Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives

By

Saira Manzoor

(Registration No: 00000361786)

Department of Biomedical Engineering and Sciences

School of Mechanical and Manufacturing Engineering

National University of Sciences & Technology (NUST)

Islamabad, Pakistan

(2024)

Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives

By

Saira Manzoor

(Registration No: 00000361786)

A thesis submitted to the National University of Sciences and Technology, Islamabad,

in partial fulfillment of the requirements for the degree of

Master of Science in
Biomedical Sciences

Supervisor: Dr. Muhammad Nabeel Anwar

Co Supervisor: Dr. Nasir Ahmad

School of Mechanical and Manufacturing Engineering

National University of Sciences & Technology (NUST)

Islamabad, Pakistan

(2024)

THESIS ACCEPTANCE CERTIFICATE

Certified that final copy of MS/MPhil thesis written by **Regn No. 00000361786 Saira Manzoor** of **School of Mechanical & Manufacturing Engineering (SMME)** has been vetted by undersigned, found complete in all respects as per NUST Statues/Regulations, is free of plagiarism, errors, and mistakes and is accepted as partial fulfillment for award of MS/MPhil degree. It is further certified that necessary amendments as pointed out by GEC members of the scholar have also been incorporated in the said thesis titled. **Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives**

Signature: 

Name (Supervisor): Muhammad Nabeel Anwar

Date: 15 - Mar - 2024

Signature (HOD):

Date: 15 - Mar - 2024

Signature (DEAN): 

Date: 15 - Mar - 2024

Form TH-4

National University of Sciences & Technology (NUST)

MASTER'S THESIS WORK

We hereby recommend that the dissertation prepared under our supervision by: Saira Manzoor (00000361786)
Titled: Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives
be accepted in partial fulfillment of the requirements for the award of MS in Biomedical Sciences degree.

Examination Committee Members

1. Name: Nasir Mahmood Ahmad Signature:

2. Name: Adeeb Shehzad Signature:

3. Name: Nosheen Fatima Rana Signature:

Supervisor: Muhammad Nabeel Anwar Signature:

Date: 15 - Mar - 2024

Head of Department 15 - Mar - 2024
Date

COUNTERSINGED

15 - Mar - 2024
Date

Dean/Principal

CERTIFICATE OF APPROVAL

This is to certify that the research work presented in this thesis, entitled "Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives" was conducted by Ms. Saira Manzoor under the supervision of Dr. Nabeel Anwar. No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Biomedical engineering and Sciences Department of SMME-NUST in partial fulfillment of the requirements for the degree of Master of Science in Field of Biomedical Science Department of Biomedical engineering and Sciences National University of Sciences and Technology, Islamabad.

Student Name: Saira Manzoor Signature: 

Supervisor Name: Dr. M Nabeel Anwar Signature: 

Name of Dean/HOD: Dr. Asim Waris Signature: 

AUTHOR'S DECLARATION

I, Saira Manzoor, hereby state that my MS thesis titled "Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives" is my own work and has not been submitted previously by me for taking any degree from National University of Sciences and Technology, Islamabad or anywhere else in the country/ world.

At any time if my statement is found to be incorrect even after I graduate, the university has the right to withdraw my MS degree.

Name of Student: Saira Manzoor

Date: 15-March-2024

PLAGIARISM UNDERTAKING

I solemnly declare that research work presented in the thesis titled "……Enhancing the Functionality of Polyethersulfone Hemodialysis Membranes Using Water-Soluble Hydrophilic Additives……" is solely my research work with no significant contribution from any other person. Small contribution/ help wherever taken has been duly acknowledged and that complete thesis has been written by me.

I understand the zero tolerance policy of the HEC and National University of Sciences and Technology (NUST), Islamabad towards plagiarism. Therefore, I as an author of the above titled thesis declare that no portion of my thesis has been plagiarized and any material used as reference is properly referred/cited.

I undertake that if I am found guilty of any formal plagiarism in the above titled thesis even after award of MS degree, the University reserves the rights to withdraw/revoke my MS degree and that HEC and NUST, Islamabad has the right to publish my name on the HEC/University website on which names of students are placed who submitted plagiarized thesis.

Student Signature: 

Name: Saira Manzoor

This work is dedicated to my parents, whose unwavering love and encouragement has supported me throughout my academic journey.

ACKNOWLEDGEMENTS

Above all, I praise Almighty Allah, the Most Benevolent and Merciful, for granting me the opportunity and enabling me to successfully finish my dissertation.

I am deeply grateful to my supervisor, Dr. Nabeel Anwar, for his assistance, guidance, and encouragement throughout the research and coursework. His insightful feedback and constructive criticism led to the successful completion of this research work.

I am especially thankful to Dr. Nasir Ahmad, my co-supervisor, for his insightful advice and encouragement, which have greatly improved the calibre of this study. His exceptional assistance in supplying all of the essential requirements for the research has been crucial in overcoming the obstacles associated with research work.

Special thanks are also due to Ph.D. scholar Imran Ahmad, whose guidance and assistance have been instrumental in helping me overcome all obstacles that came my way during the research journey.

I am forever indebted to my beloved parents, Manzoor Karim and Rukhsana Manzoor, for their unconditional love, support, and belief in me. Their prayers and well wishes have been the driving force behind my academic pursuits.

Lastly, I would like to acknowledge myself for the devotion, persistence, and hard work I put into this thesis. My perseverance and dedication enabled me to successfully complete this research work despite all of the challenges.

TABLE OF CONTENTS

LIST OF TABLES

Page No.

LIST OF FIGURES

Page No.

LIST OF ABBREVIATIONS AND ACRONYMS

CA	Contact angle
ESRD	End stage renal disease
FFR	Flux recovery ration
HD	Hemodialysis
PEG	Polyethylene glycol
PES	Polyethersulfone
PVP	Polyvinylpyrrolidone
WSP	Water soluble

ABSTRACT

The kidneys play a critical part in maintaining internal equilibrium of the body. However, renal diseases present a significant public health concern, affecting millions of individuals worldwide. Polyethersulfone (PES) based hemodialysis membranes can provide a life-sustaining treatment procedure for patients suffering from renal disease. Nevertheless, the intrinsic hydrophobic nature of PES contributes to an inefficiency of uremic toxin clearance and a compromised hemocompatibility. This work evaluates the individual and combined effects of two water-soluble hydrophilic additives, polyethylene glycol (PEG) and polyvinylpyrrolidone (PVP), on the functionality of polyethersulfone (PES) membranes. The membranes were synthesized by the non-solvent phase inversion method by using NMP as the solvent. The fabricated membranes were characterized by using Scanning Electron Microscopy, ATR-FTIR, tensile testing, porosity, and contact angle analysis. The SEM images demonstrated the successful fabrication of the membranes. Each membrane possessed a thin skin layer and an asymmetric porous framework. As a result of the synergistic effect, the membrane with dual WSP—2.5% PVP and 2.5% PEG—performed better than membranes with a single water-soluble hydrophilic additive. The membranes comprising the two additives had excellent hydrophilicity, increased porosity, and a high-water retention capacity. Moreover, they showed a urea clearance of 77.3%, a pure water flux of 96 $L/m^2/h$, and an outstanding BSA rejection of 99.10%. RSM modelling was employed to determine the urea clearance that verified the ideal conditions for urea removal were concentrations of 1200 mg/L and 0.6 MPa. The effectiveness of membrane containing dual WSP for hemodialysis was further demonstrated by hemocompatibility

tests, which provided promising results (APTT 32s, PT 14s, plasma recalcification time 205.5s, and hemolysis rate 1.32%).

Keywords: Hemodialysis, Ultrafiltration membranes, Hydrophilic blending, Polyethersulfone, urea clearance, Hemocompatibility.

CHAPTER 1: Introduction

1.1 Renal disease

Millions of individuals around the world are impacted by renal disorders, commonly known as kidney diseases. The Renal diseases provide a serious public health concern around the globe. The kidneys play a critical part in preserving the body's internal equilibrium. This is done by removing waste materials, extra fluid, and toxins from the blood and controlling electrolyte levels and blood pressure (Yang et al., 2020). However, there are a number of factors, which includes diabetes, hypertension, infections, and genetic susceptibility that prompt these vital organs to become dysfunctional (J.-C. Lv & Zhang, 2019). There are a numerous kinds of kidney diseases, among the top one is the common ailment known as chronic kidney disease (CKD). This disease is characterised by a progressive decline in kidney function over time. According to a recent survey it is estimated that around 800 million people around the globe suffer from chronic renal disease. Those people who already have health conditions like diabetes, hypertension, and cardiac diseases are at more risk of getting renal health problems. Other than that, people belonging to low-income economies that do not have resources for health management are also at greater risk (Raharjo et al., 2022). When chronic renal disease progresses to the next stage it is called end-stage renal disease. This stage of renal ailment is often very critical and cannot be reversed to a normal state again. Treatment options for ESRD are very limited that can cause a physical, mental, and financial burden on the patient (Gupta et al., 2021).

1.2 Prevalence

According to the World Health Organization (WHO) renal diseases are said to have a major contribution to morbidity and mortality worldwide. Acute kidney diseases can be reversed if treated on time, however, chronic kidney diseases often progress into end-stage renal disease (Yang et al., 2020). The end-stage renal disease is treated by renal replacement therapy which is needed by an estimated 4.6 to 7.1 million people globally (Gupta et al., 2021). The worldwide increase in renal diseases is often driven by

hypertension, diabetes mellitus, obesity, and age which are further aggravated by infections, environmental toxins, and chemicals. According to a recent estimate, 10% of the adult population worldwide suffers from chronic kidney disease. Early on, the kidney ailment is frequently asymptomatic, making it difficult to detect and control until it reaches an advanced stage (Yang et al., 2020). Nevertheless, the acute kidney disease not only impacts the health conditions but it can also have a significant impact on a patient's life. It can affect the economic, mental, and physical health of the patient. In addition to having profound consequences on the overall quality of life, the kidney disease can put a financial and social burden on the patient.

1.3 Major types of renal diseases

Acute Kidney disease (AKD) and Chronic Kidney Disease (CKD) represent distinct renal disorders that possess distinct onsets, progression, and clinical symptoms.

1.3.1 Chronic kidney Disease

The slow and permanent loss of kidney function over a lengthy time, usually longer than three months, is the hallmark of CKD. Reduced glomerular filtration rate (GFR) below 60 mL/min/1.73 m2 or the presence of kidney damage indicators such albuminuria, abnormalities in urine sediment, or electrolyte imbalances are two of the main signs of CKD (Ronco & Clark, 2018). Since CKD frequently takes years or even decades to develop, the body is able to undertake compensatory changes to keep GFR and electrolyte balance. However, as this condition worsens, these compensatory systems cease to operate as well, which further impairs kidney function.

1.3.2 Acute kidney Disease

Acute Kidney disease, in contrast, is a very rapid and severe reduction in kidney function that takes place over a brief period of time. It can happen typically within hours or days. Acute factors such as severe infections, extreme dehydration, or high exposure to nephrotoxic chemicals frequently causes AKI (Irfan et al., 2019). In contrast to CKD, it

may be treatable if the underlying cause is found correctly. However, it can occasionally advance quickly, resulting in a high reduction in GFR and diminished urine production.

1.3.3 End stage renal disease (ESRD)

An end-stage renal disease is a severe form of renal disorder where the kidneys lose their function necessitating external support for survival. Chronic kidney disease often progresses to ESRD when it is not treated and cured on time. The glomerular filtration rate drops below 15 mL/min/1.73 m2 which is not enough to clear the excess water and uremic toxins from the body (Westphalen et al., 2020). At this point, it becomes necessary for the patient to use renal replacement therapy to maintain the body's equilibrium. The first and the most viable option to treat ESRD is a kidney transplant. However, finding a compatible donor can be challenging as hundreds of people often wait for kidney reception. Even after finding a donor, transplant rejection and immunosuppression after surgery can be a major challenge. Another renal replacement therapy is hemodialysis where the blood is filtered outside the body of the patient in a dialyser machine. The process of ultrafiltration aids in the removal of excess water and toxins from the body that occurs between the blood and dialysate (Irfan et al., 2019). As kidney transplants cannot be availed by every ESRD patient, therefore, hemodialysis sets in as a viable option for millions of patients worldwide. Despite all the significance, hemodialysis has its drawbacks such as having three to four sessions per week with each session lasting for several hours (Wei et al., 2022). It is estimated that more than 2 million people around the globe were receiving HD globally in 2010 to deal with ESDR. The number is expected to double in 2030. Another RRT option is peritoneal dialysis where the filtration of blood is carried inside the peritoneal cavity of the body.

1.4 Treatment options for End stage renal disease (ESRD)

Hemodialysis, peritoneal dialysis, and kidney transplantation are the three main forms of treatment for ESRD.

1.4.1 Hemodialysis

The first treatment option for ESRD patients is hemodialysis. It is a treatment procedure where the blood is drawn out of the body into a dialysis machine. Clean and detoxified blood is returned to the body after the successful elimination of wastes and excess fluids (Alayande et al., 2019). A semipermeable membrane is placed between the blood compartment and the dialysate compartment, which are the two primary sections of the machine. The membranes filter out the uremic toxins and excess fluid from the blood. The dialyzer imitates the kidney's function by restoring the body's electrolyte balance (Claudel et al., 2021). On average the hemodialysis is carried out three times a week with each session lasting for several hours. This therapeutic method helps restore the body's lost equilibrium; however, it can affect the standard of life of the patient.

1.4.2 Peritoneal dialysis

An alternate method of RRT is peritoneal dialysis, in which the patient's own peritoneum—a membrane lining the abdominal cavity—serves as the dialyzer. Waste materials and extra fluid diffuse across the peritoneal membrane into the specific dialysis solution that is infused into the peritoneal cavity (Mollahosseini et al., 2020). The used dialysis solution is emptied from the abdomen and fresh solution is infused after a period of dwell time. Home peritoneal dialysis enables patients to manage their treatment with more independence and flexibility.

1.4.3 Kidney transplant

When an appropriate donor kidney becomes available, kidney transplantation is thought to be the best possible treatment option for ESRD (Westphalen et al., 2020). A successful kidney transplant restores kidney function to nearly normal levels and vastly enhances the patient's quality of life. However, in order to perform a kidney transplant, a compatible donor is needed, and potential patients must go through a thorough assessment to make sure they are good candidates (Mollahosseini et al., 2020). Immunosuppressive drugs must be used by patients after transplantation in order to avoid organ rejection and extend the life of the transplanted kidney.

Table 1.1 Types of treatment options for kidney disease.

Aspect	Hemodialysis	Peritoneal Dialysis	Kidney Transplant
Treatment Method	Machine filters blood outside body	Abdominal cavity with dialysis solution	Transplant healthy kidney into recipient
Risk of Infections	Potential risk from access sites (catheters, fistulas)	Lower risk of bloodstream infections	Higher risk initially, lower with proper post-transplant care
Frequency of Treatment	3 times/week, 3-4 hours/session	Daily exchanges at home	Single procedure, on-going monitoring
Quality of Life	Impact on quality of life	Generally better	Improved quality of life
Long-Term Cost	Generally higher	Typically lower	Initial costs higher

1.5 Research Gap

Hemodialysis is a life-sustaining treatment option for people suffering from renal diseases. Millions of people around the globe rely on the hemodialysis as a treatment option for ESRD. This treatment method supports the life of the patient by removing excess water and uremic wastes from the blood of the patient in the dialyzer machine. The fundamental component of the dialyzer is a semipermeable membrane that separates the blood and dialysate compartment through which the process of ultrafiltration occurs. Various polymeric membranes are commercially employed including PAN, PVDF, cellulose acetate, and PES (Ronco & Clark, 2018). Among all other polymers PES based membranes are preferred owing to their strong mechanical strength, high chemical resistance, and high pH resilience. However, one thing that limits the performance of the PES membranes despite the tremendous significance is the intrinsic hydrophobicity (M. Sun et al., 2010). The hydrophobic nature of PES limits the performance of the membrane in two ways. Firstly, a hydrophobic surface allows the adherence of substances on the surface or within

the pores of the membrane leading to a phenomenon known as fouling. Fouling is the clogging of the pores or the formation of a cake layer on the surface of the membrane that substantially leads to a reduction in the fluid flow and decline in the overall performance. To sustain the steady flux it becomes imperative to increase the trans-membrane pressure that ultimately leads to increased energy consumption and decreased operational life (Heidari et al., 2021). Secondly, the hydrophobicity of membrane leads to compromised hemocompatibility. In circumstances where a foreign material comes in contact with the blood, it is important that the material should not lead to coagulation of blood. Nevertheless, a hydrophobic surface is an ideal condition for proteins and platelets in the blood to adhere to the surface. Once adhered firmly to the material, the platelets are activated which further initiates the coagulation cascade. Either intrinsic or extrinsic pathway of coagulation is activated through which the blood clot is formed (Mollahosseini et al., 2020). Consequently, it is of great significance to enhance the hydrophilicity to limit the fouling and enhance hemocompatibility, both of which are essential in hemodialysis. It is imperative to investigate the effects of introduction of hydrophilic pore-former, particularly PVP and PEG, into the PES membranes. More research is required to comprehend how different hydrophilic pore-formers impact the morphology and performance of membranes when they are used solely and in tandem. Moreover, in-depth research is requisite to understand the influence of addition of hydrophilic additives on the hemocompatibility of HD membranes.

1.6 Objectives of Research

- Fabrication of PES membranes using varied concentration of water soluble pore-former additives, (PEG) and (PVP), individually and in tandem.
- Determination of the impact of varied porosity on the performance of membranes in terms of water flux.
- Evaluation of antifouling properties of membranes in terms of BSA rejections.
- Investigation of potential of synthesized membranes for hemocompatibility in terms of urea clearance and hemocompatibility.

1.7 Research framework

The total work that has to be accomplished in this research is divided into three phases.

- **Phase 1**

The initial step entails the production of casting solutions by adjusting the concentrations of the utilised polymers (PES/PVP/PEG) as well as adjustments in temperature and time required to make homogenous solutions. The second step involves the fabrication of membranes with varying compositions and characteristics.

- **Phase 2**

Following the successful fabrication of polymeric membranes, a number of characterisation techniques will be used to examine the physical and chemical features. The techniques include Scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (ATR-FTIR), tensile testing, water retention, contact angle and flux determination.

- **Phase 3**

The final phase entails testing which includes the determination of performance of membrane in terms of BSA rejection, antifouling, urea clearance and hemocompatibility evaluation of membranes using various tests.

CHAPTER 2: Literature Review

2.1 Hemodialysis

For individuals with ESRD, hemodialysis is one of the most prominent and efficient RRT options. In hemodialysis, a semipermeable membrane inside a dialyzer filters the patient's blood outside the body (Raharjo et al., 2022). The dialyzer restores the body's electrolyte balance by filtering particles and extra fluid from the blood. The patient's body is subsequently given back the cleaned blood. Three times a week, on average, hemodialysis is carried out, and each session lasts for several hours (Irfan et al., 2019). To maintain the balance of electrolytes and avoid fluid overload, it is imperative that the patient follow a rigorous dietary and fluid consumption plan.

2.1.1 Substances removed and retained during hemodialysis

2.1.1.1 Urea and Creatinine

These are molecules that are products that remain from the metabolism of proteins. Both urea and creatinine are by-products of the breakdown of amino acids in muscles (Rosner et al., 2021). Each must be effectively eliminated to avoid building up in the blood, which can result in uremic toxicity and issues associated to the kidneys.

2.1.1.2 Electrolytes

Potassium and phosphorus needs to be efficiently removed from the blood. Hyperkalaemia, which can result from high potassium levels, can trigger fatal cardiac arrhythmias. Hypophosphatemia, which can cause bone and cardiovascular issues in kidney patients, is a result of elevated phosphorus levels (Rosner et al., 2021).

2.1.1.3 Middle size molecules (Beta-2-microglobulin and leptin)

Beta-2 microglobulin is an intermediate molecule that builds up in kidney failure and, if not properly eliminated, can cause dialysis-related amyloidosis (Clark et al., 2019).

Elevated levels of leptin in renal patients are linked to obesity because it affects metabolism and satiation.

2.1.1.4 Excess fluids

Edoema, hypertension, and congestive heart failure can all result from fluid overload, which can be avoided by eliminating extra fluid.

2.1.1.5 Toxins and metabolites

Two uremic toxins that contribute to cardiovascular and other problems in renal failure are indoxyl sulphate and p-cresol. Their elimination lessens the chronic inflammation that renal patients encounter (Magnani & Atti, 2021).

2.1.1.6 Substances retained

Important electrolytes like sodium, calcium, and magnesium, which support fluid balance, neuronal function, and bone health, must be kept in the blood during hemodialysis. In the maintenance of osmotic pressure, immunological response, and delivery of nutrients, proteins like albumin and immunoglobulins play important functions (Rosner et al., 2021). Erythropoietin, a hormone, and vitamin D are crucial for the synthesis of red blood cells, bone health, and other physiological processes. Growth factors help with development, repair, and growth (Clark et al., 2019). One such growth factor is insulin-like growth factor-1 (IGF-1). Red and white blood cells and platelet are essential for oxygen transport, immunological function, blood clotting, and wound healing. In conclusion, nutrients like glucose and amino acids act as fuel and building blocks for vital cellular functions (Magnani & Atti, 2021). Therefore, during hemodialysis, all of these chemicals must be retained within the blood.

2.2 Basic mechanisms of hemodialysis

In patients with kidney failure, diffusion, ultrafiltration, and osmosis are crucial processes that work synergistically to efficiently remove waste products, control fluid balance, and maintain electrolyte levels during hemodialysis.

2.2.1 Diffusion

Diffusion is the movement of solutes (dissolved substances, such as electrolytes and waste products) from a region of higher concentration to one of lower concentration (Pstras et al., 2022). Blood travels through one side of the dialyzer, carrying waste materials and extra electrolytes. Dialysate is a special fluid that is present on the other side of the membrane. The dialysate's composition is managed to have a lower concentration of wastes and electrolytes than the blood.

2.2.2 Osmosis

Osmosis is the flow of water from a region with a lower concentration of solutes to a region with a higher concentration of solutes through a semipermeable membrane. Specific electrolyte concentrations are achieved by carefully formulating the dialysate solution (Raharjo et al., 2022). Water moves from the blood across the membrane into the dialysate to equalise concentrations if the blood contains more solutes (such as electrolytes) than the dialysate.

2.2.3 Ultrafiltration

The process of ultrafiltration helps to maintain the fluid balance in the body by removing extra fluid and nitrogenous waste from the bloodstream. Pressure variations across the semipermeable membrane are required for it to force out water from the bloodstream and through the membrane into the dialysate compartment by pressure (Ronco & Clark, 2018). The dialyzer membranes are designed to retain bigger molecules like proteins while allowing water to pass through (Irfan et al., 2019). A net migration of fluid from the circulation into the dialysate is caused by equilibrium between hydrostatic pressure and osmotic pressure.

2.2.4 Convection

The second process involved in the filtration in hemodialysis is convection. The process refers applying hydraulic pressure to remove solutes and fluid from the blood

(Westphalen et al., 2020). Convection involves the movement of solutes and fluid as a result of the physical force of the fluid flow itself, as opposed to diffusion and osmosis, which depend on concentration gradients.

2.3 Major components of hemodialyser

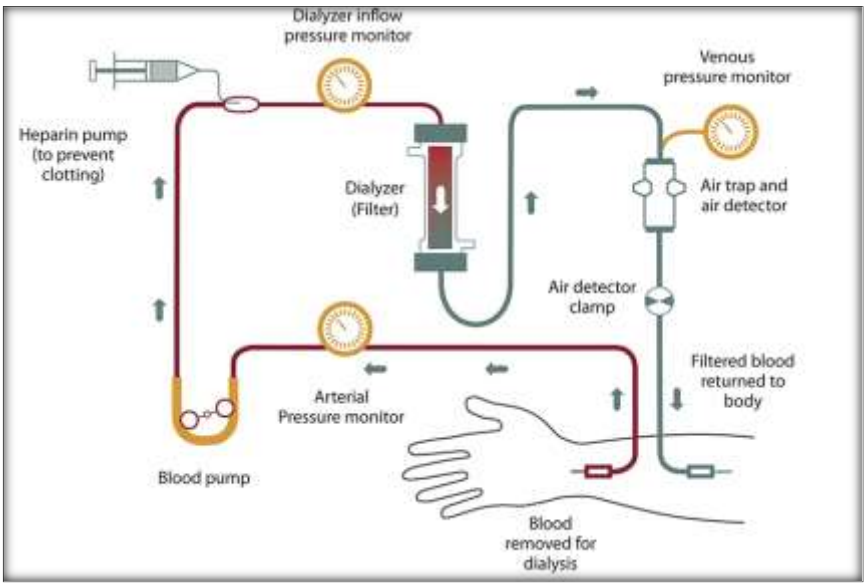


Figure 2.1: Simplified illustration of Hemodialysis system

The next important part of the hemodialyzer is the blood compartment. Here the blood from the patient is injected into the dialyzer. The semipermeable membrane is used to separate it from the dialysate compartment (Specifications, 2020). Blood from the patient body flows in this compartment which makes it possible for the phenomenon of dialysis to occur.

2.3.1 Dialysate compartment

The most important component of the dialysis system is dialysate compartment. A specific fluid termed dialysate is kept in this compartment. The semipermeable polymeric barrier lies between the blood compartment and the dialysate compartment (Area, 2020). One of the most important aspects is to keep a balanced composition of the dialysate. Any inconsistencies can greatly jeopardize the overall efficiency of the treatment (Irfan et al.,

2019). It is important to keep a balance osmotic gradient in the dialysate as to keep the process of the hemodialysis in a steady state.

2.3.2 Semipermeable membrane

A most crucial element that divides the blood and dialysate compartments is the semipermeable membrane. Based on their molecular size and gradient in concentration, it enables the selective diffusion of solute. Small waste molecules from the blood diffuse out of the membrane to the dialysate, particularly urea and creatinine (Specifications, 2020). By the process of diffusion, osmosis and convection the uremic toxins flow out the semipermeable polymeric membrane into the dialysate compartment. The essential components from the dialysate enter the blood compartment. A few dialyser use hollow fibres of porous membrane which can significantly enhance the surface area for waste removal.

2.4 Working principle of dialyser

The dialyzer imitates the actions of the kidneys by using the phenomena of diffusion, ultrafiltration, and osmosis. The process of dialysis is simple and efficient. The first step is the select a vascular access point. This point can be used to draw out blood from the patient and to deliver into the blood compartment (Pstras et al., 2022). Once a connection is made to draw blood out, it is flown into blood compartment. There a semipermeable membrane separating the blood compartment from the dialysate compartment. In the dialysate compartment the specialised solution called the dialysate is present. Between the two compartments the most important part, the semi permeable porous polymeric membrane, is present. It allows for the selective passage of waste materials particularly urea, creatinine and beta macroglobulin from the blood (Irfan et al., 2019). Meanwhile, the precisely controlled composition of dialysate produces an osmotic gradient that causes waste materials to flow out by osmosis. As a result of the pressure gradient created across the semipermeable membrane, ultrafiltration occurs (Ronco & Clark, 2018). This happens when the hydrostatic pressure on the dialysate side is greater compared to that on the blood side. Excess fluids and certain solutes are successfully removed from the circulation with

this procedure (Area, 2020). After a thorough circulation of the whole blood through the dialyser during a couple of hours the cleaned blood is returned to the body of patient. In this way the dialyzer supports patients with end-stage kidney disease by aiding to maintain fluid levels and electrolyte balance through this complex process (Specifications, 2020).

2.5 Semi permeable Polymeric membranes

The function of kidneys is to filter the unwanted waste and retain the substances that are required by the body. The glomerulus of the nephron provides a network through which the process of filtration is carried out. Similarly, inside the dialyzer machine, a polymeric membrane is installed that works by filtering the substances based on size (Azhar et al., 2021). This thin membrane contains several thousands of tiny pores that span inside the structure from the top to bottom. The pores are interconnected which provides a channel for the fluid to pass across thereby halting the larger substances to move. Conversely, there is another type of membrane that does not contain pores called the non-porous membrane (Asif Khan et al., 2023). These kinds of polymeric membranes are employed for packaging in various industries. In conclusion, there are two types of membranes based on the presence of pores, porous and non-porous membranes. Moreover, other types include symmetrical and asymmetrical based on morphology. The membranes used for hemodialysis are porous and asymmetrical (W. Sun et al., 2013). The porous nature of polymeric membranes is very essential to its performance as the interconnected pores provide a pathway for the fluids to pass through while not letting the larger molecules move across the structure. In scientific terms the working principle of membranes is size exclusion where the smaller fluid molecules are selectively permeable whereas the larger molecules are sieved off (Wei et al., 2022). In the case of hemodialysis, the excess water from the blood is allowed to move to the dialysate side along with small unwanted molecules like urea and creatinine. While larger particles like blood cells and proteins are size excluded.

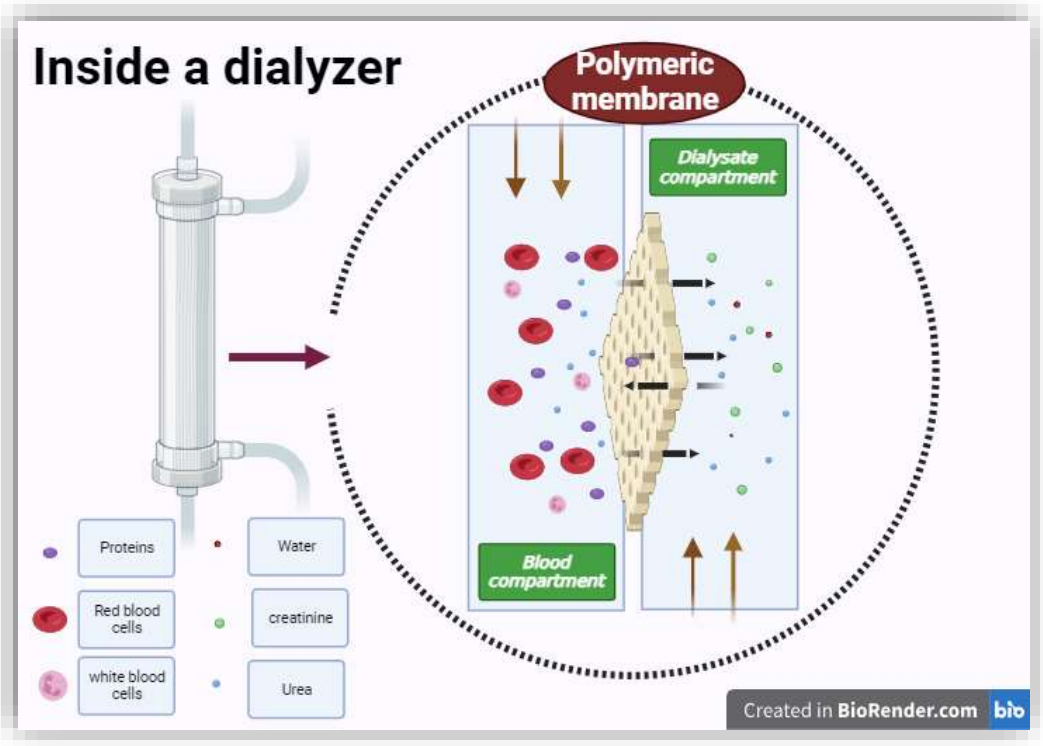


Figure 2.2: Depiction of process of hemodialysis.

The selectivity and permeability of the membrane is most essential and it is influenced by the size and structure of these pores. The permeability works in a way that smaller pores improve selectivity but it can reduce the flux. Whereas larger pores increase permeability and water flux but it may reduce selectivity (J. Lv et al., 2018). Therefore the membranes are prepared depending on the required characteristics and intended use. Typical polymers utilised in membrane fabrication Polyamide (PA), polyethersulfone (PES), Polysulfone (PSU), polyvinylidene fluoride (PVDF), and cellulose-based compounds (Wang et al., 2022). Among these cellulose based membrane are widely used. All of these polymers are important in their own ways because each type of polymer has unique properties (Alayande et al., 2019). For instance they have the properties like chemical resistance, mechanical endurance, and thermal stability.

Irrespective of the polymer used, hydrophobicity or hydrophilicity is a key factor for determining the performance of these membranes. For pressure-driven operations, hydrophobic polymers with good mechanical, chemical, and thermal resilience are used (Irfan & Idris, 2015). However, hydrophobic membranes are not widely employed as the lesser wettability is not a preferred feature for various applications. Hydrophilic membranes, in contrast, have higher surface tension and can create hydrogen bonds with the water molecules (Mokarizadeh & Raisi, 2021). This feature can minimise membrane fouling by rejecting organic molecules and not letting the proteins to adhere onto the surface of membrane. Therefore, hydrophilic membranes are the preferred choice for biomedical applications.

2.6 Types of membranes

The membranes are categorised on various basis which include porosity, morphology and size of pores. The membranes which are non-porous are used in application like food and product packing. Other than that membranes are categorized on the basis of filtration properties (Shi et al., 2014). Porous polymeric membranes can be divided into different categories. Reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), microfiltration (MF), and other types of separation procedures all rely on pressure-driven mechanisms for their functioning (Shi et al., 2014).

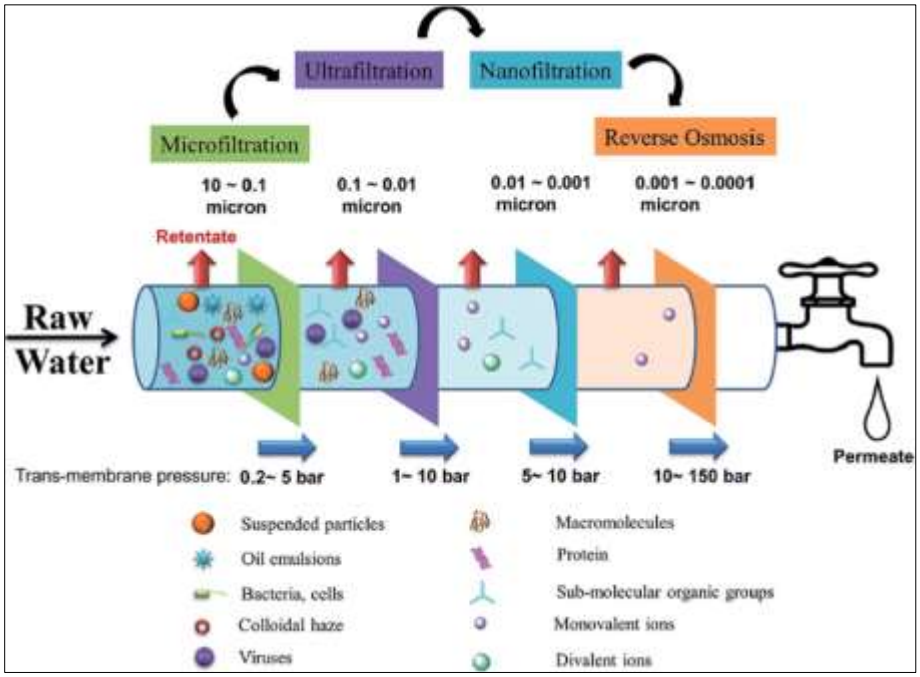


Figure 2.3: Various types of polymeric membrane

2.6.1 Microfiltration membranes

The first types of porous membranes are microfiltration membranes. These membranes have pores that are relatively big, ranging in size from 0.1 to 10 micrometres (Anis et al., 2019). These membranes are effective at removing larger colloidal species, bacteria, and suspended particles from liquids. MF is frequently used when achieving coarse filtration is the main objective and finer separations are not required.

- Applications of MF membranes

Microfiltration membranes are used in various sectors including wastewater treatment, food and beverage, and pharmaceuticals companies. In wastewater treatment the microfiltration membranes are employed to filter out the larger sized particles as a pre-treatment to ultrafiltration and reverse osmosis processes (Mollahosseini et al., 2020). In

microfiltration larger particles like colloidal particles, bacteria, microorganism and larger viruses can be filtered out from the raw water. In food and beverage industry the microfiltration membranes are employed to filter out larger particles suspended in solution (Anis et al., 2019). Undesirable particles like bacteria and yeast are also removed to sterilize and concentrate juice, dairy products and other beverages in beverage industry (Bilad et al., 2012). Other than that these membranes have a great importance in biomedical settings as these membranes are employed for blood filtration in hemodialysis, cell separation and sterilisation of medical equipment in some cases (Anis et al., 2019).

2.6.2 Ultrafiltration membranes

The next types of membranes are ultrafiltration membranes which have a wide variety of applications ranging from water treatment to biomedical applications. The membranes having a pore size of 0.003-0.01μm are called ultrafiltration membranes. The pore size is smaller than that of microfiltration and larger than that of nano-filtration membranes (Al Aani et al., 2020). These membranes have a thick outer layer called the skin/dense layer and a network of interlinked pores that enable the selective separation of molecules according to their size and form.

- **Applications of UF membranes**

Ultrafiltration membranes are more selectively permeable to substances than microfiltration membranes. Colloidal substances, bacteria, and viruses can be successfully filtered out using ultrafiltration membranes (Shi et al., 2014). The process of ultrafiltration is mostly used before nano-filtration to remove the larger particles to aid in the nanofiltration. Most often, ultrafiltration is used to purify raw and brackish water mostly from the industry effluents (Mokarizadeh & Raisi, 2021). Moreover, it is used in the pharmaceutical and biomedical industry for various purposes such as purification and concentration of proteins. Other than that, hemodialysis membranes fall under the category of ultrafiltration membranes.

2.6.3 Nano filtration membranes

Nanofiltration membranes have pores that are even smaller than UF, ranging in size from 0.001 to 0.01 micrometres. Monovalent and divalent ions, as well as organic compounds, can be separated using NF. Typically, thin-film composite materials are used to create nanofiltration membranes (Mohammad et al., 2015). These membranes contain a porous support layer underneath a dense active layer. The active layer has nanoscale pores with a particular surface chemistry that enable interactions with solutes dependent on charge and size.

- **Applications of NF membranes**

In contrast to conventional water softening techniques, NF membranes can efficiently remove divalent ions from water, including calcium and magnesium. Additionally, NF is used to concentrate important components in industrial effluent streams and to eliminate colour- and odor-causing substances from drinking water (Oatley-Radcliffe et al., 2017). Proteins, peptides, and other biomolecules are purified and concentrated using nanofiltration in pharmaceutical research and drug development. It helps to achieve highly pure products and eliminate contaminants.

2.7 Reverse osmosis membrane

The tiniest pores among all the porous membranes, which typically range from 0.0001 to 0.001 micrometres, are found in reverse osmosis membranes. RO is very selective and capable of removing most organic compounds, ions, and salts to make a highly purified permeate. These membranes are widely employed in wastewater treatment to produce high-quality effluent, water purification for producing drinking water, and desalination of seawater (Hailemariam et al., 2020). This membranes works by rejecting dissolved solutes and ions based on interactions between size and charge, the active layer's nanoscale pores enable the passage of solvent molecules (Al Aani et al., 2020).

- **Applications**

Seawater desalination is one of the most substantial applications for reverse osmosis membranes. RO technology is widely utilised to create fresh drinking water from seawater, giving areas with limited access to clean water a stable source (Hailemariam et al., 2020).

In labs and research settings, RO systems are also frequently utilized to provide deionized water. This particular type of water is required for certain tests and analytical processes where the presence of contaminants and ions might affect the results (Shi et al., 2014).

2.8 Membrane fabrication (Phase inversion technique)

The polymeric membranes are important because of their porous structure wihch can be created using various techniques. The most prominent methods are track etching, electro-spinning, ionizing radiations, Nano imprinting, and phase inversion method. Among all of these methods, phase inversion is the simple and straightforward (Hołda & Vankelecom, 2015). This technique does not require additional chemicals or reactions which makes it a good choice for making porous membranes. Using this technique homogeneous polymer solution can be transformed into a porous structure. Phase inversion has a number of benefits including ease of use, scalability, and precise control over porosity. Phase inversion methods include thermal-induced phase separation (TIPS), nonsolvent-induced phase separation (NIPS), and vapor-induced phase separation (VIPS) (Young & Chen, 1995).

2.8.1 Non-solvent-induced phase separation (NIPS)

The process of non-solvent phase inversion involves combining polymer dope solution with non-solvent. A homogeneous polymer solution is produced by dissolving the polymer in a solvent. When the thin film of polymer solution is submerged in a non-solvent phase inversion occurs (Hołda & Vankelecom, 2015). The solvent from the polymer solution mixes with the non-solvent creating two phases, Polymer-rich phase and polymer lean phase. Now as the polymer in the polymer-rich phase is not soluble in non-solvent it starts to precipitate. The polymer lean phase makes pores and voids within the membrane structure. This demixing between solvent-non solvent produces asymmetric membranes (Alayande et al., 2019). The top layer of the membrane is usually very dense and the bottom layer is made of voids.

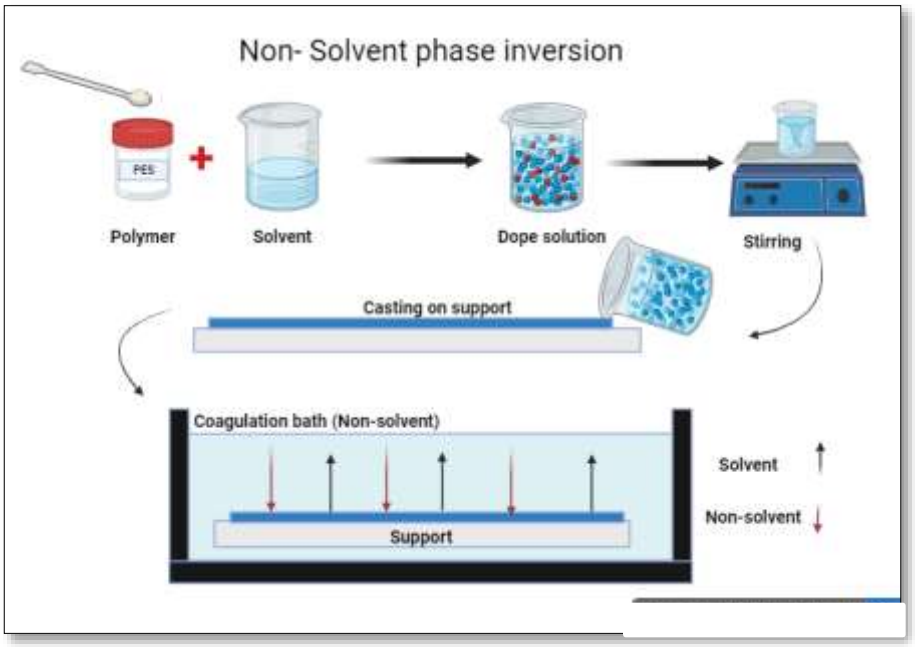


Figure 2.4: complete process of non-solvent induced phase inversion.

2.8.2 Thermally induced phase separation (TIPS)

Another method for making porous polymeric membranes is thermal-induced phase inversion. The polymer is dissolved in a solvent at a regulated temperature to create a polymer solution (Hołda & Vankelecom, 2015). The polymer in the thin film becomes insoluble as the temperature is altered. This causes the precipitation of the polymer creating a porous membrane. The properties of the membrane, such as its overall shape and pore size, are strongly influenced by the pace of cooling and its final temperature (Warsinger et al., 2018).

2.8.3 Vapour induced phase inversion (VIPS)

Another method of phase inversion that uses vapour rather than a liquid non-solvent is called vapour-induced phase inversion. The process is similar to NIPS, where a thin film of polymer solution is applied to a support. The Vapour causes phase inversion; this vapour might be a specific volatile chemical or just regular water vapour. (Young & Chen, 1995). The polymer is insoluble in the vapour used in this procedure, whereas the solvent is

miscible in it. A concentration gradient is produced when the thin layer is exposed to vapour. The solvent evaporates when the vapour is absorbed by the thin layer. The film precipitates when the solvent evaporates, and the vapour is absorbed into it thereby greatly reducing the solubility of the polymer. Therefore, the dynamics of evaporation and absorption have a crucial part in determining the structure of membrane (Dong et al., 2021).

2.9 Fouling of polymeric membranes

The process of filtration is brought about by the presence of pores which help in the permeation of water thereby obstructing larger substances that pollute water. However, the clogging of pores can be a challenging issue that might significantly reduce the performance of membranes. The phenomenon of clogging of pores by various substances that decrease the filtration efficiency of membranes is known as fouling (Yin & Zhang, 2021). There are various types of fouling depending upon the type of foulant. For instance, blockage of pores with bacterial and viral debris is known as biofouling, whereas, organic substances may cause organic fouling. The other types include scaling and colloidal fouling. Most of the time, the foulant is removed by backwashing of the membranes allowing a steady fluid flow across the membrane. However, it becomes a matter of great concern when the foulant is trapped inside the pores making it an irreversible fouling. This can happen when the foulant is dissolved in fluid and pushed inside the pores which cannot be simply removed by back washing of membrane (Azhar et al., 2021).

In the case of hemodialysis, fouling of membranes can be a critical limitation that can seriously jeopardize the life of an ESRD patient. Firstly, the clogging of pores can greatly reduce the uremic toxin clearance (Shi et al., 2014). Inefficient removal of wastes causes an imbalance in the body's equilibrium which can worsen the already declining renal condition. In addition to that, adherence of proteins on the membrane surface can elicit a coagulation cascade. The formation of clots on the membrane surface or within the pores further reduces the ultrafiltration efficiency (Asif Khan et al., 2023). Even more concerning is that the clots can lead to serious health conditions with fatal outcomes. Therefore, it is imperative to synthesize membranes that have antifouling properties (Chen et al., 2022), (Yamamoto et al., 2005).

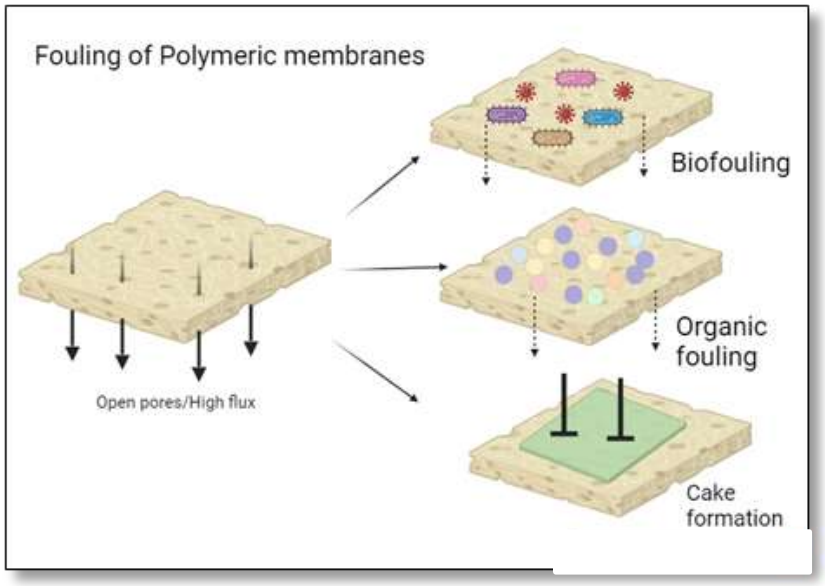


Figure 2.5: Various types of fouling of polymeric membrane.

2.10 Sources of fouling of hemodialysis membrane

2.10.1 Proteins

Among many substances from the blood, proteins have the highest affinity to bind to the polymeric membranes. In particular, albumin and fibrinogen have the greatest tendency to adhere to the surface of polymeric membranes (Howe & Clark, 2002). A protein-rich layer is created which might reduce the effective pore size and change the permeability of the membrane (Abe et al., 2021). The flux is reduced and uremic toxins are not effectively eliminated. This compromises the effectiveness of dialysis and could have detrimental effects on the patient's health. According to the kind of foulant, the type of fouling that proteins may cause is called biofouling or organic fouling. Adherence of proteins not only causes fouling of membranes but also leads to eliciting of inflammatory and thrombotic events. The coagulation cascade can be initiated following the adherence of proteins which can jeopardize the life of the patient during hemodialysis.

2.10.2 Blood clots

When the blood comes in touch with the hydrophobic surface of the membrane, the proteins start to adsorb on the surface. Platelets from the blood also adhere to the surface which causes their activation (Claudel et al., 2021). The activated platelet initiates the coagulation cascade either using the intrinsic or the extrinsic coagulation pathway. Once coagulation is initiated it produces clots on the surface of the polymeric membrane. The blood clots can clog the pores of the membranes thereby reducing the flux (Irfan et al., 2019). In addition to this, clotting of blood can be extremely dangerous for the patients which can worse into fatal results.

2.11 Detrimental effects of fouling of polymeric membranes

- **Decreased permeability**

Once the pores within the membranes are clogged with various particles and wastes, the pathway for solvent transport is limited. This causes a reduced waste water and toxin removal thus making the whole process less effective (Yamamoto et al., 2005). . This can ultimately be detrimental for the patient who is completely dependent on renal replacement treatment for ESRD

- **Increased trans-membrane pressure**

During hemodialysis, resistance to blood flow is created as fouling builds up on the membrane surface and interior. In order to maintain appropriate blood flow rates, needs higher trans-membrane pressure (Zainol Abidin et al., 2022). However, it raises the danger of membrane degradation and losing is structural integrity

- **Inflammatory response**

When platelets adhere to the surface of the membrane they trigger clotting. The organic fouling can also cause release of chemicals into blood which can lead to inflammatory events. This can jeopardize the safety and efficiency of hemodialysis (Mollahosseini et al., 2020).

- **Thrombosis**

When the surface of membrane is hydrophobic platelets may adhere to it. Once the platelets are adhered and activated they may initiate the coagulation cascade. Both intrinsic and extrinsic pathways are activated which causes the conversion of soluble fibrinogen into fibrin (Irfan et al., 2019). The fibrin makes a secondary plug on the surface of the membrane thus making clots. These clots can be extremely dangerous often leading to fatal events. Therefore, it is imperative to use membranes which are hemocompatible.

2.12 Antifouling techniques

Owing to the above mentioned adverse effects of membrane fouling it is imperative to investigate into the fouling resistant features of membranes. Table 2 presents various methods to induce antifouling character into the material using some of the widely employed techniques. To increase the antifouling capabilities and provide improved performance and longer-term use a number of methods have been considered.

2.12.1 Surface modifications

The first method employed to avoid fouling is to make surface modifications. It is a typical method for improving the antifouling capabilities of polymeric membranes (Song et al., 2021). Fouling substances are less likely to adhere to the membrane when hydrophilic functional groups or zwitterionic moieties are integrated onto the surface.

- **Coating**:

The surface of a substance is the first component to come into contact during any interaction. Next to the surface is the bulk, or matrix. Consequently, altering the surface may be crucial to reducing membrane fouling. The process of applying a substance (the coating) on the surface of a material is known as coating (Banerjee et al., 2011). The substratum is the material on which a coating is applied. Coating a material involves applying a single layer or multiple layers of a substance on the substrate. The goal is to give the material desirable and supplementary features. When it comes to membranes, the coatings provide the substrate membranes with the desired characteristics (Asif Khan et al., 2023). It is ensured that the coating is uniformly distributed all over the membrane. The

membrane surface is coated using a variety of methods, including electro-spinning, spin coating, and dip coating depending upon the nature and application of the material (Banerjee et al., 2011). Coatings are used to improve the functionality, hydrophilicity, and functionality of polymeric membranes.

- **Grafting**:

Another method for improving the antifouling characteristics of membranes is grafting. Grafting entails attaching antifouling functional groups to the membrane surface by chemical bonding (Banerjee et al., 2011). Examples of grafting include covalently attaching reactive monomers on the surface to improve the hemocompatibility of HD membranes.

- **Incorporation of nanomaterial:**

The addition of nanomaterials into the polymer is another way of modification of membranes. In recent research, scientists are incorporating nanoparticles into polymeric membranes to alter the intrinsic properties and induce desired characteristics. For instance, the incorporation of silver nanoparticles, carbon nanotubes, and graphene oxide particles in membranes to bring favourable attributes have gained great attention (Fahrina et al., 2021).

2.12.2 Bulk modifications

As opposed to surface modification which involves the alteration of the outermost layer of the material, bulk modification involves the alteration of both the matrix and the surface. This type of modification holds importance as it involves the alteration of the overall chemical composition of the material (Kadanyo et al., 2022). The additive is uniformly dispersed throughout the material giving it consistent features. The bulk modification is be achieved by employing various techniques which as follows (Heidari et al., 2021).

- **Blending of hydrophilic additives**:

Producing a homogenous polymer mixture to alter the chemical and physical properties of a material is known as blending. This method of bulk modification is considered simpler than other techniques as it does not require any additional step in the final material fabrication (Otitoju et al., 2018). In the case of membranes, the hydrophobicity of the material is altered by blending hydrophilic polymers into the material. For instance, PES is a hydrophobic polymer that limits the functionality and performance of membranes due to low wettability. However, the addition of hydrophilic additives is proven to improve the wettability character of the PES membranes (J. Lv et al., 2018).

2.13 Hemocompatibility

Hemocompatibility testing refers to the testing of response of a biomaterial in case of interaction between foreign material and blood. This phenomenon is critically important in situations where a foreign body comes in direct contact with the blood. For instance, the blood contact with biomaterial includes the interaction with stents, vascular grafts, and dialysis systems. The interaction between blood and foreign bodies encompasses several aspects such as thrombosis, hemolysis, immunogenicity, and inflammation (Nalezinková, 2020). In the case of hemodialysis, the most important event in hemocompatibility is the activation of the blood coagulation system. It involves a series of events that causes the activation of clotting factors which ultimately lead to the formation of a clot. In simple terms, coagulation means the conversion of soluble fibrinogen into insoluble fibrin which acts as a meshwork to seal an injury (Wei et al., 2022). Coagulation is of significant importance when it is formed in instances where the body needs it naturally such as healing after injury. However, coagulation and the formation of clots when not necessary can cause adverse effects. For instance, clot formation in the dialysis system can adversely impact the efficiency of dialysis. Coagulation of blood in a dialyzer machine happens when the polymeric membranes employed for ultrafiltration are not hemocompatible (Mollahosseini et al., 2020). One of the main reasons for hemo incompatibility is the hydrophobic nature of the membranes. The hydrophobicity enhances the protein and platelet adsorption on the surface of polymeric membranes thus leading to the activation of coagulation cascade. Therefore, it is of utmost significance to have membranes that are hydrophilic in nature

and that do not promote the adherence of proteins on the surface of membranes (Irfan & Idris, 2015).

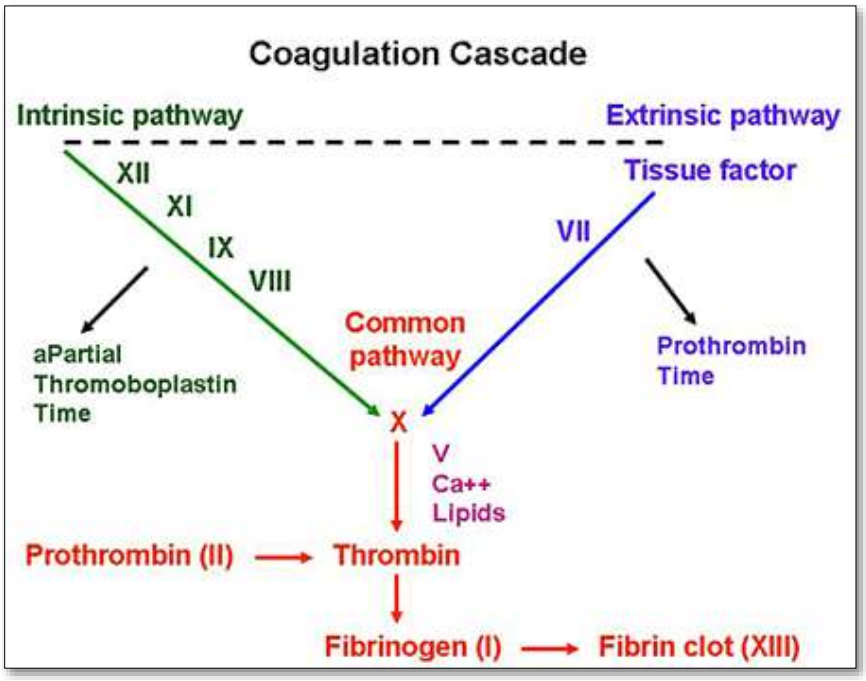


Figure 2.6: Complete process of coagulation cascade showing intrinsic, extrinsic and common pathway.

The intrinsic pathway is also known as the contact activation pathway which is activated when blood comes in contact with a negatively charged surface. A cascade of enzymatic events is activated which causes the formation of a clot. This type of pathway is particularly important in the activation of coagulation systems in foreign materials like medical devices (Mollahosseini et al., 2020).The most important factor is the Hageman factor also known as factor XII which initiates the cascade of coagulation event. When this factor comes in contact with negative charges it is converted into activated XIIa. Following the activation of the Hageman factor, factor XI is activated. This factor further stimulates the conversion of factor IX into IXa (Irfan et al., 2019). This activated IXa along with its cofactor makes the tenase complex. In the presence of calcium ions and phospholipids, the intrinsic tenase complex activates factor X. Here factor X is converted into Xa. At this point the intrinsic pathway converges with the extrinsic pathway, therefore it is known as

a common pathway (Kohlová et al., 2019). The intrinsic pathway is slightly complex and it takes much longer to make a clot than the extrinsic pathway. The test conducted to measure the amount of time for the formation of clots using intrinsic pathway is known as activated partial prothrombin time (APTT).

2.13.1 Extrinsic pathway

Unlike the intrinsic pathway, the extrinsic pathway is activated in a biological response to an injury. When the blood is exposed to tissue factor after an injury this pathway is activated that is simpler and quicker in comparison to the intrinsic pathway (Nalezinková, 2020). The rapid action of clot formation is important to effectively stop excessive blood loss. The amount of time it takes for a clot to form using an extrinsic pathway is measured using partial thromboplastin time (PTT) (Irfan et al., 2019). The clinical range is normally less than 14 seconds.

When there is an injury, blood is exposed to the tissue factor, which intensifies the coagulation cascade. When tissue factor, a glycoprotein that is ordinarily absent from the blood, gets exposed to it, the extrinsic route is triggered. (Nalezinková, 2020). Factor VII is activated which further activates factor XI. As XI is part of the common pathway, the coagulation is sped up. The activation of X into Xa causes the convergence of intrinsic and extrinsic pathways called the common pathway (Mollahosseini et al., 2020).

2.14 Polyethersulfone (PES)

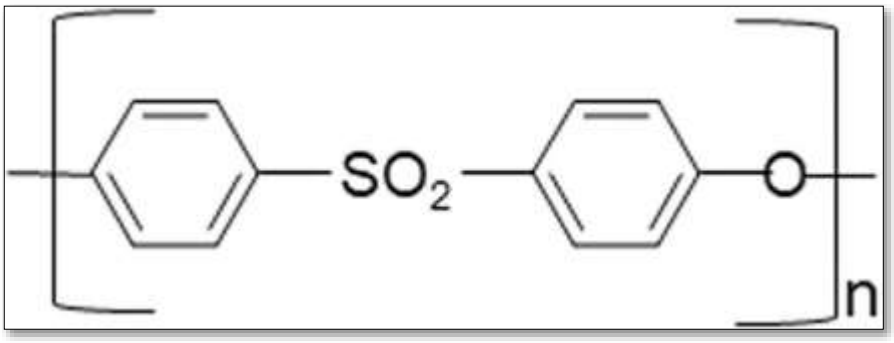


Figure 2.7: Chemical structure of polyethersulphone.

Polyethersulfone is an amorphous thermoplastic polymer known for its high thermal and oxidative resilience. The molecular structure of the PES is made of repeating units of sulfone and ether groups (Mokarizadeh & Raisi, 2021). The remarkable features for which PES is widely used for numerous applications include high mechanical strength, good resistance to acid-bases, and thermal stability. The thermal properties are noteworthy, enhancing its suitability for high-temperature applications. However, PES has a low thermal conductivity making it a good insulator (Azhar et al., 2021). Owing to the mentioned attributes PES has a diverse set of applications, with the most important ones in the biomedical industry. The Polymer PES is used in a wide variety of medical devices where biocompatibility and resistance to sterilization are crucial. Additionally, PES is used in the manufacturing of membranes ranging from microfiltration to nanofiltration and reverse osmosis for the purpose of water treatment and gas separation (Al Malek et al., 2012). However, the polymer is not without limitations. The high thermal stability and resilience of pH can make it challenging to recycle the polymer. Furthermore, its intrinsic hydrophobic nature causes hindrance in the process of filtration.

2.15 Polyethylene glycol

Polyethylene glycol is a hydrophilic polymer made up of repeating units of ethylene glycol. This polymer is synthesized in various molecular weights which broadens its applications from biomedical to pharmaceutical industry. Moreover, the attribute to attach various reactive functional groups to the terminal of this polymer further enhances its applicability (Ma et al., 2011). The fact that PEG is non-toxic and hydrophilic makes it a suitable option for use in biomedical and pharmaceutical applications. The common uses of PEG include drug delivery, tissue scaffold, cell culture, and wound healing. PEGylation is a term used for the process where the PEG is covalently grafted onto molecules (Heidari et al., 2021). This is used to enhance the water solubility and biocompatibility of the molecules which are mostly employed for drug delivery. For drug delivery applications, PEG is used for the fabrication of liposomes, dendrimers, and micelles (Ma et al., 2011).

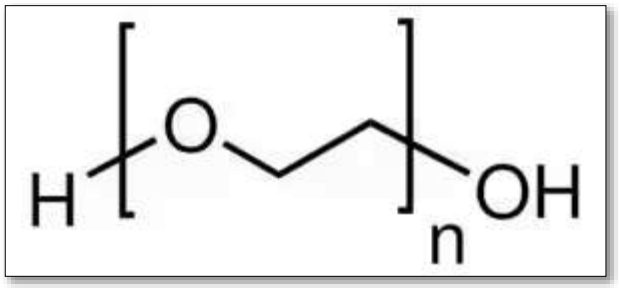


Figure 2.8: Chemical structure of polyethylene glycol.

2.16 Polyvinylpyrrolidone PVP

Polyvinylpyrrolidone is a water-soluble and non-toxic polymer that is composed of repeating units of N-vinylpyrrolidone. This polymer is present in various molecular weights according to which the characteristics change (Mireles et al., 2020). Owing to its high-temperature stability, pH resistance, and biocompatibility this polymer is widely used in biomedical applications. In drug delivery systems this polymer is used to encapsulate hydrophilic and lipophilic drugs (Schwarz, 2018). Moreover, PVP has been utilized in novel drug delivery formulations, orthopedics, and tissue engineering applications. Before medical applications, PVP was utilized in the hair spray industry to make hair fixative agents.

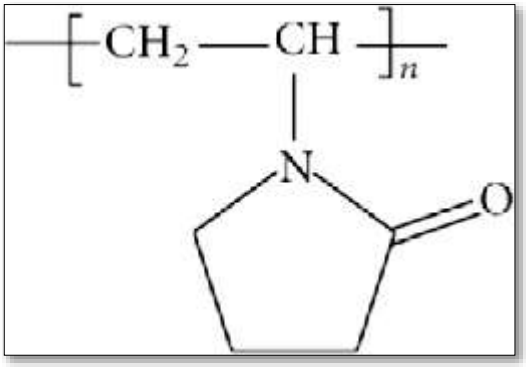


Figure 2.9: Chemical structure of PVP

CHAPTER 3: Methodology

3.1 Chemical reagents

Analytical-grade chemicals were used throughout the entire experimentation. During the fabrication process, deionized water (DI) was used for the coagulation of membranes. The base polymer of membrane, polyethersulfone (PES) of molecular weight of 58000 g/mol, was acquired from Ultrasone Germany. Polyvinylpyrrolidone (PVP), of molecular weight 40,000 g/mol was purchased from Avantar vwr. Polyethyleneglycol 1000 g/mol (PEG) was acquired from Merck Germany. N-methyl-2-pyrrolidone (NMP) solvent was acquired from Sigma Aldrich, Germany. BSA (purity>97%) and Urea were purchased from Sigma Aldrich, Germany. Polyethylene fabrics were used as support during membrane casting.

3.2 Membrane fabrication

The membranes were synthesized using a variety of solutions with different levels of polymer concentration. PES was employed as the base polymer with a fixed amount in each type of solution. PES was steadily added into the solvent to prevent polymer clumping and to form a homogeneous solution. Various concentrations of PVP and PEG were dissolved in NMP to achieve a total solution of 100% wt for each of the dope solutions. The temperature of 60 °C and the stirring speed of 400 rpm were set to ensure optimal polymer dissolution. The procedure was carried out until the PES and all the associated components were completely homogenised. The mixture was then left overnight to release the trapped air bubbles.

Table 0.1: Chemical composition of the fabricated membranes along with the codes

Membrane code	**PES %**	**PVP %**	**PEG %**
M1	18	2.5	0
M2	18	5	0

M3	18	0	2.5
M4	18	0	5
M5	18	2.5	2.5

The prepared homogeneous solutions were uniformly cast using a 150 mm thick casting knife and an automatic film applicator (Filmography, Elcometer) with a casting speed of around 2 cm/s. Thin films were created on a glass plate-mounted support made up of flexible polyethylene/polypropylene. The casting was carried out at a controlled temperature of around 24-25°C and relative humidity of 20%. The membranes produced were subsequently preserved in glycerol for four hours to retain the pore structure. Membrane pieces were precisely cut, rinsed, and dried thoroughly before each test.

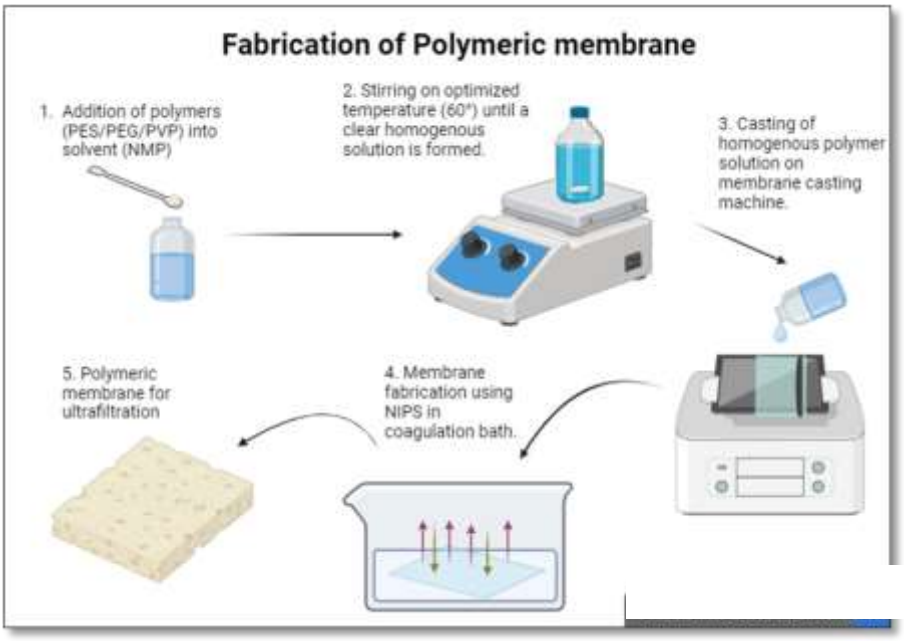


Figure 0.1: Schematic diagram fabrication process of polymeric membrane.

3.3 Characterization of synthesized membranes

3.3.1 SEM analysis

The cross-sectional morphology of the fabricated PES membranes were assessed using SEM (JEOL-JSM-6490LA) operating at a 20 kV electron beam. Liquid nitrogen was used to freeze and break the samples before the analysis. Multiple images were taken at different magnifications to observe the symmetry and morphology of the fabricated membranes.

3.3.2 ATR-FTIR analysis

To assess the chemical structure of the fabricated membranes ATR-FTIR analysis was conducted. The Agilent Cary 630 FTIR spectrometer with an Attenuated Total Reflection (ATR) module was employed. Membrane samples were cut into pieces of 1 cm^2. The samples were then subjected to a spectral resolution of 2 cm^2 within the 400–4000 cm^2 wavenumber range. Reliable databases and literature were used to compare the detected spectrum peaks.

3.3.3 Contact angle analysis

To determine the wettability and hydrophilicity of membranes contact angles were measured. KRüss DSA-25 Drop Shape Analyzer was employed for the analysis. The contact angle was measured using the built-in software following the injection of a drop of DI water onto the membrane surface. The contact angle was measured on three distinct points on each membrane to ensure the accuracy of the results.

3.3.4 Tensile strength analysis

One of the most important characterization techniques used to access the strength of the material. For that purpose the Shimadzu AG-X plus model of the Universal Testing Machine (UTM) was utilized to assess the mechanical strength of the synthesized membranes. The samples were prepared per the ASTM D882 standard. The membranes were carefully cut into rectangular pieces that measured 24.5 mm in length and 15 mm in width. All specimens were subjected to uniform loading conditions by applying a testing velocity of 50 mm/min. To guarantee the accuracy of the findings, three samples of each membrane were examined.

3.3.5 Porosity %

To measure the porosity percentage (ε), the membrane samples were cut into 2 cm^2 pieces, immersed in 10 ml of DI water in a vial and thoroughly soaked for 24 hours. Following the immersion period, the samples were taken out, and excess water from the surface was removed by gently placing them between dry filter paper. After that, the weights of the wet membrane samples (Ww) were measured using a calibrated balance. In order to determine the dry weight (Wd), the samples were heated in a vacuum oven at 30˚C for 2 hours and then the weights of the dry samples were measured using a weighing balance. Then, the following formula was used to determine the porosity percentage.

$$\boldsymbol{\varepsilon = \frac{Ww - Wd}{A \times \rho \times \delta} \times 100} \qquad \textbf{(I)}$$

here ρ is the water density (0.998 $g \cdot cm^{-3}$), A is area of the membrane, and δ is the thickness of sample.

3.3.6 Water retention capacity

For the measurement of water retention capacity, a precision blade was used to cut each membrane sample into pieces measuring 2 cm^2. Then, a calibrated balance was used to measure the dry weight (Wd) of each sample. Following the measurement of dry weights, the sample pieces were immersed in a vial containing 10 ml of DI water for 24 hours. After the immersion period, the samples were removed from the vial and excess water from the surface was gently removed using dry filter paper. Finally, the samples were reweighted (Ww) using a calibrated balance. The following formula was used to determine the water retention capacity.

$$\boldsymbol{Water\ retention} = \frac{\mathbf{Ww - Wd}}{\mathbf{Ww}} \times \mathbf{100} \qquad \text{(II)}$$

3.4 Membrane performance

3.4.1 Pure water flux

Membranes of equal dimensions were securely positioned within the dead end filtration cell, which was connected to a nitrogen cylinder to uphold a constant pressure of 0.2 MPa. A preconditioning procedure was carried out to make sure the membranes were free of any trapped air and to help open the pores. To achieve a steady and wet state, the membranes were pressurised for 30 min. Once preconditioning was completed, DI water was passed through the membranes, and the amount of time it consumed for a fixed volume of filtrate to pass was carefully noted. The obtained values were then put into the following equation:

$$J = \frac{\mathrm{V}}{AT} \qquad \text{(III)}$$

Whereas 'V' indicates the volume of pure water permeated, 'A' denotes the effective area of the membrane, and 'T' is the amount of time it takes for water to pass through it. 'J' stands for the permeate flux, which is computed in $L.m^{-2}h^{-1}$.

3.4.2 BSA rejection and Antifouling

The antifouling property of the synthesized membranes was examined using BSA as the reference protein. An aqueous solution of BSA (1 g/L) was prepared at room temperature. The pure water J1 ($L.m^{-2}h^{-1}$) flux was first measured at 0.2 MPa pressure as described above. BSA solution was then passed through the filtration cell to evaluate the flux. The filtrate was collected and set aside to determine the BSA rejection percentage. After that, the membranes were slightly rinsed with distilled water and another batch of pure water was filtered using the same membrane to determine the J2. The antifouling capacity of the membranes was measured using the flux recovery ratio (FRR %) and BSA concentration in filtrate was measured using a UV-vis spectrometer at 270nm as explained in previous studies

$$BSA\ rejection\ \% = \frac{1-\mathrm{Cp}}{cf} \times 100 \quad \text{(IV)}$$

$$FRR\% = \frac{\mathrm{J2}}{\mathrm{J1}} \times 100 \quad \text{(V)}$$

3.4.3 RSM for Urea Clearance

Membrane M5 was selected for urea clearance performance testing based on its ideal attributes, which include outstanding hydrophilicity, best flux, and antifouling performance. Central composite design (CCD) in Response surface modelling was employed to identify and analyse the ideal combination of properties of the synthesized membrane M5 for urea clearance. For evaluation of the impact of the input factors on the urea clearance, response surface plots were created using the Design Expert software. CCD provided 11 permutations consisting of 3 centrally coded levels. Pressure and concentration were identified as two main factors influencing the membrane's performance. Experiments were carried out in accordance with the −α and +α levels generated by the software.

Table 3.2: Input variables and their high/low ranges used in central composite design.

	Name	**Units**	**Low**	**High**	**-alpha**	**+alpha**
A	**concentration**	mg/l	800	1200	717.157	1282.84
B	**pressure**	MPa	0.2	0.6	0.117157	0.682843

3.5 Hemocompatibility tests

3.5.1 Activated partial thromboplastin time (APTT)

The hemocompatibility behaviour of the prepared membrane M5 was assessed using human blood and its plasma. Human blood was obtained into 3 ml sodium citrate blood collection tubes with a blood-to-anticoagulant ratio of 9:1. A membrane sample (1.0 × 1.0 cm2) was equilibrated in PBS at 37 °C for 1 h. Then the sample was taken out and

immersed in 1 mL of PPP at 37 °C for 1 h. Fully Automated Coagulation Analyzer CA-620 Syesmex was used to measure the APTT and PT.

3.5.2 Hemolysis ratio

To determine the hemolytic activity of the membrane whole blood was collected from a healthy volunteer by venepuncture into tubes containing sodium citrate. To dilute the blood PBS buffer was added at a 2:8 ratio. 1x1 cm^2 of each sample was incubated with 1 mL of diluted blood for two hours at 37 °C. Following incubation, blood samples were centrifuged at 1500 g for 10 minutes at 4 °C, and plasma Hb levels were determined spectrophotometrically at 540 nm. Calculations were made to determine the absorbance of the test samples, the negative control (DI water), and the positive control (PBS buffer). The following formula was used for the calculation of the final hemolysis ratio (HR).

$$hemolysis\ \% = \frac{\mathrm{Hs}-\mathrm{Hn}}{\mathrm{Hp}-\mathrm{Hn}} \times 100 \qquad \text{(VI)}$$

Where absorbance of membrane sample, negative control and positive control is Hs, Hn, and Hp respectively.

3.5.3 Plasma recalcification time

The sample membranes were cut into 1 × 1 cm2 pieces, then were rinsed three times with PBS and were allowed to equilibrate for one hour at 37 °C. After that, the PBS was removed, and 0.5 ml of fresh PPP was added to the membrane at 37 °C. Finally, 0.5 ml of aqueous $CaCl_2$ solution (0.025 mol/L) was added. To identify fibrin threads, a stainless-steel hook was submerged in the solution, and time was recorded from the addition of $CaCl_2$ solution to the first fibrin thread that appeared on the hook.

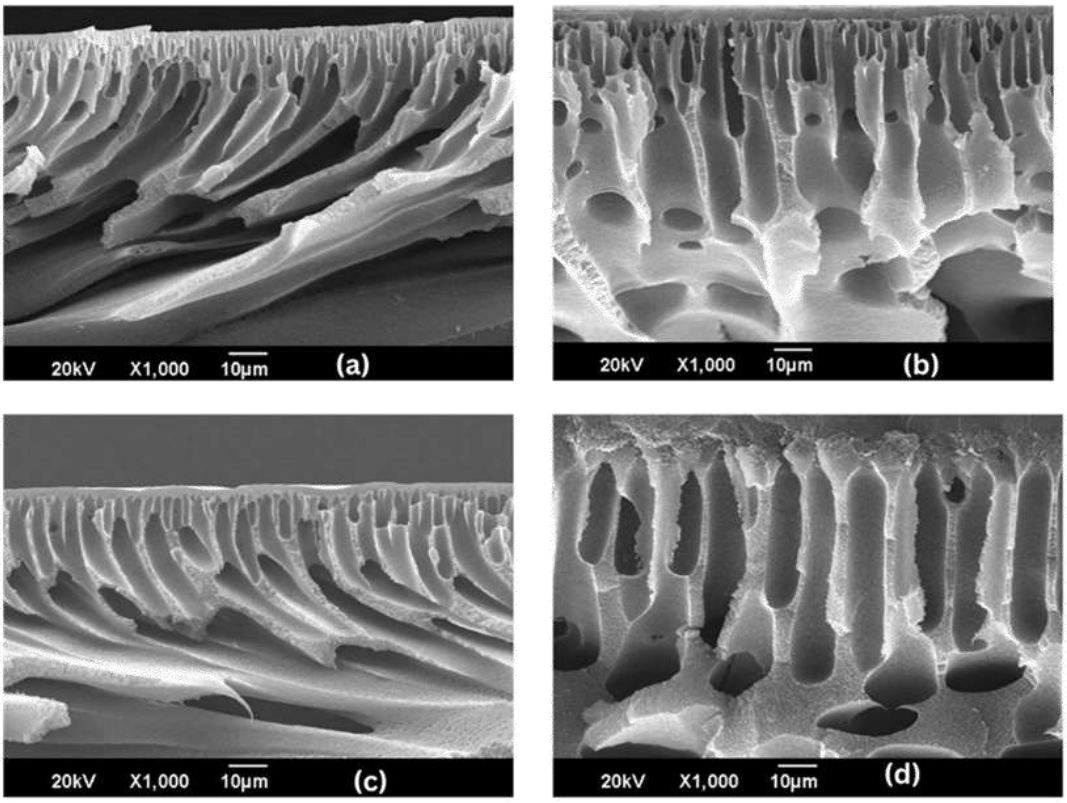
3.5.4 Statistical analysis

For the statistical analysis Graphpad Prism 10 was used. The statistical difference between membranes was evaluated using one way ANOVA. Bonferroni correction was used as post hoc test for doing multiple group comparison.

CHAPTER 4: Results

4.1 Scanning electron microscopy

Scanning electron microscopy was employed to investigate the cross-sectional microstructure of the membranes. Figure 4.1 illustrates that the SEM observations confirmed that each membrane sample had a different bilayer structure with a compact top layer and characteristic macro-void architecture in the lower segment. These findings substantiate the precise and effective homogeneity of polymeric components throughout the membrane structure. When the casting solution is initially immersed in a non-solvent (DI water), the top layer immediately solidifies, resulting in a surface that is densely packed. As the diffusion rates decrease over time, the bottom layer takes on the appearance of finger-like structures.



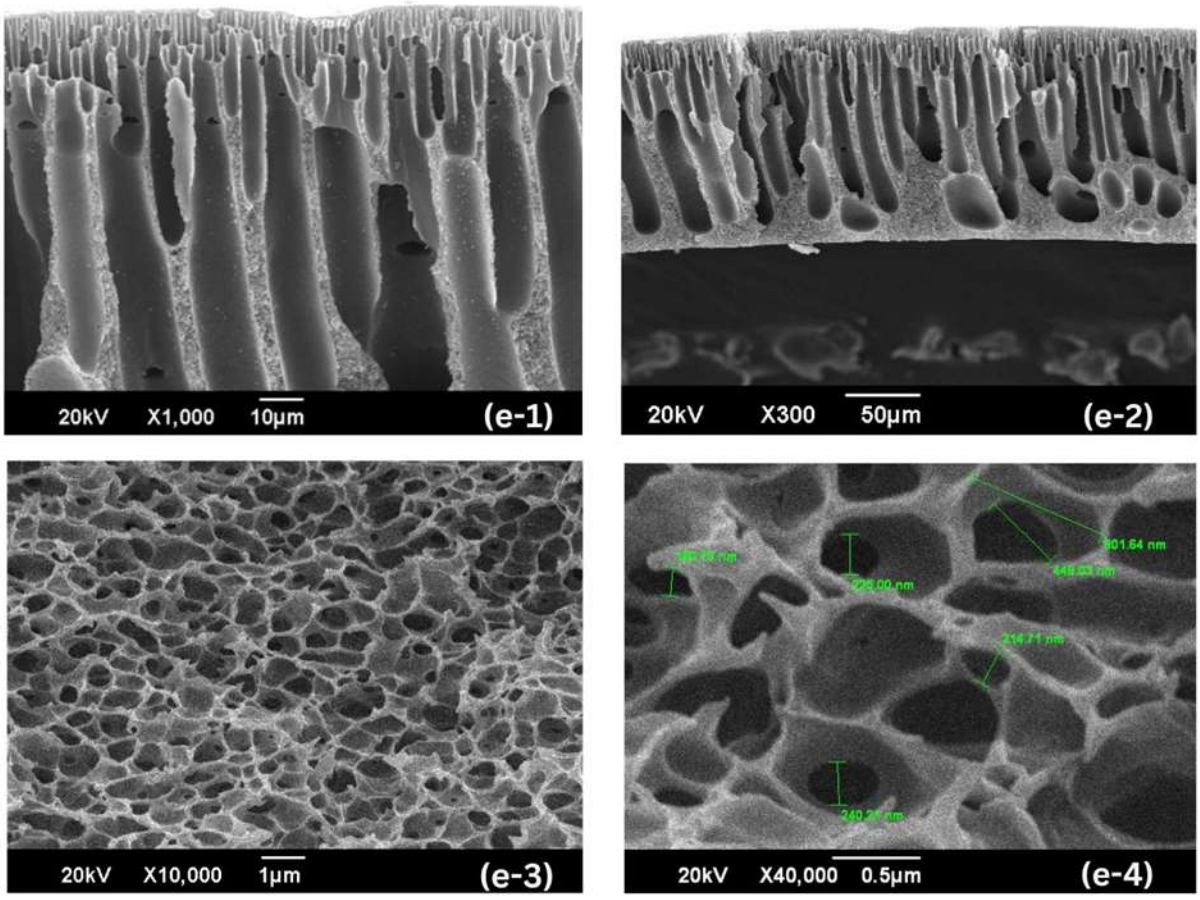


Figure 4.1: SEM cross sectional images of the fabricated membranes.

As seen in SEM images(a) M1 (b)M2 (c) M3 (d) M4 (e) M5 (1,2,3,4 images of membrane on various magnifications) , the morphological characteristics of the PES membranes were influenced by the pore-forming agent that was utilized. When PEG was employed, the membranes displayed long, continuous, finger-like channels that extended from the upper dense region to the lower sections as seen in figure 4.1(c) and (d). Conversely, as can be seen in figs. 4.1(a), membranes synthesized with PVP exhibited finger-like channels that diverged laterally as opposed to forming long, continuous channels that extended to the bottom of the membrane.

SEM images of membrane M1 show that the lower concentration of polymer appears to accelerate solvent and non-solvent exchange during phase inversion. The formation of larger and broader voids in the bottom layer of the membrane is indicative of rapid solvent diffusion rates. At 5% PVP concentration, membrane M2 shows a slightly thicker dense skin layer due to higher viscosity and slower demixing of solvent-non solvent. Given the elevated PVP content, this morphology indicates a delayed phase inversion process. Membrane M3 which has 2.5% PEG, has a thinner skin layer. The mild phase inversion kinetics is associated to lower PEG concentration in this membrane. The bottom layer is comparatively more prominent and includes numerous voids. Conversely, membrane M4 has a skin layer of intermediate thickness at higher polymer concentrations. Decreased solvent-non solvent exchange rates resulted in the formation of finger-like channels that are fewer in number yet closely packed. Membrane M5 has a distinct morphology with an intermediately thick skin layer due to the simultaneous addition of two hydrophilic polymers. The appearance of finger-like channels, which have characteristics in between those of PVP and PEG-only membranes, suggest a synergistic effect on the phase inversion process. The well-developed skin and bottom layer indicate a stable association between the two pore-forming agents. In this membrane the demixing time is greatly enhanced due to higher viscosity of solution (Hołda & Vankelecom, 2015). As a result smaller and narrower voids as well as a greater number of pores are developed within the membrane structure (Alibakhshi et al., 2019). The SEM micrographs in Figure 4.1 offer strong evidence that the kind of pore former, polymer concentration, and dope solution viscosity all had a significant impact on the formation of pores and macro-voids within the membrane.

4.2 FTIR analysis

Spectroscopic analysis of pure and hydrophilic blended PES is presented in Figure 4.2. The appearance of similar peaks in pure and blended membranes shows the successful fabrication of membranes. All of the membrane samples display a characteristic peak at 1350 cm^{-1} which indicates the presence of the sulfone functional group of (O = S = O) of PES (M. Sun et al., 2010). The appearance of a peak at 1510cm^{-1} points to the aromatic bond of the benzene ring in PES. Membrane M1 contains PVP, the characteristic peak for

which is indicated by the presence of the C=O stretching bond of the amide band of the pyrrolidone ring on 1610 cm-^{1} (Mireles et al., 2020). Membrane samples M1 and M2 had similar compositions with only difference in concentration of PVP, therefore, both of the samples showed comparable results (thus M2 is not shown in the figure). In the case of M3 and M4, which had PEG as a hydrophilic additive appears to display a peak at 3400 cm-^{1} and 1480 cm-^{1} that indicate the OH and CH_2 groups respectively (Dinç & Güner, 2017). Again M3 and M4 had similar compositions owing to which they had similar peaks (M4 not shown in graph). The last membrane, M5, which incorporates two hydrophilic additives, has the respective peaks for both, indicating successful fabrication of the membranes. There is a discernible difference in the spectra of all samples since PES is the major polymer with higher concentration with PVP and PEG as additives having low concentration.

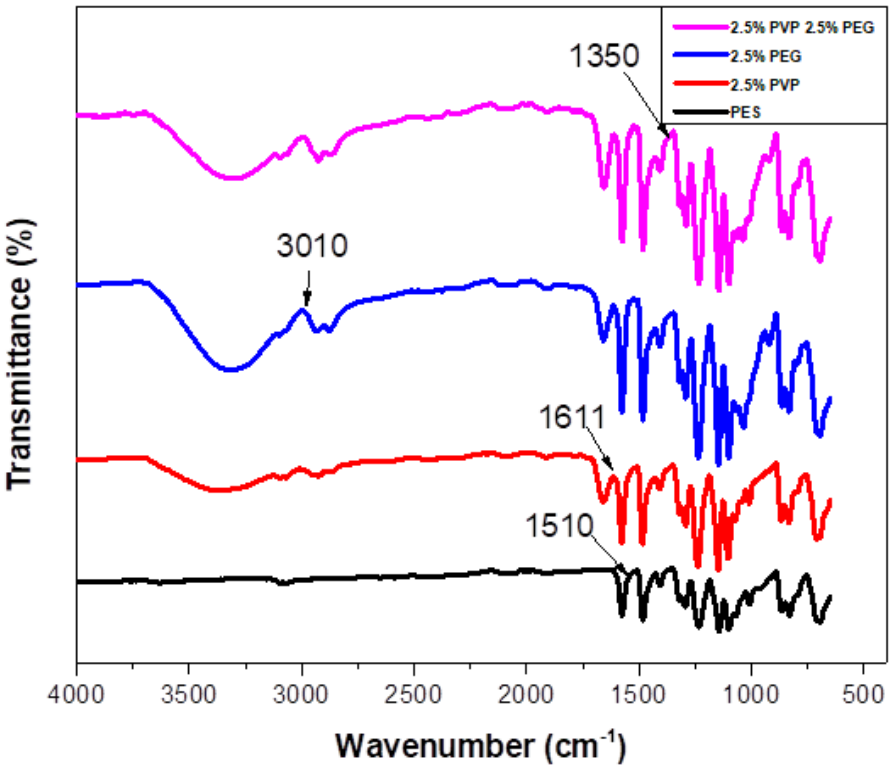


Figure 4.2: FTIR analysis of the fabricated membranes.

4.3 Contact angle analysis

Given that polyethersulfone is naturally hydrophobic, membranes made entirely using it have low surface wettability properties. Blending hydrophilic compounds can effectively increase the hydrophilicity. The results show that the addition of WSP, PEG, and PVP significantly improves the wettability of the membranes.

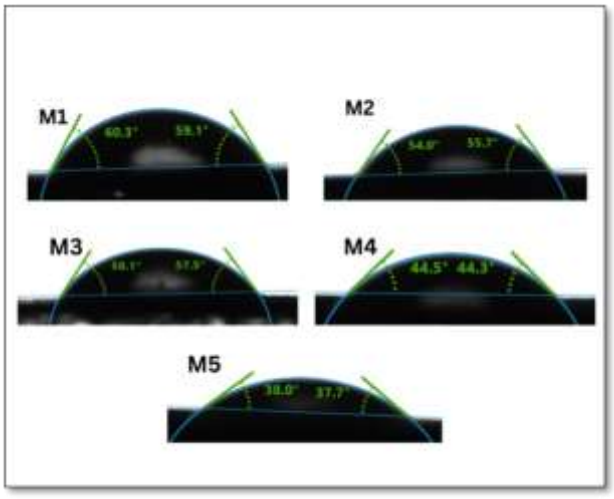


Figure 4.3: Contact angles of the hydrophilic enhanced membranes.

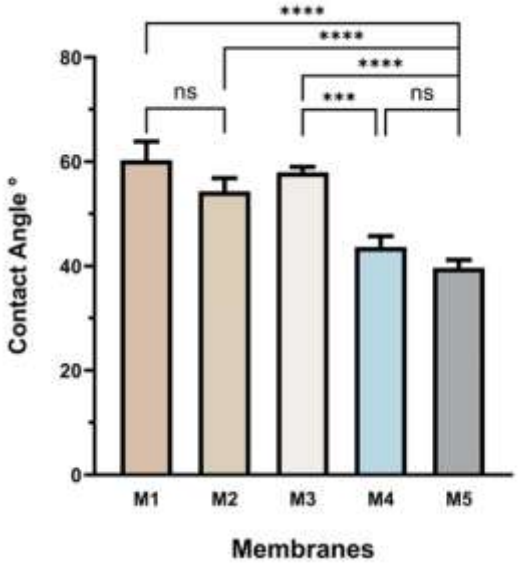


Figure 4.4: Graphical presentation of the contact angles of the membranes.

As can be seen in figures 4.4 (a) and (b), membrane M1, which has a 2.5% PVP concentration, has a contact angle of 60°; however, when the concentration in M2 is increased to 5%, this angle decreases to 54.7°. Comparably, membranes M3 and M4 exhibit significant decreases in contact angles with increasing PEG concentrations; they drop from 54° at 2.5% PEG to 44° at 5%. It was observed that PEG-based membranes exhibited superior hydrophilicity when compared to PVP-based membranes. A reduced contact angle of 38° indicates that the combination of dual WSP PVP and PEG in membrane M5 further increased the hydrophilicity. Additionally, employing both of the hydrophilic pore formers together yielded better results in terms of wettability and hydrophilicity than using them separately even at higher concentrations (Heidari et al., 2021). The results show a strong correlation between the composition of the membrane and surface wettability, indicating that these additions significantly increase hydrophilic properties. These modifications are crucial for hemodialysis because they can improve the membrane's blood compatibility and ability to eliminate toxins from the blood (Mokarizadeh & Raisi, 2021).

4.4 Water retention

The ability of the membranes to retain water was assessed, as seen in figure 4.5. Capacity of membrane M1 was only 50.8%, but increased to 56.42% when PVP content in M2 was increased to 5%. Following a similar trend the water retention capacity of membranes M3 measures 54.02% increased to 58.1% in membrane M4 when the PEG concentration was raised from 2.5% to 5%. Membranes containing PEG are found to be slightly more hydrophilic than those containing PVP. Membrane M5 had the greatest water absorption of 65.4% among all membranes, which is most likely the result of blend of the two hydrophilic polymers. These results suggest that the water uptake characteristics might be carefully adjusted to meet ultrafiltration needs. This can be achieved by altering the membrane's composition, specifically the proportion of hydrophilic components (Ma et al., 2011). This knowledge may be especially helpful when developing HD membranes, where water retention and permeability control are crucial.

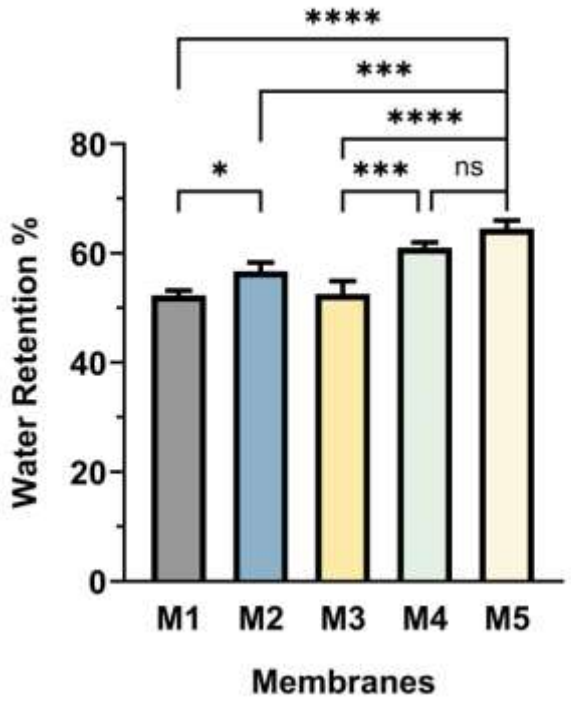


Figure 4.5: Graphical presentation of water uptake capacity of the fabricated membranes.

4.5 Porosity

One of the most important metrics is the porosity of membranes that evaluates the structural features and, consequently, performance of the ultrafiltration membranes. Increased permeability, flux, and antifouling properties of ultrafiltration membranes are dependent on a porosity percentage.

Figure 4.6 presents compelling evidence of a direct relationship between the concentration of pore-forming polymer and the resultant porosity %. With both PVP and PEG additions, membrane M5 had the greatest porosity percentage (57.3%) out of all the membranes evaluated. With 5% PVP, M2 exhibits a notable porosity of 51.3%. The porosities of membranes M1, M3, and M4 range from 41% to 42%. SEM images clearly demonstrate a complex network of linked pores spanning the membrane structure providing validity to these results. It is understood that the Solvents can pass more easily through the membrane matrix when there is an abundance of passageways formed by increased porosity. The Fouling reduction is an additional benefit of a highly porous

structure composed of interlinked pores (Alayande et al., 2019). It is well understood that Fouling agents such as suspended particles and macromolecules can clog the membrane surface and matrix during filtration processes. However, when a membrane includes interconnected pores, the likelihood of fouling agents impairing the membrane's function is much reduced (Khan et al., 2020). The linked pores provide multiple pathways for solute transport and reduce the possibility of fouling agent trapping, extending the operating lifetime of membrane.

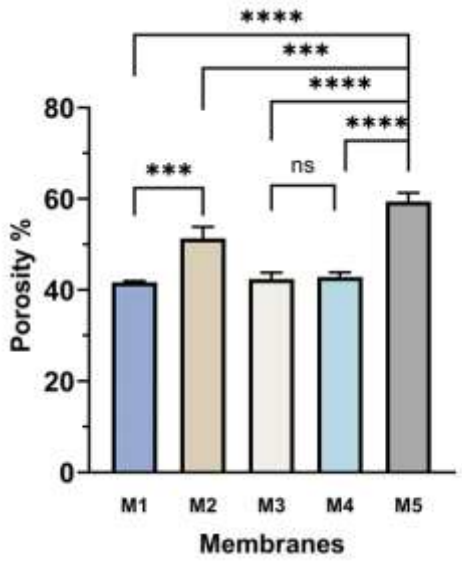


Figure 4.6: Porosity percentage of the various membranes.

4.6 Tensile strength

Blood filtration under pressure is necessary for hemodialysis, therefore, HD membranes need to have tensile strength to guarantee structural strength and durability during the procedure. Membranes with significant tensile strength prevent rupture or distortion during filtration, ensuring safety of patient (Ronco & Clark, 2018). The PES-based membranes that are altered with addition of PVP and PEG have tensile strength determined by the concentration of polymeric additives.

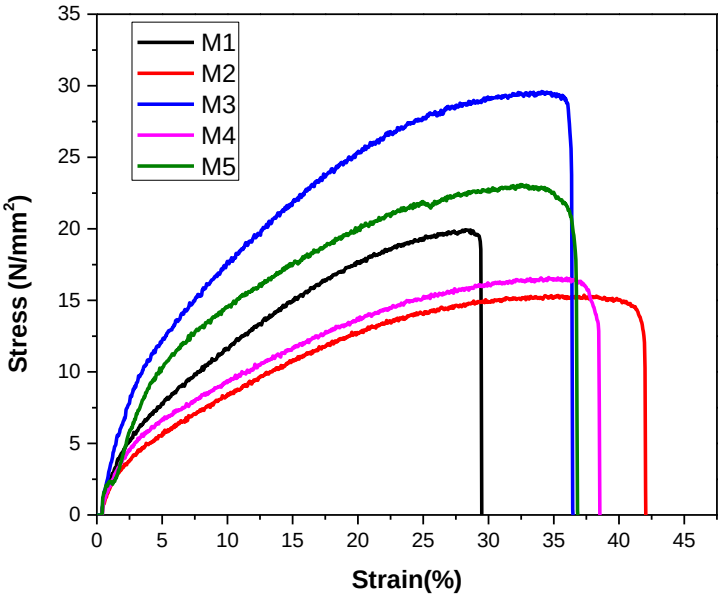


Figure 4.7: Stress-Strain curve of the membranes.

Figure 4.8 (a) and (b) illustrate that when 2.5% PVP is added to PES, the membrane M1 shows a moderate elastic modulus (2.15 MPa) and an ultimate tensile strength (19.92 MPa). Both characteristics decline in M2, which contains a higher PVP content, suggesting that increased concentration of pore-former has a negative effect on the tensile strength of membranes. The incorporation of PEG in M3 and M4 demonstrates that a higher amount of PEG results in a slight reduction in tensile strength, whereas a smaller amount has a discernible effect. The morphology of PES membranes changed from a slightly porous to a highly porous structure with interconnected pores when 5% PEG was introduced. Higher concentrations of hydrophilic additives are thought to have a significant impact on the phase inversion process, which modifies the internal structure thereby significantly influencing the mechanical strength. The PEG, which may eliminated during the membrane production process, promotes increased porosity, resulting in a slight decline in elastic modulus. Similarly, during the phase inversion, PVP, which is soluble in water, diffuses out and encourages the formation of macrovoids. The presence of numerous voids in the membrane structure frequently leads to a reduction in tensile

strength. Compared to other membranes, M5 has a greater elastic modulus (2.76 MPa), however it is not as high as M3 (3.06 MPa) which only includes 2.5% PEG. This implies that complex interactions among PVP, PEG, and the PES in matrix affect the tensile characteristics. Higher PEG and PVP concentrations may increase porosity at the expense of mechanical qualities, a careful balance between membrane porosity and structural integrity must be maintained (Elele et al., 2019).

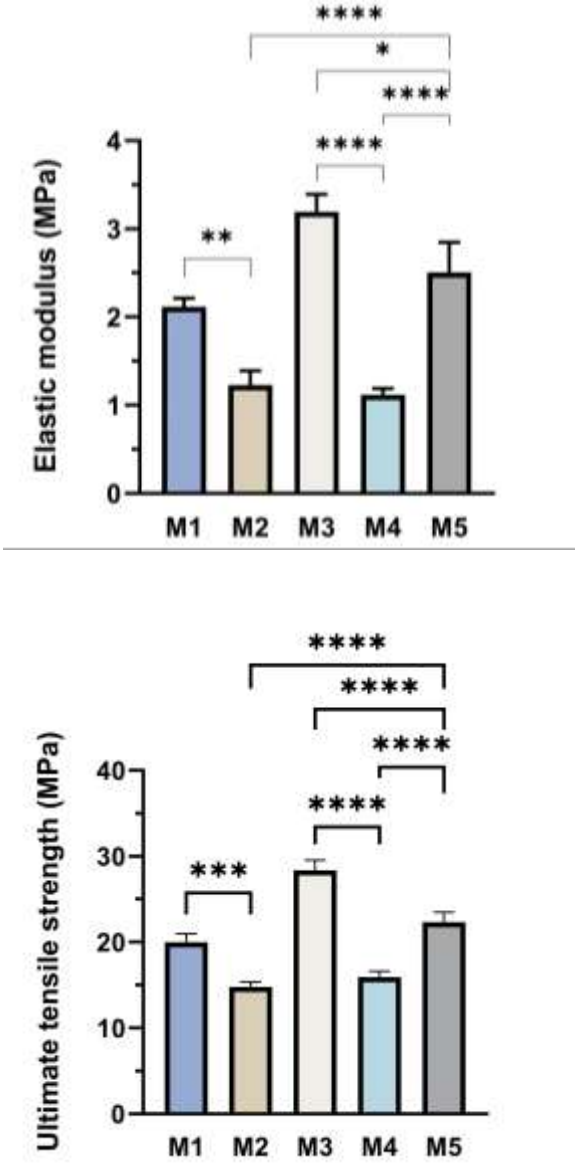
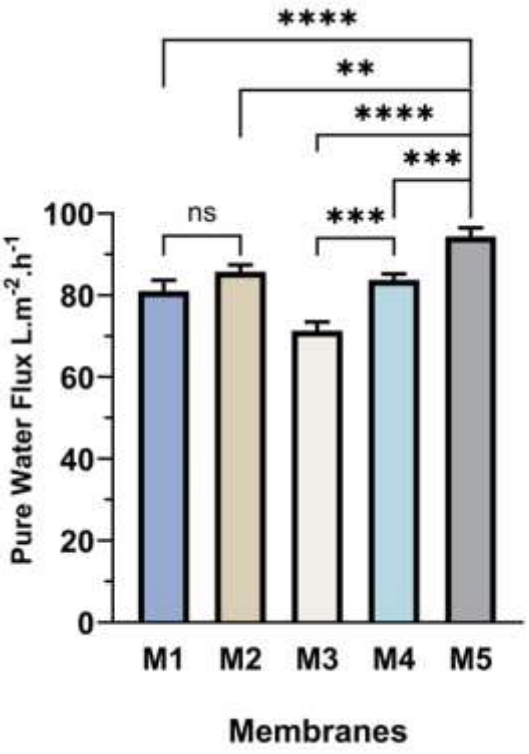


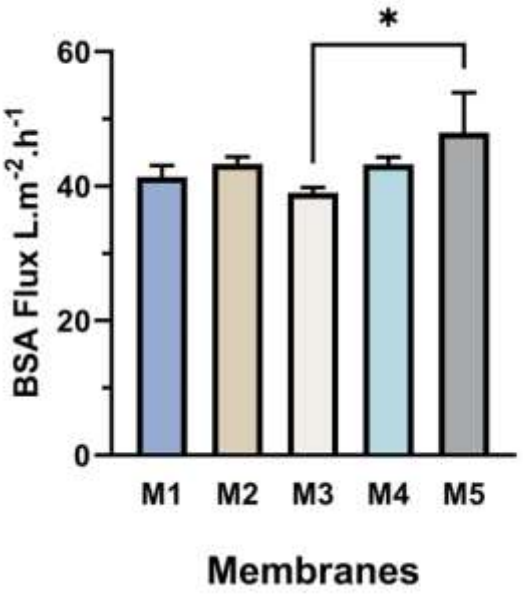
Figure 4.8: (a) Young's modulus of the membranes. (b) Ultimate tensile strength of the membranes.

4.7 Water flux

The rate of fluid flow across the polymeric membrane is indicative of the performance of excess water and uremic toxins clearance in hemodialysis. The higher the flux the more efficient the membranes are considered to be. The results in Figure 4.9 (a) and (b) indicate the correlation between the addition of hydrophilic pore-former and the consequent effect on the fluid flow across the membrane. For membrane M1, a moderate flux of 80 L/m²/h was recorded which is improved to 87.27 L/m²/h in M2 when the PVP concentration in the membrane is increased from 2.5% to 5% respectively. This indicates that increasing the concentration of PVP drastically increases the fluid permeation rate of membranes. Similarly, a comparable trend was observed for membranes with PEG as a hydrophilic additive. Membrane M3 measured a flux of 72 L/m^2/h which further improved to 82 L/m^2/h upon increment of concentration of PEG additive from 2.5% to 5%. The comparison of the impact of individual additives on flux indicates that PVP provides a higher porosity with a vast network of interconnected pores owing to which PVP-containing membranes performed well in fluid permeation as compared to PEG-based membranes. Finally, a drastic increase in flux was evident in membrane M5 which measured 96 L/m2/h. This significant increase in flux is attributable to the synergistic effect of the two hydrophilic polymers used in tandem. As already observed in porosity and contact angle measurements, membrane M5 outperformed all other membranes. A similar trend is evident in flux measurements that show PVP and PEG complements each other to optimize the fluid flow. A delicate balance in porosity, tensile strength, and hydrophilicity facilitates the membrane M5 to perform well in fluid permeation. In addition to that, it can be inferred that pores are well connected, particularly, in membrane M5 which further aids in enhancing the fluid flow (Tufekci et al., 2019).



(a)



(b)

Figure 4.9: (a) Pure water Flux and (b) BSA Flux of the fabricated membranes

4.8 Antifouling and Flux recovery

BSA is a common foulant used to study antifouling characteristics because of its tendency to adhere to the surface of the membrane. The BSA rejection test of the membranes was carried out by filtering 100 mg/L of the BSA solution using a dead-end filter cell under 0.2 MPa of pressure. As shown in figure 4.9(b), there is a drop in flux for membrane M1 from 80 L/m^2/h for pure water to 41.14 L/m^2/h for BSA and back to 60 L/m^2/h for flux recovery Fig 4.10. This indicates a moderate flux and antifouling behaviour of M1. M2 shows higher flux rates for both water and BSA, with a better flux recovery of 68.57 L/m^2/h, indicating enhanced antifouling that might be due to a higher PVP content. With lower pure water and BSA flux, M3 maintains an adequate flux recovery of 62.61 L/m^2/h. This might be caused by the lower porosity and lesser interconnected pores in the structure. M4, which has a greater concentration of PEG, shows a slightly greater flux recovery of 65.45 L/m^2/h than M3. This suggests that adding more PEG can enhance the antifouling characteristic having a small impact on flux value. M5 shows a maximum flux of 96 L/m^2/h and a flux recovery of 73.85 L/m^2/h, suggesting that combining PVP and PEG may significantly increase the membrane's hydrophilicity and antifouling properties, eventually improving membrane performance as a whole. The remarkable properties of this membrane are most likely due to the synergistic impact of PVP and PEG on improving the membrane's chemical structure, surface roughness, and structural characteristics.

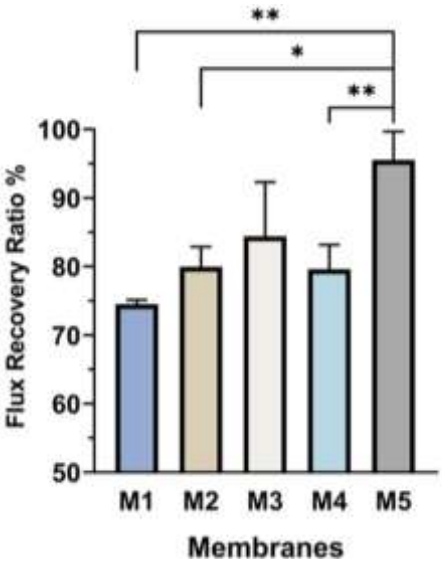


Figure 4.10: Graphical presentation of flux recovery ratio.

4.9 BSA rejection

Considering the molecular sizes of BSA and HSA are similar, BSA can be a reliable substitute for measuring how effectively membranes remove uremic toxins. In order to ensure the effective removal of high-molecular-weight toxins from the patient's blood, BSA rejection is essential for hemodialysis membranes.

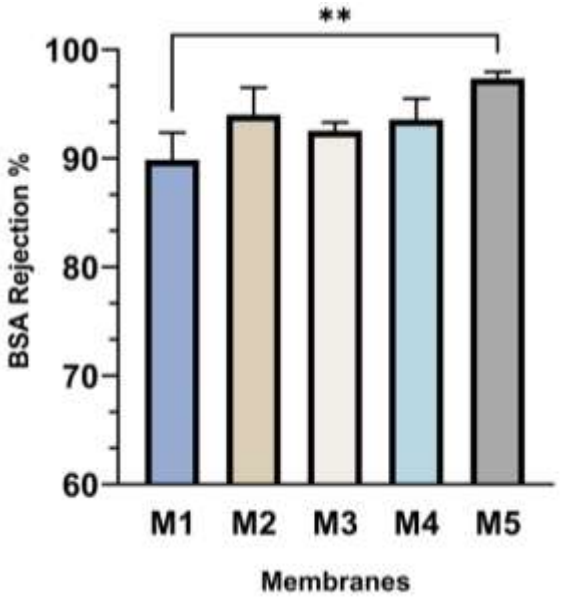


Figure 4.11: BSA rejection percentage of the membranes.

Figure 4.11 illustrates how the kind and mix of pore-forming substances used impact the BSA rejection rates for PES-based membranes. PVP and PEG have similar BSA rejection efficiency, as seen in membrane M1 and M3, which had rejection rates of 91.51% and 91.64% respectively for 2.5% concentration. However, M2 performs better than M1, because of its greater PVP content, indicating that PVP improves selectivity. M4 has an impressive rejection rate of 98.64%, suggesting that membrane BSA rejection ability is much enhanced by a greater PEG content. The maximum rejection rate of 99.10% is achieved by combining PVP and PEG in M5, demonstrating the synergistic effects of using dual WSP. This combination probably produces a perfect balance of porosity, hydrophilicity, and surface topology that reduces fouling and protein adsorption and enhances the performance of hemodialysis membranes.

4.10 Urea clearance

Table 4.1: Variables and different response of the urea clearance.

	Factor 1	Factor 2	Response 1
Run	**A:concentration**	**B:pressure**	**urea clearance**
	mg/l	**bar**	**%**
1	1000	0.4	75.2
2	800	0.6	75.3
3	1000	0.4	75.2
4	717.157	0.4	73.8
5	1000	0.682843	75.6
6	800	0.2	74.2
7	1000	0.117157	74.3
8	1000	0.4	75.2
9	1200	0.2	76.4
10	1200	0.6	77.8
11	1282.84	0.4	77.2

Urea clearance is a measure of a membrane's ability to remove urea from the blood and a key component of therapeutic efficacy. It is one of the most significant performance metrics in hemodialysis (Raharjo et al., 2022). Effective urea clearance illustrates the

membrane's capacity to replicate kidney function by eliminating toxic waste products from the blood and it is largely responsible for maintaining the patient's health following renal failure. According to the results discussed above in each section membrane M5 outperformed all other membranes. The membrane M5 was the best option for real-world application due to its exceptional porosity, enhanced hydrophilicity, higher flux, and potent antifouling characteristics. Therefore, only membrane M5 was selected for further assessment of urea clearance and following hemocompatibility tests. In order to evaluate the response of urea clearance two variables, concentration of urea (ppm) and pressure (Mpa) across the membrane were assessed using Response Surface Methodology (RSM). Central code design in design expert was used to simulate and analyse how urea clearance across ultrafiltration membrane M5 was affected by operating pressure and solute concentration as given in table 4.1. The results acquired showed a high coefficient of determination (R^2) of 0.9438 by the developed model shown in table 4.2. A good correlation between the observed and predicted values is shown by R2 values, which is close to 1 suggesting that the model is able to provide accurate predictions. This was further strengthened by a high adjusted R^2 of 0.9297 and a predicted R^2 of 0.8747, indicating good predictive capabilities. The expected vs. real plot in Figure 23 further confirms the accuracy of the model by displaying a close clustering of data points around the line of perfect prediction.

Table 4.2: ANOVA of the urea clearance response.

Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	**p-value**	
Model	13.65	2	6.83	32.74	0.0001	significant
A-concentration	11.30	1	11.30	54.20	< 0.0001	
B-pressure	2.35	1	2.35	11.28	0.0099	
Residual	1.67	8	0.2085			
Lack of Fit	1.67	6	0.2780			
Pure Error	0.0000	2	0.0000			
Cor Total	15.32	10				

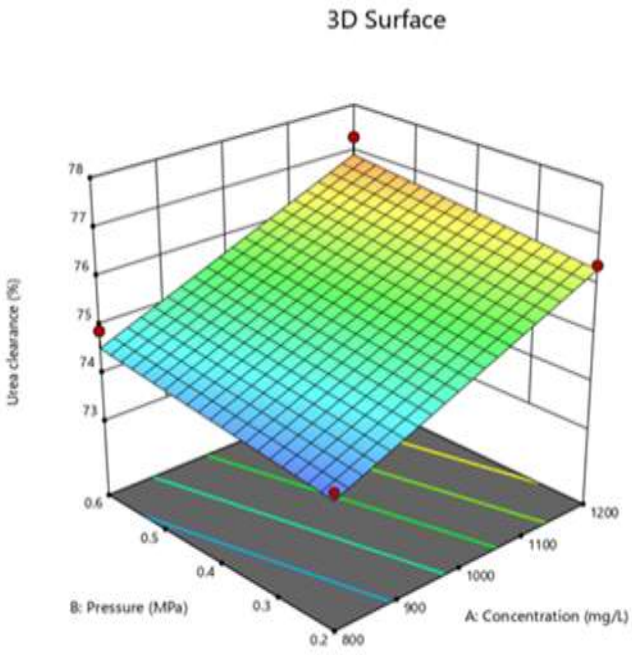


Figure 4.12: Contour plot of the variables and their impact on the urea clearance for membrane M5.

Considering all that, the RSM model appears to be a good indicator of urea clearance, which has consequences for maximizing the effectiveness of hemodialysis membranes. The trans-membrane pressure and the urea content in the feed solution are critical parameters that considerably impact the rates of urea clearance in the membrane M5. Figure 4.12 gives a demonstration of this connection using a surface contour plot, which illustrates the interaction between these two independent variables and their combined influence on the response variable, urea clearance. A direct trend was evident in this plot: the urea clearance effectiveness increased in tandem with an increase in urea concentration and operating pressure table 4.1. The membrane demonstrated optimal performance at a concentration of 1200 mg/L and an operating pressure of 0.6 MPa. At this point, it achieved 77.3% of urea clearance, as seen in Table 5.

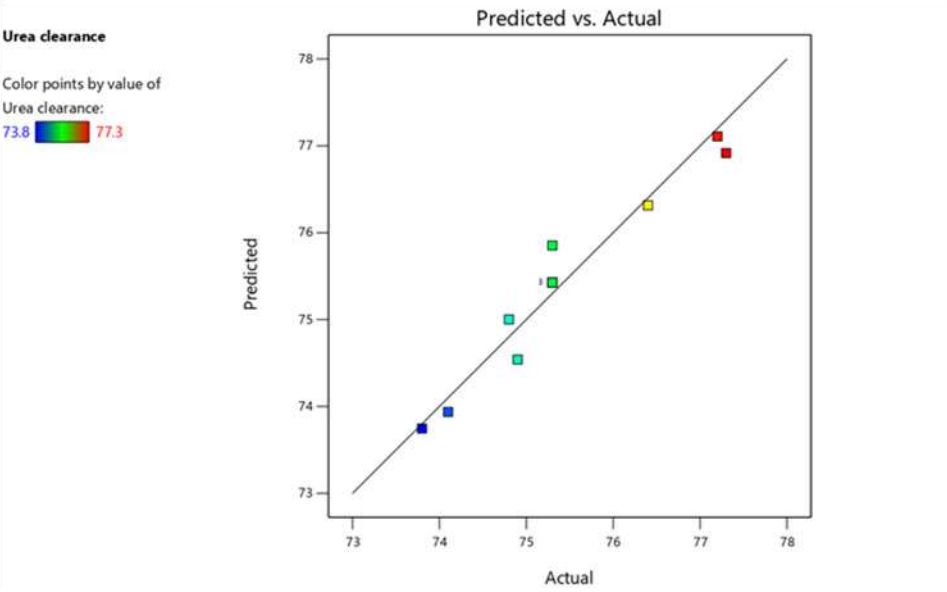


Figure 4.13: Predicted Vs Actual response graph.

The remarkable urea clearance performance may be ascribed to the M5 membrane's morphological characteristics, which comprise a significant active surface area, improved hydrophilicity for improved wettability, and precisely calibrated pore network interconnectivity.

4.11 Hemocompatibility (APTT, PT)

In the context of hemodialysis, polymeric membrane hemocompatibility is crucial in many ways. When the blood comes in contact with the membrane it should not trigger the formation of blood clot as it may be fatal for the patient. Therefore, the hemocompatibility levels of the polymeric membranes should fall within the medical reference values (Westphalen et al., 2020). Two coagulation tests, Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT), were conducted to evaluate the membrane M5's hemocompatibility. This membrane was selected as it outperformed all other membranes in terms of having optimal characteristic features for ultrafiltration. In hemocompatibility test the APTT measures the time it takes for a clot to form using the intrinsic and common coagulation pathways (Claudel et al., 2021). PT is the time it takes for the clot to form using extrinsic pathway. Table 4.3 illustrates that the PT value is 14 seconds and the APTT

value is 32 seconds. The values obtained are both within the defined clinical reference range as extrinsic pathway is slightly more complicated then intrinsic pathway therefore the time taken by in APTT is more than that of PTT. These results imply that the membrane has no effect on the intrinsic or extrinsic coagulation pathways because both coagulation times are within the typical clinical range. It is further implied that the membrane M5 lacks procoagulant activity, which is a feature that hemodialysis membranes should have to avoid clot formation during therapy. Increased hydrophilicity naturally resulted in increased hemocompatibility when dual WSP PVP and PEG were used in together. As a result, membrane M5 has the ability to resist thrombogenicity and reduce the likelihood of blood clot formation.

Table 4.3: Various hemocompatibility tests performed on the polymeric membranes and their results.

Hemocompatibility Measure	**Result**
Activated partial thromboplastin time (APTT)	32 seconds
PTT (Partial thromboplastin time)	14 seconds
Hemolysis	1.32 %
Plasma Recalcification time	205.5 seconds

4.12 Plasma recalcification time (PRT)

When evaluating the hemocompatibility of biomaterials, especially HD membranes, plasma recalcification time is considered to be a crucial measure. The calcium ions play a crucial role as they act as cofactors in various steps of the blood coagulation cascade. In the laboratory setting when calcium ions are reintroduced into the citrated blood the coagulation cascade is initiated (Kohlová et al., 2019). The PRT measures the amount of time it takes for blood plasma to clot when these calcium ions are added. The hydrophilic optimization of M5, which prevents deviance from the average values, is probably the reason for its maximum value of 205.5 seconds. PRT is crucial for HD membranes because it sheds light on the potential for the membrane to initiate coagulation pathways. Lesser PRT raises the possibility that the membrane could promote the development of thrombus

and lessen the benefits of dialysis (Nalezinková, 2020). A longer PRT is therefore preferred for HD membranes since it suggests a lower propensity to cause clotting and a lower risk of thrombosis.

4.13 Hemolysis

To maintain a steady blood flow inside the dialyser a constant pressure is applied which in some cases produce shear force. This force may disrupt the red blood cells leading to escape of haemoglobin from the cells. The phenomenon of rupturing of erythrocytes thereby releasing haemoglobin is known as hemolysis. According to ASTM F-756–08 standard, a biocompatible material should have hemolysis percentage less than 5% (Nalezinková, 2020). Membrane M5 measured 1.32% hemolysis which is considered a safe for hemodialysis. When the hemolysis percentage is higher it indicates a condition where the released haemoglobin causes toxicity or nephropathy. The already existing anemia can be worsen to jeopardize the safety of ESRD patients (Mollahosseini et al., 2020)

Summary

Table 0.1: Summary of the results of various tests of the fabricated ultrafiltration hemodialysis membranes.

TEST	***Unit***	***M1***	***M2***	***M3***	***M4***	***M5***
Contact Angle	θ˚	60	54	58	44	38
Porosity	%	41.08	42.49	41.79	51.13	57.38
Water Retention	%	50.86	56.42	54.02	58.10	65.40
Pure water flux	$L/m^{-2}/h$	80	87.27	72	82.28	96
Flux recovery Ratio	$L/m^{-2}/h$	60	68.57	62.60	65.45	73.84
BSA rejection	%	91.64	94.52	91.64	98.63	99.10
Urea clearance	%	-	-	-	-	77.8
Hemolysis	%	-	-	-	-	1.32
Plasma recalcification time	sec	193	194.3	198	192	205.5
APTT	sec	-	-	-	-	32
PTT	sec	-	-	-	-	14

CHAPTER 5: CONCLUSION AND FUTURE RECOMMENDATIONS

In conclusion, this work investigates the blending of hydrophilic additives to deal with the intrinsic hydrophobicity of the PES membranes. Two widely used non-toxic and biocompatible hydrophilic additives PEG and PVP were inspected for their individual and combined impact on the performance of PES membranes. The fabricated membranes were characterized using Scanning electron microscopy, ATR-FTIR analysis, tensile test, porosity, water retention, and contact Angle measurements. The performance for fluid permeation and antifouling was assessed using a dead-end filtration cell. The SEM results were evidence of the successful synthesis of membranes having two distinct layers with a thin skin layer and a dense layer containing finger-like channels. Furthermore, the characteristic spectral peaks indicated the presence of respective additive polymers in the membranes according to the composition. The contact angle and porosity measurements indicated that the concentration of PVP and PEG content substantially impacts the characteristics of the membranes. The contact angle can be significantly decreased to a particular level by increasing the hydrophilic additive content. Particularly higher levels of PVP and PEG up to 5% can decrease the contact angle as low as 54˚ and 44˚ respectively. Moreover, the porosity percentage can be enhanced up to 41% for PVP and 51% for PEG at 5% each. Water retention capacity shows a similar trend of increment with an increase in hydrophilic additive. Although, the blending of individual pore-formers has a moderate improvement in the characteristic features of membranes, conversely, incorporation of two hydrophilic additives simultaneously enhances the desired features in the PES membranes drastically. For instance, the contact angle drops to 38˚, porosity upsurges to 57%, and water retention capacity increases to 65% when 2.5% of both PVP and PEG are added to the membrane simultaneously. The results for tensile testing indicate that higher content of pore-former can adversely impact the tensile strength of the membranes. Maintaining a balance between porosity and mechanical strength is important as higher porosity may render a compromised mechanical strength. The results indicated that M5 which contains both WSP has a good balance of both of these features. Furthermore, M5 had the highest

pure water flux values (96 L/m^2/h), suggesting that it had the highest flow efficiency out of all the membranes. BSA rejection rates of 99.10% were achieved in M5, indicating the strongest antifouling capabilities measured by flux recovery and BSA rejection. Response Surface Methodology (RSM) study was used to analyze M5 for urea clearance due to its ideal characteristics. The results showed good efficacy (77.3% clearance), particularly at 1200 mg/L concentration and 0.6 MPa pressure. A low risk of RBC degradation and blood coagulation was indicated by the results of hemocompatibility testing, including the APTT (32 seconds), prothrombin time (14 seconds), plasma recalcification time (205.5 seconds), and hemolysis rate (1.32%). These tests confirmed that M5 was a favorable candidate for hemodialysis. In summary, using dual WSP (PVP and PEG) during membrane production significantly improves hemodialysis membrane performance.

REFERENCES

1. Abe, M., Masakane, I., Wada, A., Nakai, S., Nitta, K., & Nakamoto, H. (2021). Dialyzer Classification and Mortality in Hemodialysis Patients: A 3-Year Nationwide Cohort Study. Frontiers in Medicine, 8, 740461. https://doi.org/10.3389/fmed.2021.740461

2. Al Aani, S., Mustafa, T. N., & Hilal, N. (2020). Ultrafiltration membranes for wastewater and water process engineering: A comprehensive statistical review over the past decade. Journal of Water Process Engineering, 35, 101241.

3. Al Malek, S. A., Abu Seman, M. N., Johnson, D., & Hilal, N. (2012). Formation and characterization of polyethersulfone membranes using different concentrations of polyvinylpyrrolidone. Desalination, 288, 31–39. https://doi.org/10.1016/j.desal.2011.12.006

4. Alayande, A. B., Obaid, M., Yu, H.-W., & Kim, I. S. (2019). High-flux ultrafiltration membrane with open porous hydrophilic structure using dual pore formers. Chemosphere, 227, 662–669. https://doi.org/10.1016/j.chemosphere.2019.04.081

5. Alibakhshi, S., Youssefi, M., Hosseini, S. S., & Zadhoush, A. (2019). Tuning morphology and transport in ultrafiltration membranes derived from polyethersulfone through exploration of dope formulation and characteristics. Materials Research Express, 6(12), 125326.

6. Anis, S. F., Hashaikeh, R., & Hilal, N. (2019). Microfiltration membrane processes: A review of research trends over the past decade. Journal of Water Process Engineering, 32, 100941.

7. Area, D. R. (2020). Setting up of Hemodialysis Unit. Indian Journal of Nephrology, 30, 1.

8. Asif Khan, R. M., Ahmad, N. M., Nasir, H., Mahmood, A., Iqbal, M., & Janjua, H. A. (2023). Antifouling and Water Flux Enhancement in Polyethersulfone Ultrafiltration Membranes by Incorporating Water-Soluble Cationic Polymer of Poly [2-(Dimethyl amino) ethyl Methacrylate]. Polymers, 15(13), Article 13. https://doi.org/10.3390/polym15132868

9. Azhar, O., Jahan, Z., Sher, F., Niazi, M. B. K., Kakar, S. J., & Shahid, M. (2021). Cellulose acetate-polyvinyl alcohol blend hemodialysis membranes integrated with

dialysis performance and high biocompatibility. Materials Science and Engineering: C, 126, 112127. https://doi.org/10.1016/j.msec.2021.112127

10. Banerjee, I., Pangule, R. C., & Kane, R. S. (2011). Antifouling coatings: Recent developments in the design of surfaces that prevent fouling by proteins, bacteria, and marine organisms. Advanced Materials, 23(6), 690–718.

11. Bilad, M. R., Vandamme, D., Foubert, I., Muylaert, K., & Vankelecom, I. F. (2012). Harvesting microalgal biomass using submerged microfiltration membranes. Bioresource Technology, 111, 343–352.

12. Chen, Y.-A., Ou, S.-M., & Lin, C.-C. (2022). Influence of Dialysis Membranes on Clinical Outcomes: From History to Innovation. Membranes, 12(2), Article 2. https://doi.org/10.3390/membranes12020152

13. Clark, W. R., Dehghani, N. L., Narsimhan, V., & Ronco, C. (2019). Uremic toxins and their relation to dialysis efficacy. Blood Purification, 48(4), 299–314.

14. Claudel, S. E., Miles, L. A., & Murea, M. (2021). Anticoagulation in hemodialysis: A narrative review. Seminars in Dialysis, 34(2), 103–115.

15. Dinç, C., & Güner, A. (2017). Solid-state characterization of poly(ethylene glycol) samples prepared by solvent cast technique. https://www.semanticscholar.org/paper/Solid-state-characterization-of-poly%28ethylene-by-Din%C3%A7-G%C3%BCner/6b815d8276ea673e803c667f6d74757c195e752d

16. Dong, X., Lu, D., Harris, T. A. L., & Escobar, I. C. (2021). Polymers and Solvents Used in Membrane Fabrication: A Review Focusing on Sustainable Membrane Development. Membranes, 11(5), Article 5. https://doi.org/10.3390/membranes11050309

17. Elele, E., Shen, Y., Tang, J., Lei, Q., Khusid, B., Tkacik, G., & Carbrello, C. (2019). Mechanical properties of polymeric microfiltration membranes. Journal of Membrane Science, 591, 117351. https://doi.org/10.1016/j.memsci.2019.117351

18. Fahrina, A., Yusuf, M., Muchtar, S., Fitriani, F., Mulyati, S., Aprilia, S., Rosnelly, C. M., Bilad, M. R., Ismail, A. F., Takagi, R., Matsuyama, H., & Arahman, N. (2021). Development of anti-microbial polyvinylidene fluoride (PVDF) membrane using bio-based ginger extract-silica nanoparticles (GE-SiNPs) for bovine serum albumin (BSA) filtration. Journal of the Taiwan Institute of Chemical Engineers, 125, 323–331. https://doi.org/10.1016/j.jtice.2021.06.010

19. Gupta, R., Woo, K., & Yi, J. A. (2021). Epidemiology of end-stage kidney disease. Seminars in Vascular Surgery, 34(1), 71–78. https://doi.org/10.1053/j.semvascsurg.2021.02.010

20. Hailemariam, R. H., Woo, Y. C., Damtie, M. M., Kim, B. C., Park, K.-D., & Choi, J.-S. (2020). Reverse osmosis membrane fabrication and modification technologies and future trends: A review. Advances in Colloid and Interface Science, 276, 102100.

21. Heidari, A., Abdollahi, E., Mohammadi, T., & Asadi, A. A. (2021). Improving permeability, hydrophilicity and antifouling characteristic of PES hollow fiber UF membrane using carboxylic PES: A promising substrate to fabricate NF layer. Separation and Purification Technology, 270, 118811. https://doi.org/10.1016/j.seppur.2021.118811

22. Hołda, A. K., & Vankelecom, I. F. (2015). Understanding and guiding the phase inversion process for synthesis of solvent resistant nanofiltration membranes. Journal of Applied Polymer Science, 132(27).

23. Howe, K. J., & Clark, M. M. (2002). Fouling of microfiltration and ultrafiltration membranes by natural waters. Environmental Science & Technology, 36(16), 3571–3576.

24. Irfan, M., & Idris, A. (2015). Overview of PES biocompatible/hemodialysis membranes: PES–blood interactions and modification techniques. Materials Science and Engineering: C, 56, 574–592. https://doi.org/10.1016/j.msec.2015.06.035

25. Irfan, M., Irfan, M., Shah, S. M., Baig, N., Saleh, T. A., Ahmed, M., Naz, G., Akhtar, N., Muhammad, N., & Idris, A. (2019). Hemodialysis performance and anticoagulant activities of PVP-k25 and carboxylic-multiwall nanotube composite blended Polyethersulfone membrane. Materials Science and Engineering: C, 103, 109769. https://doi.org/10.1016/j.msec.2019.109769

26. Kadanyo, S., Gumbi, N. N., Matindi, C. N., Dlamini, D. S., Hu, Y., Cui, Z., Wang, H., Hu, M., & Li, J. (2022). Enhancing compatibility and hydrophilicity of polysulfone/poly (ethylene-co-vinyl alcohol) copolymer blend ultrafiltration membranes using polyethylene glycol as hydrophilic additive and compatibilizer. Separation and Purification Technology, 287, 120523. https://doi.org/10.1016/j.seppur.2022.120523

27. Khan, B., Haider, S., Khurram, R., Wang, Z., & Wang, X. (2020). Preparation of an Ultrafiltration (UF) Membrane with Narrow and Uniform Pore Size Distribution via Etching of SiO2 Nano-Particles in a Membrane Matrix. Membranes, 10(7), 150. https://doi.org/10.3390/membranes10070150

28. Kohlová, M., Amorim, C. G., Araújo, A., Santos-Silva, A., Solich, P., & Montenegro, M. C. B. (2019). The biocompatibility and bioactivity of hemodialysis membranes: Their impact in end-stage renal disease. Journal of Artificial Organs, 22, 14–28.

29. Lv, J., Zhang, G., Zhang, H., Zhao, C., & Yang, F. (2018). Improvement of antifouling performances for modified PVDF ultrafiltration membrane with hydrophilic cellulose nanocrystal. Applied Surface Science, 440, 1091–1100. https://doi.org/10.1016/j.apsusc.2018.01.256

30. Lv, J.-C., & Zhang, L.-X. (2019). Prevalence and Disease Burden of Chronic Kidney Disease. In B.-C. Liu, H.-Y. Lan, & L.-L. Lv (Eds.), Renal Fibrosis: Mechanisms and Therapies (pp. 3–15). Springer. https://doi.org/10.1007/978-981-13-8871-2_1

31. Ma, Y., Shi, F., Ma, J., Wu, M., Zhang, J., & Gao, C. (2011). Effect of PEG additive on the morphology and performance of polysulfone ultrafiltration membranes. Desalination, 272(1), 51–58. https://doi.org/10.1016/j.desal.2010.12.054

32. Magnani, S., & Atti, M. (2021). Uremic toxins and blood purification: A review of current evidence and future perspectives. Toxins, 13(4), 246.

33. Mireles, L. K., Wu, M.-R., Saadeh, N., Yahia, L., & Sacher, E. (2020). Physicochemical Characterization of Polyvinyl Pyrrolidone: A Tale of Two Polyvinyl Pyrrolidones. ACS Omega, 5(47), 30461–30467. https://doi.org/10.1021/acsomega.0c04010

34. Mohammad, A. W., Teow, Y. H., Ang, W. L., Chung, Y. T., Oatley-Radcliffe, D. L., & Hilal, N. (2015). Nanofiltration membranes review: Recent advances and future prospects. Desalination, 356, 226–254.

35. Mokarizadeh, H., & Raisi, A. (2021). Industrial wastewater treatment using PES UF membranes containing hydrophilic additives: Experimental and modeling of fouling mechanism. Environmental Technology & Innovation, 23, 101701. https://doi.org/10.1016/j.eti.2021.101701

36. Mollahosseini, A., Abdelrasoul, A., & Shoker, A. (2020). A critical review of recent advances in hemodialysis membranes hemocompatibility and guidelines for future

development. Materials Chemistry and Physics, 248, 122911. https://doi.org/10.1016/j.matchemphys.2020.122911

37. Nalezinková, M. (2020). In vitro hemocompatibility testing of medical devices. Thrombosis Research, 195, 146–150.

38. Oatley-Radcliffe, D. L., Walters, M., Ainscough, T. J., Williams, P. M., Mohammad, A. W., & Hilal, N. (2017). Nanofiltration membranes and processes: A review of research trends over the past decade. Journal of Water Process Engineering, 19, 164–171.

39. Otitoju, T. A., Ahmad, A. L., & Ooi, B. S. (2018). Recent advances in hydrophilic modification and performance of polyethersulfone (PES) membrane via additive blending. RSC Advances, 8(40), 22710–22728.

40. Pstras, L., Ronco, C., & Tattersall, J. (2022). Basic physics of hemodiafiltration. Seminars in Dialysis, 35(5), 390–404.

41. Raharjo, Y., Zainol Abidin, M. N., Ismail, A. F., Fahmi, M. Z., Saiful, Elma, M., Santoso, D., Haula', H., & Habibi, A. R. (2022). Dialysis Membranes for Acute Kidney Injury. Membranes, 12(3), 325. https://doi.org/10.3390/membranes12030325

42. Ronco, C., & Clark, W. R. (2018). Haemodialysis membranes. Nature Reviews Nephrology, 14(6), Article 6. https://doi.org/10.1038/s41581-018-0002-x

43. Rosner, M. H., Reis, T., Husain-Syed, F., Vanholder, R., Hutchison, C., Stenvinkel, P., Blankestijn, P. J., Cozzolino, M., Juillard, L., & Kashani, K. (2021). Classification of uremic toxins and their role in kidney failure. Clinical Journal of the American Society of Nephrology, 16(12), 1918–1928.

44. Schwarz, W. (2018). PVP: a critical review of the kinetics and toxicology of polyvinylpyrrolidone (povidone). CRC Press.

45. Selatile, M., Sinha Ray, S., Ojijo, V., & Sadiku, R. (2018). Recent developments in polymeric electrospun nanofibrous membranes for seawater desalination. RSC Advances, 8, 37915–37938. https://doi.org/10.1039/C8RA07489E

46. Shi, X., Tal, G., Hankins, N. P., & Gitis, V. (2014). Fouling and cleaning of ultrafiltration membranes: A review. Journal of Water Process Engineering, 1, 121–138.

47. Song, X., Ji, H., Zhao, W., Sun, S., & Zhao, C. (2021). Hemocompatibility enhancement of polyethersulfone membranes: Strategies and challenges. Advanced Membranes, 1, 100013. https://doi.org/10.1016/j.advmem.2021.100013

48. Specifications, H. M. (2020). Selection and Use of Machine, Dialyzer and Dialysis Fluid for Maintenance Hemodialysis. Indian Journal of Nephrology, 30, 1.

49. Sun, M., Su, Y., Mu, C., & Jiang, Z. (2010). Improved Antifouling Property of PES Ultrafiltration Membranes Using Additive of Silica−PVP Nanocomposite. Industrial & Engineering Chemistry Research, 49(2), 790–796. https://doi.org/10.1021/ie900560e

50. Sun, W., Liu, J., Chu, H., & Dong, B. (2013). Pretreatment and Membrane Hydrophilic Modification to Reduce Membrane Fouling. Membranes, 3(3), Article 3. https://doi.org/10.3390/membranes3030226

51. Tufekci, M., Gunes-Durak, S., Ormanci-Acar, T., & Tufekci, N. (2019). Effects of geometry and PVP addition on mechanical behavior of PEI membranes for use in wastewater treatment. Journal of Applied Polymer Science, 136(7), 47073.

52. Wang, C., Lin, B., & Qiu, Y. (2022). Enhanced hydrophilicity and anticoagulation of polysulfone materials modified via dihydroxypropyl, sulfonic groups and chitosan. Colloids and Surfaces B: Biointerfaces, 210, 112243. https://doi.org/10.1016/j.colsurfb.2021.112243

53. Warsinger, D., Chakraborty, S., Tow, E., Plumlee, M., Bellona, C., Loutatidou, S., Karimi, L., Mikelonis, A., Achilli, A., Ghassemi, A., Padhye, L., Snyder, S., Curcio, S., Vecitis, C., Arafat, H., & Lienhard, J. (2018). A review of polymeric membranes and processes for potable water reuse. Progress in Polymer Science, 81. https://doi.org/10.1016/j.progpolymsci.2018.01.004

54. Wei, Q., Feng, S., Zhang, Z., Liu, L., & Wu, L. (2022). A high-protein retained PES hemodialysis membrane with tannic acid as a multifunctional modifier. Colloids and Surfaces B: Biointerfaces, 220, 112921. https://doi.org/10.1016/j.colsurfb.2022.112921

55. Westphalen, H., Saadati, S., Eduok, U., Abdelrasoul, A., Shoker, A., Choi, P., Doan, H., & Ein-Mozaffari, F. (2020). Case studies of clinical hemodialysis membranes: Influences of membrane morphology and biocompatibility on uremic blood-membrane interactions and inflammatory biomarkers. Scientific Reports, 10(1), 14808.

56. Yamamoto, K., Hiwatari, M., Kohori, F., Sakai, K., Fukuda, M., & Hiyoshi, T. (2005). Membrane fouling and dialysate flow pattern in an internal filtration-enhancing dialyzer. Journal of Artificial Organs, 8(3), 198–205. https://doi.org/10.1007/s10047-005-0303-2

57. Yang, C.-W., Harris, D. C. H., Luyckx, V. A., Nangaku, M., Hou, F. F., Garcia Garcia, G., Abu-Aisha, H., Niang, A., Sola, L., Bunnag, S., Eiam-Ong, S., Tungsanga, K., Richards, M., Richards, N., Goh, B. L., Dreyer, G., Evans, R., Mzingajira, H., Twahir, A., … Tonelli, M. (2020). Global case studies for chronic kidney disease/end-stage kidney disease care. Kidney International Supplements, 10(1), e24–e48. https://doi.org/10.1016/j.kisu.2019.11.010

58. Yin, J., & Zhang, H. (2021). A combined physical blending and surface grafting strategy for hydrophilic modification of polyethersulfone membrane toward oil/water separation. Polymer, 233, 124177. https://doi.org/10.1016/j.polymer.2021.124177

59. Young, T.-H., & Chen, L.-W. (1995). Pore formation mechanism of membranes from phase inversion process. Desalination, 103(3), 233–247.

60. Zainol Abidin, M. N., Nasef, M. M., & Matsuura, T. (2022). Fouling Prevention in Polymeric Membranes by Radiation Induced Graft Copolymerization. Polymers, 14(1), Article 1. https://doi.org/10.3390/polym14010197