisation laboratory apparatus preparation	47



3.7	The flow chart of the procedure for polymerisation and sulphonation of PU	48
3.8	Schematic diagram of dry/wet inversion spinning technique	51
3.9	Glass plate and glass rod used for flat-sheet membrane casting	60
3.10	C3a standard solution	65
3.11	The summary procedure of protein adsorption	69
3.12	The summary procedure of APTT and PT testing	70
3.13	The summary procedure of sample preparation for TAT, C3a and C5a complement activation	71
3.14	Schematic diagram for platelet adhesion procedure	74
4.1	Mechanism of synthesis of sulphonated PU by polymerisation and sulphonation	76
4.2	ATR-FTIR spectra for synthesised PU	78
4.3	ATR-FTIR spectra for sulphonated PU	78
4.4	The $^1\text{H}$ NMR spectra of the sulphonated polyurethane.	79
4.5	Maldi-TOF spectra for synthesised PU	80
4.6	Maldi-TOF spectra for sulphonated PU	81
4.7	Contact angle measurement for hollow fibre spun with different air gap between spinneret and coagulation bath and constant DER ( $3\text{ cm}^3/\text{min}$ ) and BFFR ( $1\text{ cm}^3/\text{min}$ )	82

4.8	ATR-FTIR analysis for hollow fibre spun with different air gap between spinneret and coagulation bath and constant DER (3 cm <sup>3</sup> /min) and BFFR (1 cm <sup>3</sup> /min).	83
4.9	The SEM images of hollow fibre membrane spun at different air gap	87
4.10	The SEM images of hollow fibre membrane with different dope extrusion rate (DER) and bore fluid flow rate (BFFR) spun at air gap 50 cm.	90
4.11	Cross sectional SEM pictures of sample A-2-1 hollow fibre membrane spun at 50cm air gap region and DER and BFFR ratio of 1:1	91
4.12	AFM images of hollow fibre membrane spun at different air gap distance	92
4.13	ATR-FTIR spectra for neat PES/PVP membrane	94
4.14	ATR-FTIR spectrum series for PES/PVP with different PU loading	95
4.15	SEM image for PES/PVP/PU4%, dense skin layer near the inner surface of the membrane and porous finger-like structure near the edge of the membrane.	96
4.16	SEM images for hollow fibre membrane spun from 0% - 5% of PU cross-sectional region at different magnification. (a)PES/PVP, (b)PES/PVP/PU1%, (c)PES/PVP/PU2%, (d) PES/PVP/PU3%, (e)PES/PVP/PU4%, (f)PES/PVP/PU5%. Magnification: 1500x.	97
4.17	SEM images for hollow fibre membrane spun from 0% - 5% of PU surface region at different	

	magnification. (a)PES/PVP, (b)PES/PVP/PU1%, (c)PES/PVP/PU2%, (d) PES/PVP/PU3%, (e)PES/PVP/PU4%, (f)PES/PVP/PU5%. Magnification: 5000x.	99
4.18	SEM image for PES/PVP/PU4%, dense skin layer near the inner surface of the membrane and porous finger-like structure near the edge of the membrane.	100
4.19	SEM images for flat-sheet membrane spun from 0% - 5% of PU cross-sectional region at different magnification. (a)PES/PVP, (b)PES/PVP/PU1%, (c)PES/PVP/PU2%, (d) PES/PVP/PU3%, (e)PES/PVP/PU4%, (f)PES/PVP/PU5%. Magnification: 500x.	101
4.20	SEM images for hollow fibre membrane spun from 0% - 5% of PU surface region at different magnification. (a)PES/PVP, (b)PES/PVP/PU1%, (c)PES/PVP/PU2%, (d) PES/PVP/PU3%, (e)PES/PVP/PU4%, (f)PES/PVP/PU5%. Magnification: 2000x	102
4.21	AFM images of hollow fibre membrane spun at different air gap distance	104
4.22	Contact angle measurement of the composite hollow fibre membrane	105
4.23	Contact angle measurement of the flat-sheet membrane	106
4.24	Surface charge of the membranes against pH	107
4.25	Thermal analysis of PES/PU blend hollow fibre membranes with different concentration of PU	109

4.26	Thermal analysis of PES/PU blend flat-sheet membranes with different concentration of PU	109
4.27	Adsorption results of BSA and FBG on the membrane surface of PES/PVP with different PU loading	111
4.28	SEM images of platelet adhesion on flat-sheet membrane (a)PES/PVP, (b)PES/PVP/PU1%, (c)PES/PVP/PU2%, (d)PES/PVP/PU3%, (e)PES/PVP/PU4%, (f) PES/PVP/PU5%	112
4.29	TAT activation for PES/PVP with different PU loading Complement Activation	114
4.30	APTTs coagulation time analysis for PES/PVP with different PU loading	115
4.31	PTs coagulation time analysis for PES/PVP with different PU loading	115
4.32	C3a complement activation for PES/PVP incorporated with different PU percentage	116

**LIST OF SYMBOLS**

$\gamma$	-	Gamma
$\delta t$	-	Solubility coefficient (MPa <sup>1/2</sup> )
$\Delta x$	-	thickness selectivity of the membrane ( $\mu\text{m}$ )
$L$	-	thickness of the support layer ( $\mu\text{m}$ )
$K_{\text{uf}}$	-	ultrafiltration coefficient of the membrane (mL/h/mmHg)
$K_{\text{d}}$	-	Dialyser clearance (mL/min)
$M_{\text{w}}$	-	Molecular weight (g/mol)
$T_{\text{g}}$	-	Glassy temperature ( $^{\circ}\text{C}$ )
C	-	Carbon
H	-	Hydrogen
N	-	Nitrogen
O	-	Oxygen
R	-	Extrusion ratio
$A_{\text{o}}$	-	Initial cross-sectional area of the spinneret
$A_{\text{f}}$	-	final cross-sectional area of the spinneret
V	-	volume of permeation (L)

$A$	-	total area of the hollow fibres ( $\text{m}^2$ )
$t$	-	time taken (h).
$C_P$	-	permeate concentrations (wt%)
$C_F$	-	feed concentrations (wt%)
$R_a$	-	mean surface roughness
DER	-	Dope extrusion rate ( $\text{cm}^3/\text{min}$ )
BFFR	-	Bore fluid flow rate ( $\text{cm}^3/\text{min}$ )
LER	-	Linear extrusion rate ( $\text{cm}^3/\text{min}$ )
CD	-	Collection drum (Hz)
$\text{CaCl}_2$	-	Calcium chloride
C3a	-	Complement 3a
C5a	-	Complement 5a
C5b-9	-	Complement 5b, 6, 7, 8, 9 (complement membrane attack complex)

**LIST OF APPENDICES**

<b>APPENDIX</b>	<b>TITLE</b>	<b>PAGE</b>
A	List of Publication	129
B	Membrane Fabrication	130
C	Flow Chart of the Polymerisation and Sulphonation Process of Synthesised Polyurethane	131
D	Calculation of Estimated Dope Extrusion Rate to Bore Fluid Flow Rate Ratio	132
E	Calculated Molecular Weight according to Structural Formula	133
F	Scanning Electron Microscopic (SEM) Images for Hollow Fibre Membrane and Flat-sheet Membrane at Different Magnification	134
G	Elemental Composition Analysis based on Energy-dispersive X-ray (EDX) Spectroscopy of Membrane Fabricated	137
H	ATR-FTIR Spectrum for Synthesised PU, Sulphonated PU and all the Fabricated PES/PVP Membrane with Different PU Percentage.	139
I	Determination of Membrane Thermal Stability based on the TGA Curve Analysis and Estimation of	

	Polymer Degradation based on Membrane Weight Loss	143
I	The Flow Chart of Human Complement Fragment 3a (C3a) ELISA Assay Procedure	147



## 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 31 <sup>st</sup> December	13,356	15,080	17,084	19,388	21,590	23,709	26,328	29,223	32,026	34,767
Functioning transplant at 31 <sup>st</sup> 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  $\delta_t = 20.5 \text{ MPa}^{1/2}$ , showed good miscibility with PES ( $\delta_t = 21.3 \text{ MPa}^{1/2}$ ), 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 diisocyanate (MDI) and dimethylolpropionic acid (DMPA) at temperature 80°C for 6 hours and then functionalising it by sulphonating with concentrated H<sub>2</sub>SO<sub>4</sub> 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<sup>3</sup>/min of dope extrusion rate, and 1 cm<sup>3</sup>/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 thermogravimetric 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 additive 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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