CHITOSAN NANOPARTICLE DIALLYL DISULFIDE COMPLEX IMMOBILIZED POLYSULFONE HOLLOW FIBRE MEMBRANE FOR HEMODIALYSIS

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ABSTRACT

Aside from the low-flux issue, biocompatibility of hemodialysis membrane is another leading cause of mortality among end-stage renal disease (ESRD) patients due to increased oxidative stress and thrombus formation that led to cardiovascular disease (CVD). Hence, the main objective of this study is to develop an antioxidant and antithrombotic polysulfone (PSF) based hollow fibre membrane (HFM) for effective uremic toxins removal. A hydrophilic chitosan nanoparticle (CNP) was first synthesized via ionic gelation method. Using diallyl disulfide (DADS), a novel CNP/DADS complex was formed through simple complexation steps with ionic gelation method. The formation of the nanoparticle complex was confirmed by ^{1}H nuclear magnetic resonance (H-NMR), attenuated total reflectance-Fourier transform infrared (ATR-FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD) and UV–Vis. An antioxidant, biocompatibility and antithrombotic properties were conducted, where the effect of DADS addition was evaluated. Both CNP and CNP/DADS showed antioxidant activity where the scavenging capacity against nitric oxide (NO) and hydrogen peroxide (HP) was superior in 1.0 mg/ml CNP/DADS with 29.4% and 32.8%, respectively. CNP/DADS showed a low hemolysis rate of <1% and complement the C3a and C5a activation that demonstrated its biocompatibility. The prolonged APTT and PT with no observation of platelet aggregation as compared to CNP also demonstrated the CNP/DADS antithrombotic properties. In the next step, 0.1 wt.%, 0.3 wt.% and 0.5 wt.% of CNP and CNP/DADS were immobilized into PSF. The HFM were spun with different spinning air-gap. The result showed that PSF HFM with 0.3 wt.% CNP spun at 50 cm air-gap produced the highest K_{UF} of 116 $ml/m^2.h.mmHg$, 95.7% BSA rejection and 85% of urea, creatinine 66%, and lysozyme 43% clearance. The promising results were due to the increased in hydrophilicity and improved morphological structure of the membrane with higher porosity and thinner membrane skin layer. At a higher CNP concentration of 0.5 wt. %, the K_{UF} value of HFM dropped by 23% which was affected by a thicker outer skin layer and lower porosity. Compared to CNP immobilized PSF HFM, CNP/DADS immobilized PSF HFM showed a reduction in K_{UF} value due to poorly dispersed agglomerated nanoparticles that created denser HFM morphological structure. Nevertheless, the membrane performances still meet the high-flux standards. The CNP/DADS immobilized PSF HFM demonstrated enhanced biocompatibility by exhibiting a lower hemolysis rate of <1%, lower protein adsorption and platelet adhesion and induced less complement C3a and C5a activation. It also significantly ($P<0.001$) prolonged APTT and PT test value which indicated the enhancement of antithrombotic properties. The CNP/DADS also promoted higher antioxidant properties for PSF HFM compared to CNP. The CNP/DADS immobilized PSF HFM displayed higher antioxidant activity against nitric oxide and hydrogen peroxide, by having scavenged percentages of 26.7% and 20.6%, respectively, compared to CNP with 4.1% and 2.7%. The findings of this study evidenced that PSF HFM with excellent antioxidant and antithrombotic properties has been successfully developed. The membrane can be potentially used for the safe and effective removal of uremic toxins in hemodialysis.

ABSTRAK

Selain daripada isu fluks rendah, bioserasi membran hemodialisis juga merupakan penyebab utama kepada kematian di kalangan pesakit buah pinggang tahap akhir (ESRD) disebabkan oleh peningkatan tekanan oksidatif dan pembentukan trombus yang membawa kepada penyakit kardiovaskular (CVD). Oleh itu, objektif utama kajian ini adalah untuk membangunkan membran gentian berongga (HFM) berasaskan polysulfona (PSF) yang mempunyai ciri-ciri antioksida dan antitrombotik untuk penyingkiran toksin uremik yang berkesan. Nanopartikel kitosan (CNP) disintesis melalui kaedah gelilasi ionik dan dikompleks dengan diallyl disulfida (DADS) dan disahkan dengan ^{1}H resonans magnetik nuklear (H-NMR), inframerah transformasi total reflektansi-fourier (ATR-FTIR), kalorimetri pengimbasan pembezaan (DSC), pembelauan sinar-X (XRD) dan UV-Vis. Penilaian kesan penambahan DADS terhadap antioksida dan antitrombotik telah dijalankan. Kedua-dua CNP dan CNP/DADS menunjukkan kesan antioksida, namun pada kepekatan 1.0 mg/ml, CNP/DADS menjerap nitrik oksida (NO) dan hidrogen peroksida (HP) pada peratusan lebih tinggi dengan masing-masing pada kadar 29.4% dan 32.8%. CNP/DADS juga memiliki kadar hemolisis dan pengaktifan C3a dan C5a yang rendah. Pemerhatian terhadap APTT yang berpanjangan dan PT tanpa penggumpalan platelet menunjukkan sifat antitrombotik berbanding CNP. Seterusnya, CNP dan CNP/DADS dengan kepekatan 0.1 wt.%, 0.3 wt.% dan 0.5 wt.% telah dimasukkan ke dalam PSF, seterusnya pemintalan HFM dilakukan dengan jurang udara yang berbeza. Dapatan kajian ditunjukkan oleh PSF HFM dengan 0.3 wt.% CNP dipintal pada jurang udara 50 cm menghasilkan K_{UF} tertinggi dengan 116 ml/m^2.h.mmHg, juga penolakan BSA sebanyak 95.7% dan pelepasan 85% urea , 66% kreatinin, dan lisozim (43%). Ini disebabkan oleh peningkatan sifat hidrofilik dan struktur morfologi membran yang lebih baik dengan liang yang lebih banyak dan lapisan kulit membran yang lebih nipis. Pada kepekatan 0.5 wt. % CNP, nilai K_{UF} HFM menurun sebanyak 23% dipengaruhi oleh lapisan kulit luar yang lebih tebal dan liang yang lebih sedikit. Berbanding dengan PSF HFM yang dimasukkan dengan CNP, PSF HFM dengan CNP/DADS menunjukkan pengurangan dalam prestasi membran tetapi masih dalam piawaian fluks tinggi, disebabkan oleh nanopartikel tergumpal dengan penyerakan kurang baik lalu menghasilkan struktur morfologi HFM yang lebih padat. Walau bagaimanapun, PSF HFM yang dimasukkan dengan CNP/DADS menunjukkan peningkatan bioserasi dengan kadar hemolisis yang lebih rendah <1%, penjerapan protin dan lekatan platlet serta pengaktifan komplemen pengaktifan C3a dan C5a yang lebih rendah. Ia juga secara signifikan ($P<0.001$) memanjangkan nilai ujian APTT dan PT yang menunjukkan peningkatan sifat antitrombotik. PSF HFM dengan CNP/DADS juga menujukkan sifat antioksida yang lebih tinggi berbanding dengan CNP. PSF HFM dengan CNP/DADS menunjukkan aktiviti antioksida yang lebih tinggi terhadap nitrik oksida dan hidrogen peroksida, dengan pengurangan masing-masing sebanyak 26.7% dan 20.6%, berbanding CNP dengan 4.1% dan 2.7%. Hasil kajian ini menunjukkan bahawa PSF HFM dengan sifat antioksida dan antitrombotik telah berjaya dibangunkan. Membran yang dihasilkan adalah selamat dan berkesan bagi tujuan penyingkiran toksin uremik untuk hemodialisis.

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LIST OF ABBREVIATIONS

APTT	-	Activated Partial Thromboplastin Time
ATR	-	Attenuated total reflectance
BSA	-	Bovine Serum Albumin
CA	-	Cellulose acetate
CTA	-	Cellulose triacetate
C3a	-	Human Complement Fragment 3a
C5a	-	Human Complement Fragment 5a
CNP	-	Chitosan nanoparticle
CVD	-	Cardiovascular disease
DAS	-	Diallyl sulfide
DADS	-	Diallyl disulfide
DATS	-	Diallyl trisulfide
DER	-	Dope Extrusion Rate
EDX	-	Energy-Dispersive X-ray Spectroscopy
ESRD	-	End-stage renal disease
FTIR	-	Fourier Transform Infrared
HFM	-	Hollow fibre membrane
HP	-	Hydrogen peroxide
MWCO	-	Molecular weight cut-off
NMP	-	N-Methyl-2-Pyrrolidone
NO	-	Nitric oxide
PAN	-	Polyacrylonitrile
PBS	-	Phosphate Buffer Saline

PES	-	Polyethersulfone
PMMA	-	Polymethylenemethylacrylate
PSF	-	Polysulfone
PPP	-	Platelet Poor Plasma
PRP	-	Platelet Rich Plasma
PRT	-	Plasma recalcification time
PT	-	Prothrombin Time
PVP	-	Polyvinylpyrrolidone
RNO	-	Reactive nitrogen species
ROS	-	Reactive oxygens species
SEM	-	Scanning Electron Microscopy
TEM	-	Transmission Electron Microscopy
TPP	-	Tripolyphosphate
UF	-	Ultrafiltration
UV	-	Ultraviolet
XRD	-	X-ray Power Diffraction

LIST OF SYMBOLS

λ	-	Incident wavelength
ε	-	Membrane porosity
θ	-	Diffraction angle
A_e	-	Effective surface area
C	-	Solute clearance
C_f	-	Concentration of feed
C_i	-	Initial concentration
C_o	-	Initial concentration
C_P	-	Permeate concentration
K_{UF}	-	Ultrafiltration coeffficient
m	-	Mass
n	-	Number of trials
R	-	Rejection
t	-	Time
V	-	Volume
W_0	-	Weight of wet membrane
W_1	-	Weight of dry membrane

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CHAPTER 1

INTRODUCTION

1.1 Research Background

The kidneys are an important organ in the human body. It helps to keep body hemostasis balanced by maintaining body fluid and chemicals, and also removes toxins and waste (Tortora and Derrickson, 2009). When the human kidneys discontinue their normal functions, it leads to toxic waste retention in the body. The prolonged kidney failure eventually leads to end-stage renal disease (ESRD). The life of ESRD patients depends on renal replacement therapy, either dialysis (peritoneal or hemodialysis) or kidney transplantation. Hemodialysis is the common choice of ESRD treatment since kidney transplant is expensive and scarcity of kidneys due to the lack of organ donors. Based on the 26th Report of the Malaysian Hemodialysis and Transplant Registry 2018, in 2018 there were 39353 patients receiving hemodialysis in Malaysia, and a higher percentage of these patients are on hemodialysis therapy (Wong and Goh, 2018). Hemodialysis is a highly successful life-saving and life-sustaining therapy for ESRD patients (Vilar & Farrington, 2011). Unfortunately, although hemodialysis may help some patients to sustain their life, a significant number of patients receiving hemodialysis treatment was reported to suffer from cardiovascular disease which led to a fatality. The phenomenon is associated with toxin accumulation in the body resulting from inadequate removal of organic waste, hemodialysis-induced oxidative stress, and membrane-induced inflammation. Therefore, improvements in hemodialysis have been focused on the development of biocompatible antioxidant dialyzer membranes (Chen *et al.*, 2014).

In hemodialysis, the dialyzer is the most important part that plays a role in purifying blood and determining the outcome of the hemodialysis process. The dialyzer consists of a semipermeable hollow fibre membrane (HFM) packed in a cylindrical tube that keep blood flowing through its lumen and separate the blood and dialysate compartment that flow in opposite direction (Mitra and Mitsides, 2016). In

the earlier days, hemodialysis membranes were made of cellulosic based membranes such as cuprophane and cellophane (Gautham *et al.*, 2013; Ahmad, 2009). However, due to the biocompatibility issue and poor performances, the cellulosic membrane was considered clinically unfavourable (Hakim, 1993). Therefore, synthetic membranes were the next to be introduced to improve membrane capabilities to uremic solutes and biocompatibility (Humes, Fissell and Tiranathanagul, 2006). Synthetic membranes such as polyamide, polymethylmethacrylate (PMMA), polyethersulfone (PES), polysulfone (PSF) and polyacrylonitrile (PAN) are generally more biocompatible compared to the cellulose-based membrane, have higher hydraulic permeability (Ahmad, 2009). These polymers can be spun into hollow fibres with various pore sizes and molecular weight cut-offs to allow the good removal of large molecules such as β-microglobulin (Kerr and Huang, 2010). However, the hydrophobic nature of most of these polymers requires the use of hydrophilic additives to avoid too much protein adsorption during membrane-blood contact (Gautham *et al.*, 2013).

The PSF-based membrane has been increasingly used in the medical field owing to its good mechanical and chemical properties (Wenten *et al.*, 2016). Despite having excellent properties, the PSF membrane has shown some drawbacks when in contact with blood during the hemodialysis process that affected its biocompatibility (Bowry, Gatti and Vienken, 2011). A study by Koga *et al.* (2018) on various PSF-based membranes showed that the fibrinogen adsorption on the membrane surfaces has led to platelet adhesions and oxidative stress production. The most common way to improve the commercially used PSF membrane performances was by immobilizing hydrophilic polymers such as polyvinylpyrrolidone (PVP K90) (Hayama *et al.*, 2004). PVP improved the membrane's biocompatibility by increasing its hydrophilicity which help to reduce the adsorption of fibrinogen (Higuchi *et al.*, 2002). Immobilization of PVP K90 into PSF based hollow fibre membrane (HFM) has been shown to improve the water flux of membranes and uremic toxins removal (Said, Hasbullah, Ismail, Abidin, *et al.*, 2017).

To provide a safe hemodialysis process without a blood clot, anticoagulant such as heparin is administered (Mitra and Mitsides, 2016). Therefore, some researchers have attempted anticoagulants such as heparin (Tang *et al.*, 2012; Gao, Liu and Xue, 2014; Morena *et al.*, 2010), citric acid (Li *et al.*, 2012; Zailani *et al.*, 2017)

and (Li *et al.*, 2017) to improve membrane blood compatibility. The immobilization of this anticoagulant introduces functional groups such as hydroxyl, amino, carboxy, and sulfonic acid groups which interact with the coagulation pathway to disrupt blood coagulation formation (Wenten *et al.*, 2016). Hence, the use of anticoagulant materials can serve as a promising approach to develop an antithrombotic membrane for hemodialysis.

Over the years, much progress has been made to overcome hemodialysis-induced oxidative stress through several modifications to improve the antioxidant properties of PSF membranes. The most frequently used approach is by introducing antioxidants such as vitamin E and linoleic acid into hemodialysis membranes (Mydlík *et al.*, 2004). Dahe *et al.* (2011) introduced D-α-tocopheryl polyethylene glycol (PEG) 1000 succinate (TPGS) to modify PSF-based copolymer membrane demonstrated an improved in vitro biocompatibility and filtration performance of the modified hemodialysis membrane. Recently, Kohlová *et al.* (2020) reported that the doping PSF membrane with α-tocopherol and α-lipoic acid not only inhibited oxidative stress but also improved the in vitro antioxidant activity. Chang *et al.* (2009) grafted Diallyl disulfide (DADS) onto PSF flat sheet surface and successfully improved membrane's protection against oxidative stress besides demonstrated anticoagulant properties. DADS is the most stable garlic-derived organosulfur compound (S. M. Kim *et al.*, 2014) that possesses antimicrobial, antioxidant, anticarcinogenic (Lu *et al.*, 2011; Songsungkan and Chanthai, 2014; Bayan, Koulivand and Gorji, 2014) and also demonstrated antithrombotic properties (Chan *et al.* 2002).

Chitosan nanoparticles (CNP) is a natural non-toxic biopolymer that possesses good biocompatibility, biodegradability and antimicrobial properties and with low immunogenicity (Pillai, Paul and Sharma, 2009). Owing to these properties, CNP can make a great material for hemodialysis application when they are immobilized into the PSF membrane. The immobilization of chitosan and CNP into PSF flat-sheet membranes has shown promise in improving the membrane's hydrophilicity and ultrafiltration performances as well as the antifouling properties (Kumar *et al.*, 2013a; Liu and Pan, 2014; Sangeetha, Kandaswamy and Vijayalakshmi, 2016). To improve CNP antioxidant and antithrombotic properties, the CNP was used to form complex with DADS via simple complexation steps (Pirak, Jangchud and Jantawat, 2012). The

synthesized nanoparticle CNP and CNP//DADS was characterized and its antioxidant, blood compatibility and antithrombotic properties were assessed. then immobilized into PSF polymer dope solution to fabricated HFM. This study was aimed to develop an antioxidant and antithrombotic PSF HFM by immobilizing CNP and CNP/DADS dope solution which then fabricated through non-solvent induced phase inversion (NIPS) dry-wet jet spinning method. The feasibility of CNP and CNP/DADS for the development of nanocomposite HFM for hemodialysis application was evaluated based on several important aspects including ultrafiltration coefficient (K_{UF}), uremic toxins removal, antioxidant, blood compatibility and antithrombotic properties.

1.2 Problem Statement

Despite its popularity in hemodialysis application, the hydrophobic nature of PSF based membrane is still the major issue that leads to membrane bio-incompatibility. The hydrophobicity of the PSF membrane caused adsorption and deposition of proteins and platelets, also activated blood cells which often cause thrombus formation and blood coagulation (Zhu *et al.*, 2017). The incorporation of hydrophilic additives such as PVP has been implemented to improve the biocompatibility of the PSF membrane. Although most PSF/PVP blend membranes showed good biocompatibility properties, the blood clot or thrombosis caused by the membrane is still the main issue (Gorbet and Sefton, 2004). A study by Oshihara *et al.* (2017) demonstrated that the amount of incorporated amount of PVP had no significant effect on the platelet adhesion on the membrane surfaces similar to conventional PSF membrane. This indicated the insufficient antithrombogenicity of PVP to prevent blood clots, hence, a new hydrophilic polymer is desired to develop an antithrombotic hemodialysis membrane.

To prevent blood coagulation or thrombus formation on the membrane during hemodialysis and provide safe therapy, an anticoagulant such as heparin was administered but it led to other severe bleeding problems. Hence, minimizing heparin usage is a quest in hemodialysis membrane research by developing an antithrombotic hemodialysis membrane grafted with an antithrombotic agent or heparin-grafted

polymer (Canaud, 2021). HepAN-AN69ST (heparin-grafted AN69), a PAN-based membrane, is one of the earliest available commercial hemodialysis membranes that are used to reduce heparin dose during hemodialysis. However, due to its symmetric dense morphological structure, the membrane is only available as a low-flux hemodialysis membrane. Evodial developed modified HeprAN that was designed for a high-flux hemodialysis has reduced 30% heparin usage in hemodialysis treatments (Morena *et al.,* 2010). However, a recent study by Zweigart *et al.* (2017) indicated that albumin losses for Evodial hemodialyzer used in therapy were recorded at 2.2 to 15.5 g per 4-hour session which is above the accepted average dialyzer albumin removal rate of 4.3 g per hemodialysis session (Boschetti-De-Fierro *et al.*, 2017).

The activation of blood cells due to membrane bio-incompatibility is linked to the oxidative stress release found in ESRD patients on hemodialysis therapy. Increased production of oxidative stress-free radicals such as reactive oxygen species (ROS) and nitric oxide (NO) has led to deleterious effects such as cardiovascular disease (CVD) (Liakopoulos *et al.*, 2017). One of the earliest approaches to reduce oxidative stress release is through the improvement of antioxidant properties in hemodialysis membrane using vitamin E to coated onto PSF membrane (Sasaki, 2006). However, the hydrophobicity of vitamin E which is coated on the inner surface of the hollow fibre may partially block and reduce the pore size present on the surface affect reducing membrane flux performances (Dahe *et al.,* 2011). In addition, D'Arrigo *et al.* (2017) concluded that there is no substantial evidence supporting the utility of vitamin E coated membrane for enhancing oxidative stress and anti-inflammation in chronic hemodialysis patients, also did not influence membrane uremic toxins clearance (Kt/V). Hence, incorporating a hydrophilic antioxidant and antithrombotic material into the hemodialysis membrane should be the focus to improve membrane biocompatibility and antioxidant properties.

To achieve excellent antioxidant and antithrombotic for better hemodialysis performances, a mixed matrix nanocomposite PSF HFM was developed. A novel CNP/DADS was immobilized into PSF HFM to enhance the antioxidant and antithrombotic properties of the membrane while enhancing its performance. CNP is a biocompatible, biodegradable, and hydrophilic biopolymer that exhibited excellent antioxidant properties (Supraja, Thiruchenduran and Prasad, 2018). However, CNP

exerts hemostatic properties which aggregate platelets and red blood cells to form a thrombus (Lima *et al.*, 2015). DADS is a compound derived from garlic that exerts antithrombotic, antiplatelet, antimicrobial, antioxidant and anti-inflammatory (Chiang *et al.*, 2006; Fujisawa *et al.*, 2008). The previous study grafted DADS on a PSF flat sheet membrane and demonstrated prolonged APTT and PT which indicated improved antithrombotic properties (Chang *et al.*, 2009), however, to coat DADS on the inside surface of HFM was challenging. Thus, in this study CNP/DADS complex was synthesized via a simple complexation step. The complex was then immobilized into PSF HFM to fabricate a mixed matrix nanocomposite membrane. Owing to the properties of the two compounds, the immobilization of the CNP/DADS complexes can enhance antioxidant, antithrombotic and hemodialysis performances of PSF HFM.

1.3 Research Objective

This study aims to develop HFM embedded with outstanding nanoparticles which can improve HFM performances, antioxidant, and antithrombotic properties. Therefore, this study was set out with the following objectives:

1. To characterize and evaluate the antioxidant, blood compatibility and antithrombotic properties of synthesized CNP and CNP/DADS.

2. To investigate the effect of spinning air-gap on morphological changes and hemodialysis performances of different concentration nanoparticles immobilized PSF HFM.

3. To investigate the effect of a series of concentration nanoparticles immobilized PSF HSM on antioxidant, biocompatibility, and antithrombotic properties.

1.4 Scope of Study

To achieve the above-mentioned objectives, the following scopes of studies have been outlined:

1) Synthesis of CNP via ionic gelation method with ratio 1:0.8 of chitosan: TPP in of 2% acetic acid.
2) Complexation of CNP and DADS via simple complexation process with ratio 1:1 of CNP: DADS in 1% acetic acid.
3) Characterization of synthesized CNP and CNP/DADS via transmission electron microscopy (TEM), energy-dispersive X-ray spectroscopy (EDX), particle size analyser (PSA), particle zeta potential, ^{1}H nuclear magnetic resonance (NMR), Attenuated Total Reflectance-Fourier-transform infrared spectroscopy (ATR-FTIR), differential scanning calorimetry (DSC), X-ray diffraction (XRD), ultraviolet-visible spectroscopy near-infrared (UV-Vis), respectively.
4) Evaluation of the antithrombotic properties of CNP and CNP/DADS based on the coagulation time in APTT and PT study.
5) Preparation of dope solutions that consists of 18 wt% PSF, 3 wt%, PVP, and different nanoparticles (CNP and CNP/DADS) concentration i.e., 0.1 wt%, 0.3 wt% and 0.5% in NMP as a solvent.
6) Fabrication of PSF HFM via dry-wet non-solvent induced phase separation technique using dual orifice spinneret dimension of 0.55/0.8 mm, with water as internal and external coagulant; bore fluid flow rate at 1ml/min and dope extrusion rate at 1ml/ml; different air-gap at 30 cm and 50.
7) Characterisation of HFM properties such as cross-section morphology using scanning electron microscopy (SEM), thermogravimetric analysis (TGA), contact angle using contact angle goniometer, zeta potential, water uptake and porosity, pore size and membrane functional group analysis using attenuated total reflection-Fourier transform infrared (ATR-FTIR).
8) Study of CNP, CNP/DADS and modified PSF HFM antioxidant activity via free radical scavenging assay of nitric oxide and hydrogen peroxide assay.
9) Evaluation of the biocompatibility of the CNP, CNP/DADS and modified PSF HFM via protein adsorption, haemolysis assay, platelet adhesion and complement activation.

10) Evaluation of the antithrombotic properties of CNP, CNP/DADS and modified PSF HFM using coagulation time via APTT and PT study.
11) Study of HFM hemodialysis performances using ultrafiltration coefficient (K_{UF}), BSA rejection and clearance of uremic toxins (urea, creatinine, and lysozyme).

1.5 Significance of Study

This study explored the development of biocompatible, antioxidant and antithrombotic membranes for hemodialysis application. This study would make huge importance towards multiple fields of research which includes nanotechnology, biomaterial, membrane technology and nephrology. The primary outcome of the study would give benefit the scientific community in the sense of filling in the knowledge gap in those mentioned fields. The employment of biodegradable, biocompatible organic modified nanoparticles in hemodialysis membrane for example could gradually expand its potential in this medical-device application. The inventive approach which combined both unique properties of organic nanoparticles and versatility of the main polymer as a host showed huge potential to cope with the biocompatibility issues commonly faced by polymeric membranes. In addition, the research on hemodialysis membranes in Malaysia is still at premature stages and scarce, there is no industrial-scale initiative to employ local membrane technology experts for hemodialysis application. Hence, this novel the invention is believed to become a steppingstone that could provide a valuable information for membranologists and lead the way to further study. The aftermath of the study will also benefit the ESRD patients by providing an antioxidative and antithrombotic hemodialysis membrane that is capable and reliable to perform exceptional blood purification with minimal adverse effect and reducing the heparin usage during therapy. Hence, this research's long-term target is to develop a locally made dialyser equipped with a highly efficient membrane to sustain the current demand, especially in Malaysia. Triggered by the general necessities of serving the social community, the study would attract industrial players that produce or supply medical devices and equipment as a platform to patent and market the product.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Zailani, M.Z.**, Ismail, A.F., Goh, P.S., Kadir, S.H.S.A., Othman, M.H.D., Hasbullah, H., Abdullah, M.S., Ng, B.C. and Kamal, F. (2021). Antioxidant and antithrombotic study of novel chitosan-diallyl disulfide inclusion complexes nanoparticles for hemodialysis applications. *Reactive and Functional Polymers*. 163(March), 104894. (**Q1, IF: 3.975)**

2. **Zailani, M.Z.**, Ismail, A.F., Goh, P.S., Kadir, S.H.S.A., Othman, M.H.D., Hasbullah, H., Abdullah, M.S., Ng, B.C., Kamal, F. and Mustafar, R. (2021). Immobilizing chitosan nanoparticles in polysulfone ultrafiltration hollow fibre membranes for improving uremic toxins removal. *Journal of Environmental Chemical Engineering*. 9(6), 106878. (**Q1, IF:5.909)**

Submitted and Under Review

1. **Zailani, M.Z.**, Ismail, A.F., Goh, P.S., Kadir, S.H.S.A., Othman, M.H.D., Hasbullah, H., Abdullah, M.S., Ng, B.C., Kamal, F. and Mustafar, R. (2022). Antioxidant, Antithrombotic and Performances Evaluation of Chitosan Nanoparticle Diallyl Disulfide Immobilized Polysulfone Hollow Fibre Membrane for Hemodialysis Application.

Book Chapter

1. Ismail, A. F., Abidin, M. N. Z., Mansur, S., **Zailani, M. Z.**, Said, N., Raharjo, Y., Rosid, S. M., Othman, M. H. D., Goh, P. S., Hasbullah, H. (2018). Hemodialysis membrane for blood purification in *Handbooks in Separation Science: Membrane Separation Principles and Applications from Material Selection to Mechanisms and Industrial Uses*, 283-309, ISBN: 978-0-12-812815-2. **(ELSEVIER)**