Development of Nano-polymer Based Dialysis Membrane

By

Somia Mazhar

(Registration No: 00000399657)

Department of Biomedical Engineering and Sciences

School of Mechanical and Manufacturing Engineering

National University of Sciences & Technology (NUST)

Islamabad, Pakistan

(2024)

Development of Nano-polymer Based Dialysis Membrane

By

Somia Mazhar

(Registration No: 00000399657)

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. Adeeb Shehzad

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. 00000399657 Somia Mazhar** 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. **DEVELOPMENT OF NANOPOLYMER BASED DIALYSIS MEMBRANE.**

Signature: 

Name (Supervisor): Adeeb Shehzad

Date: 25 - Jul - 2024

Signature (HOD): 

Date: 25 - Jul - 2024

Signature (DEAN): 

Date: 25 - Jul - 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: Somia Mazhar (00000399657)
Titled: DEVELOPMENT OF NANOPOLYMER BASED DIALYSIS MEMBRANE. be accepted in partial fulfillment of the requirements for the award of MS in Biomedical Sciences degree.

Examination Committee Members

1.	Name: Aneeqa Noor	Signature:
2.	Name: Muhammad Asim Waris	Signature:
3.	Name: Waheed Miran	Signature:

Supervisor: Adeeb Shehzad Signature:

Date: 25 - Jul - 2024

Head of Department 25 - Jul - 2024

Date

COUNTERSINGED

25 - Jul - 2024

Date Dean/Principal

CERTIFICATE OF APPROVAL

This is to certify that the research work presented in this thesis, entitled "**Development of Nano-polymer Based Dialysis membrane**" was conducted by **Ms. Somia Mazhar** under the supervision of Dr Adeeb Shehzad.

No part of this thesis has been submitted anywhere else for any other degree. This thesis is submitted to the Department of Biomedical Engineering and Sciences in partial fulfillment of the requirements for the degree of Master of Science in Field of Biomedical Sciences.

Department of Biomedical Engineering and Sciences, National University of Sciences and Technology, Islamabad.

Student Name: Somia Mazhar Signature: _____

Supervisor Name: Dr Adeeb Shehzad Signature: _____

Name of Dean/HOD: Dr Muhammad Asim Waris Signature: _____

AUTHOR'S DECLARATION

I Somia Mazhar hereby state that my MS thesis titled "**Development of Nano-polymer Based Dialysis membrane**" 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: Somia Mazhar

Date: 25-07-2024

PLAGIARISM UNDERTAKING

I solemnly declare that research work presented in the thesis titled "**Development of Nano-polymer Based Dialysis membrane**" 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: Somia Mazhar

This work is dedicated to my parents whose unwavering love and support propelled me through my academic journey. This degree is the proof of their endless sacrifices and belief in me.

ACKNOWLEDGEMENTS

I praise Almighty Allah for giving me the chance and making it possible for me to complete my dissertation.

I owe a debt of gratitude to my supervisor, Dr. Adeeb Shehzad, for his help, guidance and inspiration throughout the research and coursework. His constructive criticism and insightful remarks led to the successful and timely completion of my research.

Words cannot express the depth of my gratitude to my parents, Shaista Irum and Mazhar Ali, for their unwavering love, belief, and support. Their prayers, well wishes and endless sacrifices has been the driving force behind my academic achievements.

Finally, I would like to acknowledge myself for all the dedication, determination, and hard work I put into this thesis. Despite all the difficulties, my perseverance and commitment allowed me to successfully complete my research work.

TABLE OF CONTENTS

LIST OF TABLES

Page No.

LIST OF FIGURES

Page No.

LIST OF SYMBOLS, ABBREVIATIONS AND ACRONYMS

CA	Contact angle
ESRD	End stage renal disease
FFR	Flux recovery ration
HD	Hemodialysis
CKD	Chronic Kidney Disease
PES	Polyethersulfone
PVP	Polyvinylpyrrolidone

ABSTRACT

The kidneys are essential for preserving the body's internal balance. However, kidney illnesses impact millions of people globally and pose a serious threat to public health. Hemodialysis membranes based on polyethersulfone (PES) can offer patients with renal impairment a life-sustaining therapeutic method. Nevertheless, the intrinsic hydrophobic nature of PES contributes to an inefficiency of uremic toxin clearance and a compromised hemocompatibility. This work evaluates the effects of hydrophilic additives, SiO_2 nanoparticles, on the functionality of polyethersulfone (PES) membranes. NMP was used as the solvent in the non-solvent phase inversion procedure to create the membranes. Tensile testing, porosity, contact angle analysis, FTIR, and scanning electron microscopy were used to characterize the manufactured membranes. 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 the highest nanoparticles concentration performed better. The membrane having the highest nanoparticles concentration had excellent hydrophilicity, increased porosity, and a high-water retention capacity. Moreover, they showed a urea clearance of 76.5%, a pure water flux of 94 $L/m^2/h$, and an outstanding BSA rejection of 96.56%. 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.

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

CHAPTER 1: INTRODUCTION

1.1 Renal diseases

Renal disorders, referred to as kidney diseases, affect millions of people worldwide. Globally, renal disorders pose a major threat to public health. The kidneys are essential to maintaining the internal body balance. Excess fluid, toxins and waste products are eliminated from the circulation and blood pressure and electrolyte levels are managed (Yang et al., 2020). However, various conditions, such as hypertension, genetic susceptibility, diabetes and infection can cause these essential organs to malfunction (Lv et al., 2019). While there are many other types of kidney diseases, the most prevalent is called chronic kidney disease (CKD). The hallmark of this illness is gradual deterioration in renal function. It is estimated that 800 million individuals worldwide are suffering from chronic renal illness, based on a recent survey. Individuals with pre-existing medical conditions such as hypertension, heart ailments and diabetes are more vulnerable to developing renal health issues. In addition, those from low-income economies who lack the means to manage their health are also at greater risk (Raharjo et al., 2022). When chronic renal illness advances to the next stage it is referred to as end-stage renal disease (ESRD). This stage of renal disease is often quite serious and cannot be recovered to a normal level. There are limited treatment choices for ESRD, which can burden patients financially, mentally and physically (Gupta et al., 2021).

1.2 Prevalence

Renal disorders are thought to be a major global cause of mortality and morbidity, according to the World Health Organization (WHO). If treated promptly, acute kidney diseases are reversible; however, chronic renal diseases frequently advance to end-stage renal disease (Yang et al., 2020). The treatment for ESRD is RTT (Renal replacement therapy) and is required for an estimated 4.6 to 7.1 million individuals worldwide (Gupta et al., 2021). The global rise in renal illnesses is frequently caused by diabetes mellitus, hypertension, obesity, and aging, all of which become worse by chemicals, environmental toxins, and infections. A recent estimate puts the global prevalence of chronic renal disease among adults at 10%. The kidney disease is often asymptomatic in

its early stages, which makes it challenging to diagnose and treat until it reaches an advanced level (Yang et al., 2020). However, acute renal illness can have a major effect on patients' life in addition to their medical concerns. It may have an impact on the patients' financial, emotional and physical wellbeing. Kidney disease may have a significant negative effect on a patient's entire quality of life in addition to financial and social hardships.

1.3 Major types of renal diseases

Chronic Kidney Disease (CKD) and Acute Kidney Disease (AKD) represent distinct renal diseases that has their own unique progression, clinical symptoms and onset.

1.3.1 Chronic kidney disease

CKD, characterized by progressive decrease of kidney function that occurs gradually over an extended period, often greater than three months. One of the primary markers of chronic kidney disease is reduced glomerular filtration rate (GFR) of less than 60 mL/min/ 1.73 m^2 or the presence of kidney damage indicators including anomalies in urine sediments, electrolyte imbalances or albuminuria (Ronco and Clark, 2018). The body can make compensatory adjustments to maintain GFR and electrolyte balance, since CKD sometimes takes years or even decades to manifest. But when the illness becomes worse, these compensatory mechanisms also stop working, which deteriorates kidney's functions even more.

1.3.2 Acute kidney disease

On the other hand, AKD is characterised by a sharp decline in kidney function that occurs rapidly over a brief period, usually it happens in a matter of hours or days. AKI is often caused by acute conditions such as increased exposure to nephrotoxic substances, severe infection, or extreme dehydration (Irfan et al., 2019). It could be curable, in contrast to CKD, if the underlying reason is known. On occasion, though, it can progress swiftly, leading to a significant decline in glomerular filtration rate and reduced urine output.

1.3.3 End-stage renal disease (ESRD)

ESRD is a serious type of renal illness in which the kidneys stop functioning and require outside assistance to survive. If treatment for chronic kidney disease is delayed, it often leads to end-stage renal disease (ESRD). The body cannot eliminate extra water and uremic toxins when GFR falls below 15 mL/min/ 1.73 m^2 (Westphalen et al., 2020). At this stage, the patient must take renal replacement therapy to keep the body balanced. Kidney transplantation is the first and most practical way to treat end-stage renal disease. Finding a suitable donor, however, might be difficult because there are hundreds of people who are waiting to get kidney. Immunosuppression and transplant rejection following a surgery can pose significant challenges, even in cases when a donor had been found. Haemodialysis, in which the patient's blood is filtered using a dialyzer machine outside of their body, is an additional renal replacement treatment. Between the blood and dialysate, the body expels excess water and toxins, which is assisted by ultrafiltration process (Irfan et al., 2019). Since not all ESRD patients can receive a kidney transplant, haemodialysis becomes a practical alternative for millions of people globally. Haemodialysis has disadvantages despite its importance, including the need for three to four session each week, each lasting several hours (Wei et al., 2022). To address ESDR, it is estimated that more than two million individuals received HD worldwide in 2010. It is estimated that the number should double by 2030. Peritoneal dialysis is an additional RRT alternative in which blood is filtered inside body's peritoneal cavity.

1.4 Treatment options for end-stage renal disease (ESRD)

The three main therapies for ESRD are peritoneal dialysis, haemodialysis, and kidney transplantation.

1.4.1 Haemodialysis

Haemodialysis is the initial therapy for ESRD patients. Blood is drawn from the body into a dialysis machine as part of the therapeutic procedure. The body gets its blood back clean and detoxified when wastes and excess fluids are successfully removed (Alayande et al., 2019). The two main portions of the dialysis machine, the dialysate compartment, and the blood compartment, are separated by a semipermeable membrane. The membrane removes excess fluids and uremic toxins from the circulation. By

reestablishing the body’s electrolyte equilibrium , the dialyzer mimics the actions of kidney (Claudel et al., 2021). Haemodialysis is often performed three times a week for several hours at a time. This therapy approach aids in reestablishing the body’s lost homeostasis, but it may have an impact on the patient's quality of life.

1.4.2 Peritoneal dialysis

Peritoneal dialysis is an alternative method of renal replacement therapy (RRT) in which the dialyzer is patient’s own peritoneum, a membrane lining the peritoneum cavity. The particular dialysis solution that is injected into the peritoneal cavity is where waste products and excess fluid permeate through the peritoneal membrane (Mollahosseini et al., 2020). After some dwell time, the old dialysis solution is removed from the abdomen and is replaced with the new solution. Patients can manage their therapy more independently and flexibly with home peritoneal dialysis.

1.4.3 Kidney transplant

Kidney transplantation is considered to be the most effective treatment option for ESRD when a suitable donor kidney becomes available (Westphalen et al., 2020). A kidney transplant that is successful returns kidney function to almost normal levels and significantly improves the patient’s quality of life. However, a compatible donor is required in order to execute a kidney transplant, and prospective patient must undergo a comprehensive evaluation to ensure they are suitable candidates (Mollahosseini et al., 2020). Patients undergoing kidney transplantation need to take immunosuppressive medications to prevent organ rejection and prolong the kidney’s life.

Table 1.1 Treatment options for ESRD

Aspects	Haemodialysis	Peritoneal dialysis	Kidney transplant
Method	Blood is filtered outside body in machine	Peritoneal cavity with dialysis solution	Healthy kidney is transplanted into recipient
Infection risk	Increased risk from access sites (fistulas, catheters)	Risk of bloodstream infection is low	Initially risk is higher, but lowers with proper post-transplant treatment
Treatment frequency	3-4 hrs/ session 3 sessions/ week	Exchange daily at home	Single procedure, ongoing monitoring
Quality of life	Impacts quality of life	Better	Improved
Cost	Higher	Typically, lower	Initial cost higher

1.5 Research gap

A life-sustaining therapy option for patients with renal diseases is haemodialysis. Haemodialysis is a therapy for ESRD that is used by millions of individuals worldwide. By eliminating excess of uremic wastes and water from the patient's blood in the dialyzer machine, this therapy approach supports the patient's life. The dialyzer primary component is a semipermeable membrane that divides the dialysate and blood compartments, through which the ultrafiltration process takes place. Commercially available polymeric membranes include PAN, PVDF, cellulose acetate and PES (Ronco and Clark, 2018). PES-based membranes are chosen above all other polymers because of their excellent mechanical strength, high pH resilience and good chemical resistance.

Nevertheless, the innate hydrophobicity of PES is one factor that restricts their performance despite their immense relevance (Sun et al., 2013). PES hydrophobicity restricts the membrane's functionality in two ways. First of all, a hydrophobic surface facilitates the adhesion of materials to membrane's surface or inside its pores, a process called fouling. Fouling is defined as the clogging of pores or the development of cake layer on the surface of membrane, which significantly lowers fluids flow and decreases the overall performance. It becomes necessary to raise the transmembrane pressure in order to maintain the constant flow, which eventually results in higher energy usage and shorter operational life (Heidari et al., 2021). Secondly, the hemocompatibility of membrane is compromised due to its hydrophobicity. Blood coagulation must not occur when a foreign substance comes into contact with the blood. Nonetheless, blood protein and platelets prefer a hydrophobic surface in order to stick to it. The platelets gets securely attached to the substance and then become activated, which start the coagulation cascade even further. The blood clot forms as a result of the activation of either the intrinsic or extrinsic coagulation pathway (Mollahosseini et al., 2020). Therefore, increasing hydrophilicity is crucial to improve hemocompatibility and to reduce fouling, both of which are important for hemodialysis. The impact of adding hydrophilic pore-formers, particularly PVP and hydrophilic nanoparticles like SiO_2 nanoparticles to PES membranes must be thoroughly studied. To fully understand how hydrophilic pore-formers and nanoparticles used in combination affect the shape and functionality of membranes. Moreover, further investigation is necessary to comprehend the impact of hydrophilic additive addition on HD membrane hemocompatibility.

1.6 Research objectives

- Fabrication of PES membranes using varied concentrations of SiO_2 nanoparticles.
- Evaluation of potential of synthesized membranes in terms of BSA rejection and urea clearance.

1.7 Research framework

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

- **Phase 1**

The first step involves the production of casting solution by adjusting the concentration of utilized polymers (PES and PVP) and hydrophilic additive SiO_2 nanoparticles. The second step entails the fabrication of membranes with varying composition and characteristics.

- **Phase 2**

After polymeric membranes are successfully fabricated, several characterization techniques will be employed to evaluate their physical and chemical characteristics. The methods include flux retention, scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), and contact angle.

- **Phase 3**

Testing is the last stage, during which membrane's performance in terms of urea clearance and BSA rejection is assessed.

CHAPTER 2: LITERATURE REVIEW

Kidneys are essential to preserving human health. They are responsible for elimination of acidic metabolic waste, for mineral and water balance, and efficient operation of endocrine system. However, medical intervention is required to maintain the patient's life when kidneys are unable to clear the wastes from the body. The most typical course of therapy for patients is hemodialysis. Patients usually undergo hemodialysis treatment for a while prior to kidney transplant.

2.1 Kidneys:

Kidneys, bean-shaped organs, have thickness, width and length of 3-4 cm, 5-6 cm, and 11 cm, respectively. Normal kidney functions to remove wastes, control acid base balance and blood pressure, regulate blood volume as well as sodium potassium levels besides endocrinal functions(Wang et al., 2014).

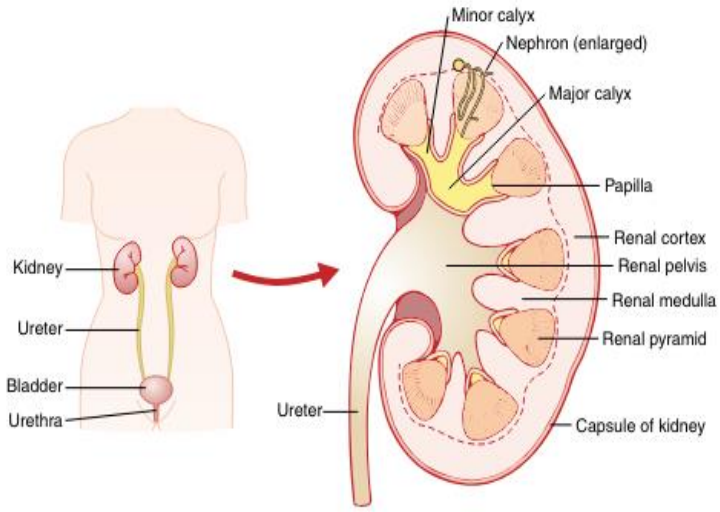


Figure 2.1 Human Kidney Location and Cross-section (Hall and Hall, 2020)

2.1.1 Kidney Failure

Kidneys are essential in keeping the human body environment in balance. Any infection, long term illness or injury to either kidney may reduce its functionality or in extreme circumstances may render it completely non-functional. In addition to balancing the body's levels of water, metabolic wastes and toxins, the kidneys also secrete

hormones (renin, erythropoietin, and calcitriol), regulate pH, ions production and concentration to control blood pressure and RBCs production.

Kidneys malfunctioning leads to misbalancing of body, disrupt water balance, lower appetite, cause exhaustion and sleep disturbances, muscle cramps, lethargy and impair attention. Elevated levels of metabolic wastes and excess of water in body can lead to severe health issues or even death.

Kidney failure or injury can affect one or both kidneys. It will cause the patient's body to be unable of eliminating excess water and wastes, which will have an impact on the body's blood volume, blood content and blood pressure. Depending on the cause, there are two forms of renal failure: Acute Renal Injury (ARI) and Chronic Renal Failure (CRF).

Acute Renal Injury (ARI) or Acute Kidney Failure (AKF) is "an abrupt decline in renal function." In medical terms, it is characterised by an unjustified increase in serum creatinine of greater than or equal to 0.3 mg/dl or decrease in production of urea (oliguria recorded at < 0.5mL/Kg per hour for more than 6 hours). It can also be defined as a 1.5-fold rise in serum creatinine from baseline or a percentage increase of greater than or equal to 50% (Mehta et al., 2007). Chronic Renal Failure (CRF) is defined by National Kidney Foundation as "*either kidney damage because of some accident or a glomerular filtration rate below 60 mL/min/1.73 m2 body surface areas for at least three months*".

1.1.2 Medical Treatments

For individuals with renal failure, there are two options for therapy and the common of which is haemodialysis. The alternative is kidney transplantation; however, this option is more expensive and restricted than haemodialysis because of the lack of kidney donors. For those who are affected, haemodialysis is used as "a bridge to transplant" extending the patients' life until the transplant.

2.2 Haemodialysis

Haemodialysis is one of the most popular and effective RRT choices for ESRD patients. It involves filtering the patient's blood outside of the body using a semipermeable membrane within a dialyzer (Raharjo et al., 2022). By removing the

surplus fluid and particulates from the blood, the dialyzer helps the body regain its electrolyte balance. The cleansed blood is then returned to the patient's body. Haemodialysis is performed three times a week on average, lasting several hours each time (Irfan et al., 2019). The patient must adhere to a strict food and hydration regimen to preserve the electrolyte balance and prevent fluid overload.

2.2.1 Substances removed and retained during haemodialysis.

2.2.1.1 Creatinine and Urea

These molecules are the leftover products of the metabolism of proteins. In muscles, the breakdown of amino acids produces both urea and creatinine as byproducts (Rosner et al., 2021). Higher levels of urea and creatinine indicates that your kidneys are not working well. High creatinine level might point to the range of underlying issues including kidney infection and failure. Each needs to be removed from the body efficiently to prevent accumulation in the blood, which can lead to uremic toxicity and renal problems.

2.2.1.2 Electrolytes

It is necessary to effectively eliminate potassium and phosphorous from the blood. High potassium levels can cause hyperkalaemia, which can lead to deadly cardiac arrythmias. Raised phosphorous levels occurs in hypophosphatemia, which can affect renal patient's bones and cardiovascular systems (Rosner et al., 2021). For the body to function properly, it is necessary for that the electrolytes are evenly balanced. Electrolyte imbalance can cause serious health issues such as cardiac arrest, coma, and seizures.

2.2.1.3 Middle-size molecules

Middle-size molecules like Beta-2 microglobulin and leptin must be eliminated. An intermediate size molecule known as Beta-2 microglobulin accumulates in renal failure and, if left unchecked, can lead to amyloidosis associated with dialysis (Clark et al., 2019). Elevated leptin levels in renal patients can lead to obesity since it impacts satiation and metabolism. These middle- size molecules contribute to the uremic toxicity as they accumulate in renal failure.

2.2.1.4 Excess fluids

Fluid overload can lead to edoema, congestive heart failure and hypertension; however, it can be prevented by avoiding excess fluid intake. Too much fluid in body raises blood pressure, which makes the heart work harder to pump blood. The heart may ultimately weaken and stop working as well, which might result in heart failure. Excess fluid may build up in the lungs and will make it harder to breathe.

2.2.1.5 Toxins and metabolites

Indoxyl sulphate and p-cresol are two uremic toxins that exacerbate cardiovascular diseases as well as other issues associated with renal failure. Patients with renal diseases experience reduced chronic inflammation when these are eliminated (Magnani and Atti, 2021). Multiple organ systems and pathways are negatively affected by uremic toxicity, such as cardiovascular damage, neurological manifestation, and increased susceptibility to infection, the major factors that affects patients' quality of life and mortality.

2.2.1.6 Substances retained.

Haemodialysis requires the maintenance of vital electrolytes in the blood, such as magnesium, sodium, and calcium, which are essential for maintaining fluid balance, brain function, and bone health. Proteins like immunoglobulins and albumins are essential for food delivery, immune response and preservation of osmotic pressure (Rosner et al., 2021). Vitamin D and the hormone erythropoietin are essential for bone health, red blood cells formation, and other physiological functions. Growth, repair, and development are aided by growth factors(Clark et al., 2019). Insulin-like growth factor-1 (IGF-1) is one example of such growth factor. Blood coagulation, wound healing, immunological response, and the transportation of oxygen all depend on red and white blood cells and platelet-rich plasma. In summary, nutrients such as amino acids and glucose serves as the building blocks and energy sources for essential cellular processes (Magnani and Atti, 2021). As a result, all these substances must be retained in the blood during haemodialysis.

2.3 Basic haemodialysis mechanisms

Osmosis, diffusion, and ultrafiltration are vital mechanisms that cooperate in renal patients to effectively eliminate waste materials, regulate fluid balance, and preserve electrolyte levels during haemodialysis.

2.3.1 Diffusion

Solutes or dissolved materials like electrolytes and waste products diffuse as they go from an area of higher concentration to an area of lower concentration (Pstras et al., 2022). Excess electrolytes and waste products are carried by blood when it passes through one side of the dialyzer. A unique fluid called dialysate is found on other side of membrane. It is managed to have a lower concentration of electrolytes and wastes in the dialysate's composition than in blood.

2.3.2 Osmosis.

Osmosis is the movement of water from an area of lower solute concentration to an area of higher solute concentration. The dialysate solution is precisely formulated to yield desired electrolyte concentration (Raharjo et al., 2022). If the blood contains more solutes (such as electrolytes) than the dialysate, water travels from the blood over the membrane and into the dialysate to balance the concentration.

2.3.3 Ultrafiltration

Through the elimination of surplus fluids and nitrogenous waste from the circulation, ultrafiltration contributes to the maintenance of the body's fluid balance. For the semipermeable membrane to drive water out of circulation and through the membrane into the dialysate compartment via pressure, pressure fluctuations across the membrane are necessary (Ronco and Clark, 2018). The dialyzer membranes are designed so that it allows the water to pass through it, but larger molecules, such as proteins, are meant to be retained (Irfan et al., 2019). The balance of osmotic and hydrostatic pressure results in a net migration of fluid from the circulation into the dialysate.

2.3.4 Convection

Convection is the second filtering technique used in haemodialysis. The procedure involves drawing fluids and solutes out of the blood using hydraulic pressure (Westphalen et al., 2020). Unlike diffusion and osmosis, which rely on concentration gradients, convection includes the movement of solutes and fluid because of the physical force of the fluid flow itself. Compared to diffusive, convective transport permits the removal of higher molecular weight solutes at a higher rate

2.4 Major components of a hemodialyzer

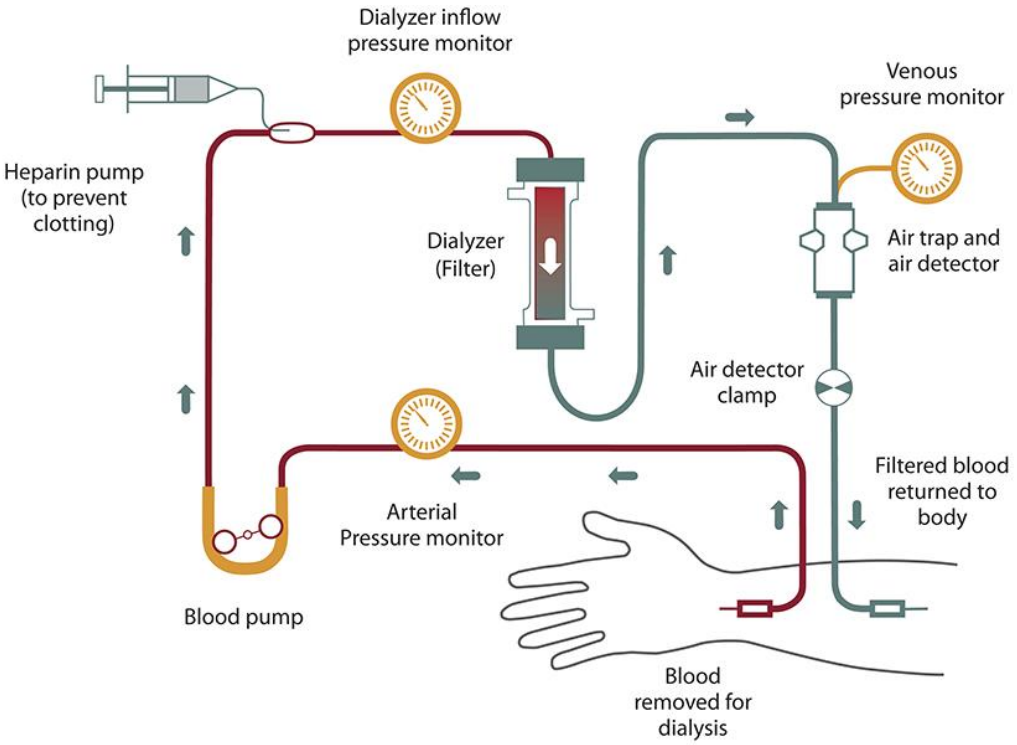


Figure 2.2 Simplified diagram of hemodialyzer.

2.4.1 Dialysate compartment

The dialysate chamber is the most important section of the dialysis machine. This compartment contains the dialysate, a particular fluid. Both the dialysate and the blood compartments are separated by a semipermeable polymeric barrier (Area, 2020). Maintaining the dialysate's balanced composition is one of the most crucial factors. Any discrepancies has the potential to seriously compromise the treatment's overall

effectiveness (Irfan et al., 2019). Maintaining a balanced osmotic gradient in the dialysate is important to keep a steady state haemodialysis procedure.

2.4.2 Semipermeable membrane

The semipermeable membrane, which separates the dialysate and blood compartments, is an essential component of the hemodialyzer. Selective solute diffusion is made possible by their molecular size and concentration gradient. Particularly urea and creatinine, which are small waste molecules from the blood, permeate out of the membrane into the dialysate (Specifications, 2020). The dialysate compartment receives the uremic toxins by the processes of diffusion, osmosis, and convection through the semipermeable polymeric membrane. The dialysate's key ingredients enter the blood compartment. Certain dialyzers employ porous membrane fibres that are hollow, which increases the surface area available for elimination of wastes.

2.4.3 Blood compartment

The blood compartment is a crucial component of the hemodialyzer. Here the patient's blood is injected into the dialyzer. It is separated from the dialysate compartment by a thin semipermeable membrane (Specifications, 2020). The dialysis phenomenon is made possible by blood flowing from the patient's body into this compartment. The transport processes across the membrane are dialysis (diffusion) and ultrafiltration (convection).

2.5 Working principle of dialyzer

The dialyzer uses the phenomenon of osmosis, diffusion, and ultrafiltration to mimic the function of kidneys. Dialysis is an easy and effective treatment. The choice of vascular access point is the initial step. Blood can be extracted from the patient and injected into the blood compartment using this location (Pstras et al., 2022). The blood is pumped into the blood compartment as soon as a connection is created. The dialysate compartment and blood compartment are divided by a semipermeable membrane. The specific solution known as dialysate is present in the dialysate compartment. The most crucial component, the semipermeable porous polymeric membrane, is located between the two compartments. Waste products from the blood, in particular urea, creatinine, and

beta microglobulin, can pass through it selectively (Irfan et al., 2019). In the meantime, an osmotic gradient created by the carefully regulated composition of dialysate pushes waste elements out by osmosis. Ultrafiltration happens as a result of the pressure gradient that is formed across the semipermeable membrane (Ronco and Clark, 2018). This occurs when the hydrostatic pressure on the dialysate side is higher than the blood side. With this process, excess fluids and certain solutes are effectively eliminated from the blood stream (Area, 2020). The patients receives their cleansed blood back in a few hours following a full circulation of their complete blood through the dialysis machine. The dialyzer helps patients with end-stage renal disease by assisting in the complicated process of maintaining fluid and electrolyte balance (Specifications, 2020).

2.6 Semipermeable polymeric membranes

The kidneys' job is to filter out unnecessary waste and hold onto the things the body needs. The network that the glomerulus of nephron creates allows for the filtration process to occur. Comparably, a polymeric membrane that filters chemicals according to size is put within the dialyzer machine (Azhar et al., 2021). This thin membrane runs the length of the structure from top to bottom and is made up of hundreds of tiny holes. Because the pores are joined, a fluid filled tunnel is created, preventing the bigger molecules from moving. On the other hand, a different kind of membrane known as a non-porous membrane is devoid of holes (Asif Khan et al., 2023). Various businesses use these types of polymeric membranes for packaging. In conclusion, membranes may be classified as either porous or non-porous depending on whether they have pores or not. Furthermore, symmetrical, and asymmetrical forms depending on morphology are among the other sorts. Porous and asymmetrical membranes are utilised in haemodialysis (Sun et al., 2013). The ability of polymeric membranes to be porous is crucial to their functionality because the linked holes allow fluid to flow through the structure while preventing bigger molecules from doing so. According to science, the way membranes function is by size exclusion, wherein the bigger molecules are sieved out and the smaller fluid molecules are selectively permeable (Wei et al., 2022). Haemodialysis allows small desirable molecules like urea and creatinine to the dialysate side of the solution along

with excess water in blood. Larger particles such as proteins and blood cells are not included in this size range.

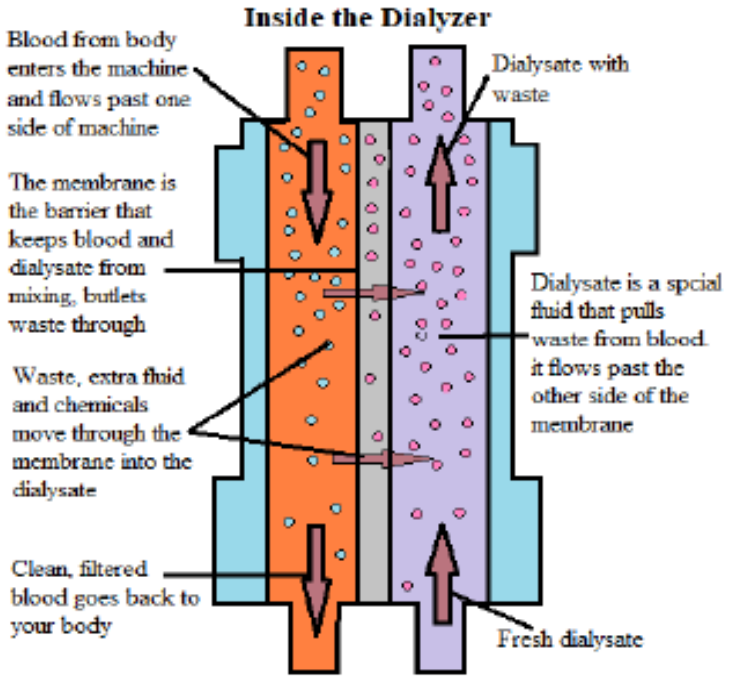


Figure 2.3 Presentation of hemodialysis process

The size and configuration of pores affects the membrane's most important properties, which are selectivity and permeability. Permeability operates in such a manner that smaller pores enhance selectivity while reducing flow. Larger pores, on the other hand, may decrease selectivity while increasing permeability and water flux (Lv et al., 2018). As a result, the membranes are created based on the necessary properties and intended use. Common polymers used in the production of membranes include cellulose based compounds, poly ether sulfone (PES), polyamide (PA), poly sulfone (PSU), and poly vinylidene fluoride (PVDF) (Wang et al., 2022). Among these, membranes made of cellulose are often utilized. Because each form of a polymer has distinct features, all of these polymers are significant in their own way (Alayande et al., 2019). For example, they possess qualities like thermal stability, mechanical durability, and chemical resistance.

The efficacy of these membranes is mostly dependent on their hydrophobicity or hydrophilicity, regardless of the polymer employed. Hydrophobic polymers with strong mechanical, thermal, and chemical resistance are employed in pressure driven processes (Irfan et al., 2015). Nonetheless, the reduced wettability of hydrophobic membranes makes them less popular for use in variety of applications. In contrast, hydrophilic membranes have a greater surface tension and are able to form hydrogen bonds with water molecules (Mokarizadeh et al., 2021). By rejecting organic molecules and preventing proteins from adhering to the membrane's surface, this property helps reduce membrane fouling. For biological applications, hydrophilic membranes are therefore the best option.

2.7 Types of membranes

The membranes are classed according to several factors, including as shape, size of holes, and porosity. Non-porous membranes are used in applications such as product and food packaging. Apart from that, filtration characteristics are used to classify membranes (Shi et al., 2014). Membranes made of porous polymeric materials can be categorised. For example, pressure-driven mechanisms are essential to the operation of reverse osmosis (RO), nanofiltration (NF), ultrafiltration (UF), microfiltration (MF), and other forms of separation techniques (Shi et al., 2014).

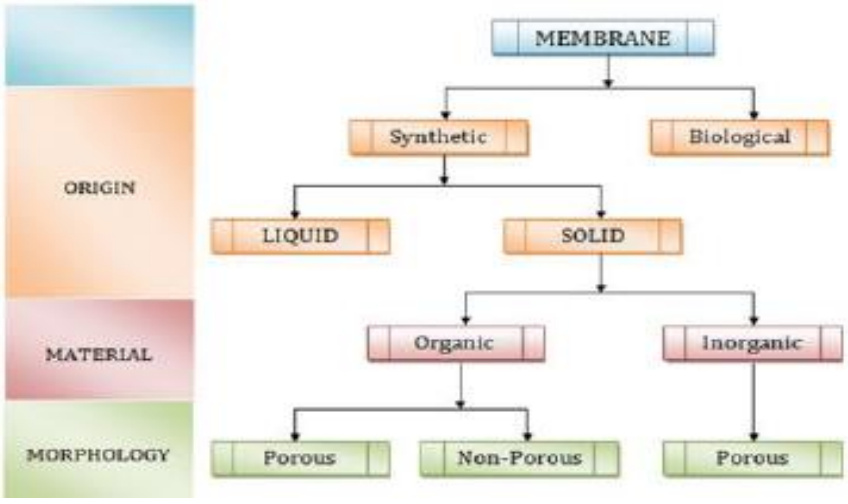


Figure 2.4 Classification of membranes on basis of origin material and morphology

2.7.1 Microfiltration membranes

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

Microfiltration membranes have application in several industries, such as medicines, food & beverage, and wastewater treatment. Microfiltration membranes are used in wastewater treatment to filter out bigger particles before undergoing the ultrafiltration and reverse osmosis procedures (Mollahosseini et al., 2020). Larger particles, such as colloidal particles, bacteria, microorganisms, and large viruses, can be removed from raw water by microfiltration. Microfiltration membranes are used in the food and beverage sector to remove bigger particles suspended in solution (Anis et al., 2019). In the beverage sector, undesirable particles such as bacteria and yeast are eliminated in order to sterilize and concentrate juice, dairy products, and other drinks (Bilad et al., 2012). Apart from that, these membranes play a critical role in biomedical environments where they are used for cell separation, blood filtration during hemodialysis, and equipment sterilization in some cases (Anis et al., 2019).

2.7.2 Ultrafiltration membranes

The next kind of membranes are ultrafiltration membranes, which are used in a broad range of fields, including biomedical and water treatment. Ultrafiltration membranes are those with a pore size of 0.003-0.01 μm. The pore size is greater than that of nano-filtration membranes and lower than that of microfiltration (Al Aani et al., 2020). These membranes have an interconnected network of holes that allow molecules to be selectively separated based on their size and shape, as well as a thick outer layer known as the skin or dense layer.

Compared to microfiltration membranes, ultrafiltration membranes are more selectively permeable to compounds. Ultrafiltration membranes can be used to effectively filter out germs, viruses, and colloidal particles (Shi et al., 2014). To help in

nanofiltration, the bigger particles are often removed by the ultrafiltration procedure prior to nanofiltration. Ultrafiltration is most frequently used to clean raw and brackish water, mostly from industrial effluents (Mokarizadeh et al., 2021). Additionally, it serves a variety of functions in the pharmaceutical and biomedical industries, including protein concentration and purification. Apart from that, haemodialysis membranes are included in the ultrafiltration membranes group.

2.7.3 Nano filtration membranes

The holes of nanofiltration membranes range in size from 0.001 to 0.01 micrometres, making them even smaller than those in UF. NF can be used to separate organic molecules, divalent and monovalent ions, and both. Nanofiltration membranes are usually made of thin-film composite materials (Mohammad et al., 2015). These membranes have a thick active layer on top of a porous support layer. Because of the specific surface chemistry of the nanoscale pores in the active layer, interactions with solutes based on size and charge are possible.

NF membranes may effectively remove divalent ions from water, such as calcium and magnesium, in contrast to traditional methods of water softening. Moreover, NF is used to remove chemicals that cause colour and odour in drinking water as well as to concentrate essential components in industrial effluent streams (Oatley-Radcliffe et al., 2017). In pharmaceutical research and medication development, proteins, peptides, and other biomolecules are concentrated and purified using nanofiltration. It aids in achieving very pure goods and getting rid of impurities.

2.7.4 Reverse osmosis membrane

Reverse osmosis membranes have the smallest holes of any porous membrane; these pores have a diameter of 0.0001 to 0.001 micrometres. With the use of RO, which is incredibly selective, most organic components, ions, and salts may be eliminated to create a highly pure permeate. These membranes are commonly used in the desalination of saltwater, water purification, and wastewater treatment processes to provide high-quality effluent (Hailemariam et al., 2020). Because of the interplay between size and

charge, this membrane rejects dissolved solutes and ions while allowing solvent molecules to flow through the nanoscale pores in the active layer (Al Aani et al., 2020).

Reverse osmosis membranes find significant use in the desalination of seawater. Seawater may be converted into fresh drinking water using RO technology, providing a reliable source of clean water for places where access to it is scarce (Hailemariam et al., 2020). RO systems are also widely used in labs and research settings to supply deionized water. For several testing and analytical procedures where the presence of impurities and ions might alter the outcomes, this specific sort of water is necessary (Shi et al., 2014).

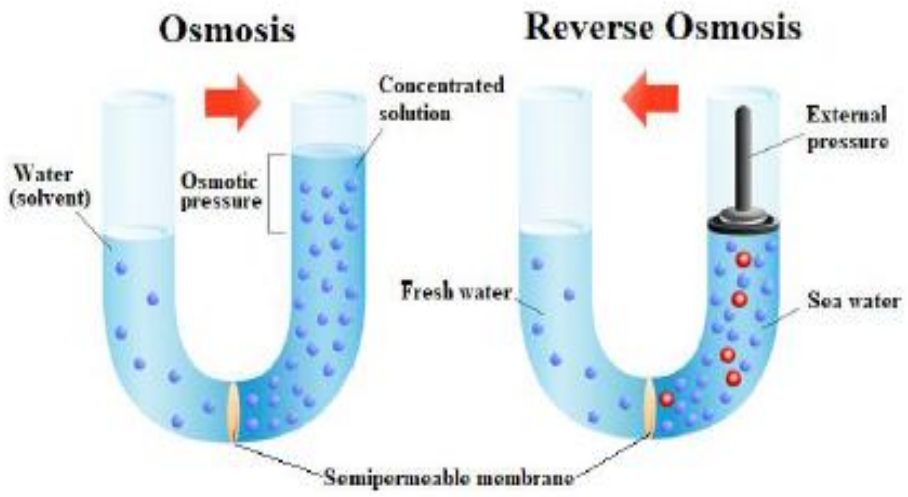


Figure 2.5 Schematic diagram of osmosis and reverse osmosis

Table 2.1 Different types of separation techniques

	Ultrafiltration	**Nanofiltration**	**Reverse osmosis**
Operation mode	Dead end and crossflow	Crossflow	Crossflow
Separation mechanism	Sieving	Exclusion and diffusion	Exclusion and diffusion
Membrane type	Asymmetric polymer, composite or ceramic	Asymmetric polymer or composite	Asymmetric polymer or composite

Module type	Spiral wound, hollow fiber, tubular, plate or frame module	Spiral wound, hollow fiber, tubular, plate or frame module	Spiral wound, hollow fiber, tubular, plate or frame module
Permeate flux	High	Medium	Low

2.8 Membrane fabrication (Phase inversion method)

Phase inversion is a common approach used in the fabrication of commercial membranes. This is a very helpful way for synthesizing membranes with various topographic characteristics. There are a number of variables that affect how the prepared membrane takes shape. The process for creating a membrane involves dissolving the polymer in the suitable solvent and then extruding it into the desired alignment or module. Subsequently, the polymer undergoes phase change precipitation, which is accomplished by adjusting the temperature or the composition of the bathing or casting solution (Durmaz and Çulfaz-Emecen, 2018). The porous nature of the polymeric membranes, which may be produced using a variety of methods, makes them significant. The most often used techniques include phase inversion, ionizing radiation, track etching, electrospinning, and nanoimprinting. Phase inversion is the most basic and easy of all these techniques (Hołda and Vankelecom, 2015). This method works well for creating porous membranes since it doesn't require any extra chemicals or reactions. This method may be used to create a porous structure out of a homogenous polymer solution. Benefits of phase inversion include precise control over porosity, scalability, and ease of usage. Thermal-induced phase separation (TIPS), nonsolvent-induced phase separation (NIPS), and vapor-induced phase separation (VIPS) are three techniques for phase inversion (Young and Chen, 1995).

2.8.1 Non-solvent-induced phase separation (NIPS)

Polymer dope solution and non-solvent are combined in the non-solvent phase inversion procedure. By dissolving the polymer in a solvent, a homogenous polymer

solution is created. Inversion happens when the polymer solution thin film is immersed in a non-solvent phase (Hołda and Vankelecom, 2015). Two phases are created, the polymer-rich phase and the polymer lean phase, when the solvent from the polymer solution combines with the non-solvent. The polymer in the polymer-rich phase is now beginning to precipitate since it is not soluble in the non-solvent. The membrane structure has holes and spaces created by the polymer lean phase. Asymmetric membranes are created by this remixing of solvent and non-solvent materials (Alayande et al., 2019). Typically, the membrane has a thick top layer and a void-filled bottom layer.

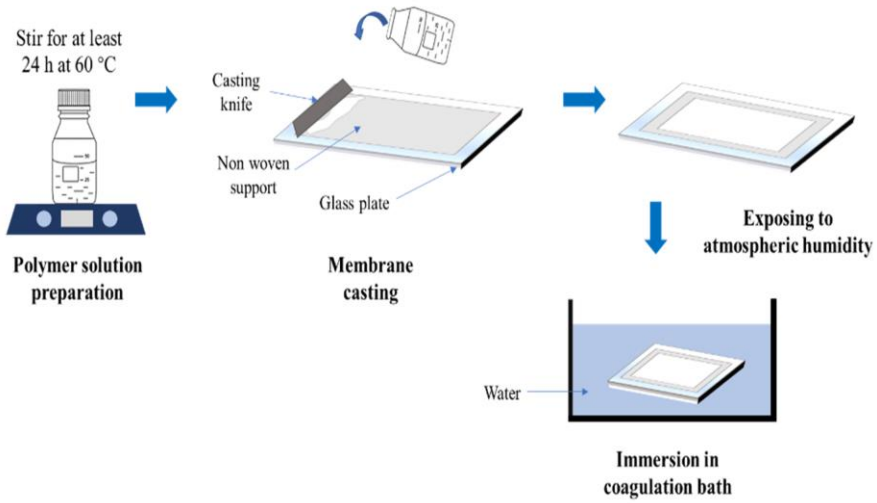


Figure 2.6 Diagrammatic representation of membrane fabrication

2.8.2 Thermally induced phase separation (TIPS)

Using heat-induced phase inversion to create porous polymeric membranes is another technique. To make a polymer solution, the polymer is dissolved in a solvent at a controlled temperature (Hołda and Vankelecom, 2015). As the temperature changes, the polymer in the thin layer becomes insoluble. This results in the polymer precipitating and the formation of a porous membrane. The rate of cooling and the membrane's ultimate temperature have a significant impact on the membrane's characteristics, including its general form and pore size (Warsinger et al., 2018).

2.8.3 Vapour induced phase inversion (VIPS)

Vapour-induced phase inversion is a different technique for phase inversion that makes use of vapour as opposed to a liquid non-solvent. The method is comparable to NIPS in that it involves applying a thin layer of polymer solution on a support. Phase inversion is brought about by the vapour, which might be ordinary water vapour or a particular volatile chemical (Young and Chen, 1995). In the vapour utilized in this process, the solvent is miscible while the polymer is insoluble. When vapour is introduced to the thin layer, a concentration gradient is created. When the vapour is taken up by the thin layer, the solvent evaporates. When the solvent evaporates, the layer precipitates and absorbs the vapour, significantly decreasing the polymer's solubility. Therefore, a key factor in shaping the membrane's structure is the kinetics of evaporation and absorption (Dong et al., 2021).

2.9 Fouling of polymeric membranes

The holes in the water aid in its penetration, preventing bigger contaminants from polluting the water and facilitating the filtering process. The efficiency of membranes may be considerably diminished by pore blockage, which can be a difficult problem. Fouling is the occurrence where the blockage of pores by different substances reduces the filtration effectiveness of membranes (Yin and Zhang, 2021). Depending on the type of foulant, there are several types of fouling: scale and colloidal fouling, biofouling (blocking of pores with bacterial and viral debris), organic fouling (organic substances may cause organic fouling), and so on. The majority of the time, the foulant is removed by backwashing of the membranes, allowing a steady fluid flow across the membrane; however, it becomes a 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, making it impossible to remove by backwashing of the membrane (Azhar et al., 2021).

Fouling of the membranes during hemodialysis can be a major drawback that puts an ESRD patient's life in grave danger. First off, uremic toxin clearance can be significantly decreased by pore blockage (Shi et al., 2014). The body's homeostasis

becomes unbalanced due to ineffective waste elimination, which might exacerbate the already deteriorating renal disease. Furthermore, adhesion of proteins to the membrane surface has the ability to trigger a cascade of coagulation. The ultrafiltration efficiency is further decreased by the development of clots within the pores or on the membrane surface (Asif Khan et al., 2023). The fact that the clots may cause life-threatening illnesses is even more worrisome. Consequently, the synthesis of membranes with antifouling capabilities is essential (Yamamoto et al., 2005).

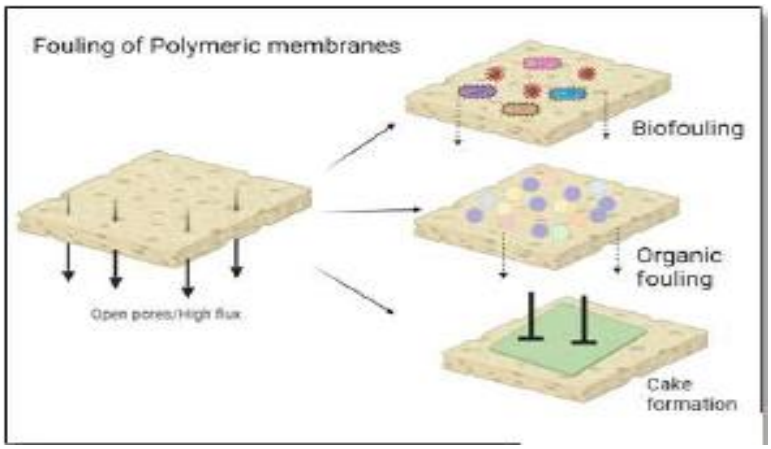


Figure 2.7 Different types of fouling of polymeric membranes

2.10 Sources of fouling o hemodialysis membranes

2.10.1 Proteins

Proteins have the highest propensity of all the compounds found in blood to bind to polymeric membranes. The proteins that are most likely to stick to the surface of polymeric membranes include albumin and fibrinogen (Howe et al., 2002). A layer rich in proteins is formed, which may alter the membrane's permeability and decrease the effective pore size (Abe et al., 2021). Uremic toxins are not fully removed, and the flow is decreased. This might be harmful to the patient's health and undermines the efficacy of dialysis. The fouling that proteins may induce is referred to as biofouling or organic fouling, depending on the type of foulant. Protein adherence results in membrane fouling as well as the induction of thrombotic and inflammatory processes. When proteins cling to one another, the coagulation cascade may be set off, endangering the patient's life while receiving hemodialysis.

2.10.2 Blood clots

Proteins on the hydrophobic membrane surface begin to adsorb when blood comes into contact with it. Also adhering to the surface are blood platelets, which activates them (Claudel et al., 2021). Either the intrinsic or the extrinsic coagulation route is used by the activated platelet to start the coagulation process. The surface of the polymeric membrane becomes covered in clots as soon as coagulation starts. The flow may be decreased by blood clots blocking the membranes' pores (Irfan et al., 2019). Furthermore, blood clotting can pose a serious risk to patients and could result in deadly consequences.

2.11 Detrimental effects of fouling of polymeric membranes

2.11.1 Decreased permeability

The route for solvent transport becomes constrained if the pores in the membranes get blocked with different pollutants and particles. This results in less waste water and toxin removal, which lowers the effectiveness of the entire process (Yamamoto et al., 2005). It leads to decreased flux, resulting in increased energy demand, membrane degradation and high operation cost. In the end, this can be harmful to the patient whose ESR treatment is totally dependent on renal replacement therapy.

2.11.2 Increased trans-membrane pressure

Fouling accumulates on both the inside and exterior of the membrane during hemodialysis, creating resistance to blood flow. Higher transmembrane pressure is required to maintain proper blood flow rates, and that will have higher energy demand and higher operation cost (Zainol Abidin et al., 2022). But it increases the risk that the membrane would deteriorate and lose its structural integrity and results in membrane degradation.

2.11.3 Inflammatory response

Clotting is triggered when platelets stick to the membrane's surface. Additionally, the organic fouling may release substances into the blood, which may result in inflammatory reactions. Haemodialysis’s effectiveness and safety may be compromised by this (Mollahosseini et al., 2020). Cells, molecules or toxins adhered to the surface can trigger various inflammatory pathways and can affect the patients’ health.

2.11.4 Thrombosis

Platelets may stick to a membrane when its surface is hydrophobic. The coagulation cascade may be started by the platelets after they have adhered and been activated. Soluble fibrinogen is transformed into fibrin through the activation of both intrinsic and extrinsic mechanisms (Irfan et al., 2019). Clots are created when fibrin forms a secondary plug on the membrane's surface. These clots can be very harmful and frequently cause catastrophic outcomes. Consequently, it is essential to employ hemocompatible membranes.

2.12 Antifouling techniques

It is essential to investigate the fouling-resistant characteristics of membranes due to the negative impacts of membrane fouling that have been stated above. In order to enhance the antifouling properties and offer better results over an extended period of time, several techniques have been explored.

2.12.1 Surface modifications

Surface changes are the first strategy used to prevent fouling. It is a common technique for enhancing polymeric membranes' antifouling properties (Song et al., 2021). Surface integration of hydrophilic functional groups or zwitterionic moieties reduces the likelihood of fouling chemicals adhering to the membrane.

- **Coating:**

In every interaction, the surface of a substance makes touch with other components first. The matrix, or bulk, is located next to the surface. Reducing membrane fouling may therefore depend on changing the surface. Coating refers to the method of applying a material (the coating) to a surface (Banerjee et al., 2011). Applying a coating to a substance is known as substratum. Layers of a substance are applied to a substrate in one or more layers during the coating process. Adding additional and desirable qualities to the content is the aim. The required properties of substrate membranes are imparted to them by the coatings (Asif Khan et al., 2023). It is guaranteed that the coating covers the membrane in an even layer. Different techniques, including as electro-spinning, spin coating, and dip coating, are used to coat the membrane surface based on the kind of

material and its intended use (Banerjee et al., 2011). Polymeric membranes may be made more functional, hydrophilic, and functional with coatings.

- **Grafting**

Grafting is another technique for enhancing the antifouling properties of membranes. One of the most promising techniques for modifying polymer membranes is grafting, which involves attaching chains of hydrophilic polymers to the membrane surface. Higher water flow may be achieved by reducing the interfacial tension with water, which is made easier by the presence of hydrophilic chains on the membrane surface. Grafting is the process of chemically connecting antifouling functional groups to the membrane surface (Banerjee et al., 2011). Covalently linking reactive monomers to the surface to increase HD membrane hemocompatibility is an example of grafting.

- **Incorporation of nanomaterials**

A further method of altering membranes is by incorporating nanoparticles into the polymer. Researchers have been adding nanoparticles to polymeric membranes in order to modify their fundamental qualities and produce desired effects. For example, adding graphene oxide particles, carbon nanotubes, and silver nanoparticles to membranes to provide beneficial properties has attracted a lot of interest (Fahrina et al., 2021).

2.12.2 Bulk modifications

Bulk modification includes changing the matrix as well as the surface of the material, as opposed to surface modification, which only modifies the material's outermost layer. Since this kind of change entails changing the material's total chemical makeup, it is significant (Kadanyo et al., 2022). The material has constant characteristics since the additive is evenly distributed throughout it. The following strategies are used to perform bulk alteration (Heidari et al., 2021).

- **Blending of hydrophilic additives**

Blending is the process of creating a uniform polymer mixture to change a material's chemical and physical characteristics. Since it doesn't call for an extra step in the manufacture of the final material, this bulk modification process is thought to be simpler than other approaches (Otitoju et al., 2018). When it comes to membranes,

hydrophilic polymers are mixed in to change the material's hydrophobicity. For example, PES is a hydrophobic polymer whose limited wettability restricts the functioning and performance of membranes. Nonetheless, it has been demonstrated that adding hydrophilic chemicals enhances the PES membranes' wettability properties (Lv et al., 2018).

2.13 Hemocompatibility

Testing a biomaterial's reaction in the event that blood and foreign material contact is known as hemocompatibility testing. This effect is quite significant when there is direct contact between the blood and a foreign substance. Blood contact with biomaterials, for example, involves contact with dialysis machines, vascular grafts, and stents. There are number of ways in which the blood and foreign bodies interact, including hemolysis, thrombosis, inflammation, and immunogenicity (Nalezinková, 2020). The blood coagulation system's activation is the most crucial hemocompatible event in hemodialysis cases. It involves a sequence of actions that activate clotting factors, which in turn induce a clot to develop. Coagulation is the process of converting soluble fibrinogen into insoluble fibrin, which functions as a meshwork to seal an injury (Wei et al., 2022). Coagulation is crucial for natural physiological processes including healing after damage. However, coagulation and the formation of clots when not necessary can cause adverse effects. On the other hand, unneeded clot development and coagulation might have negative consequences. For example, clot development in the dialysis system might negatively affect dialysis's effectiveness. Blood in a dialyzer machine coagulates when the polymeric membranes used for ultrafiltration are not compatible with human blood (Mollahosseini et al., 2020). The hydrophobic characteristic of the membranes is one of the primary causes of hemo-incompatibility. The coagulation cascade is activated by the hydrophobicity, which improves platelet and protein adsorption on the surface of polymeric membranes. As a result, it is critical to have membranes that are hydrophilic in nature and do not enhance protein adhesion to membrane surfaces (Irfan et al., 2015).

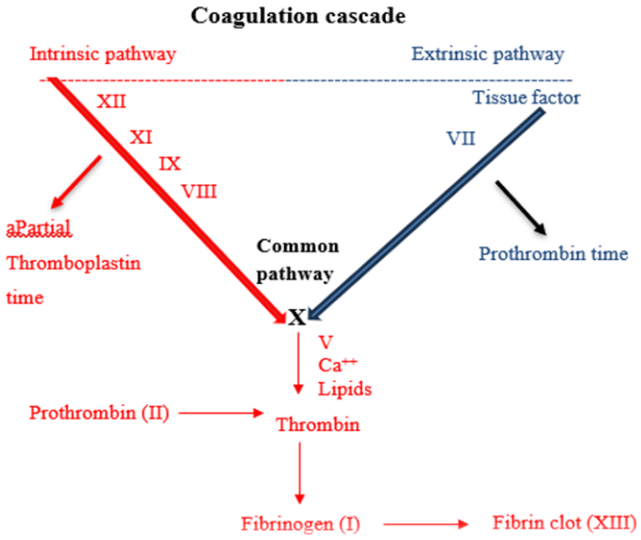


Figure 2.8 Complete process of coagulation cascade showing intrinsic, extrinsic and common pathway

2.13.1 Intrinsic Pathway

Blood that comes into touch with a negatively charged surface activates the intrinsic route, also referred to as the contact activation pathway. A clot forms as a result of the activation of a series of enzyme reactions. When foreign objects like medical devices activate their coagulation systems, this kind of route is very crucial (Mollahosseini et al., 2020). The most significant component is the Hageman factor, sometimes referred to as factor XII, which starts the coagulation cascade. This component becomes activated XII(a) when it comes into touch with negative charges. Factor XI becomes active once the Hageman factor is engaged. This component encourages factor IX to become factor IX(a) even more (Irfan et al., 2019). Tenase complex is formed by this activated IXa and its cofactor. When phospholipids and calcium ions are present, the intrinsic tenase complex triggers factor X. In this case, factor X is changed to Xa. This is the point at which the intrinsic and extrinsic pathways converge, giving rise to the term "common pathway" (Kohlová et al., 2019). Compared to the extrinsic process, the intrinsic pathway is slightly more complicated and requires a longer time to form a clot. Activated partial prothrombin time is the term for the test used to determine how long it takes for clots to develop utilizing the intrinsic route (APTT).

2.13.2 Extrinsic pathway

The extrinsic pathway is triggered in a biological reaction to an injury, in contrast to the intrinsic pathway. This system, which is simpler and faster to activate than the intrinsic pathway, is triggered when the blood is exposed to tissue factor following an injury (Nalezinková, 2020). It takes clot formation to work quickly to successfully halt excessive blood loss. Partial thromboplastin time (PTT) is a measure of how long it takes for a clot to develop through an extrinsic route. Typically, the clinical range is less than 14 seconds.

Blood is exposed to tissue factor when there is an injury, which heightens the coagulation cascade. The extrinsic pathway is initiated when tissue factor, a glycoprotein that is normally absent from the blood, comes into contact with it (Nalezinková, 2020). After factor VII is triggered, factor XI is also triggered. Since XI is on the same route, the coagulation process moves more quickly. The convergence of intrinsic and extrinsic routes, known as the common pathway, is brought about by the activation of X into Xa (Mollahosseini et al., 2020).

2.14 Polyether sulfone (PES)

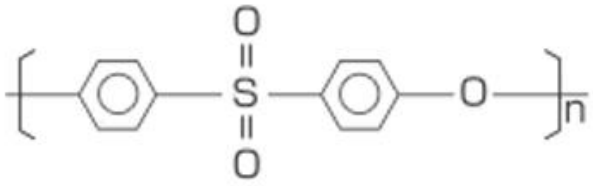


Figure 2.9 Chemical structure of polyethersulfone

The amorphous thermoplastic polymer polyethersulfone is well-known for its strong resistance to oxidation and heat. Repeating units of ether and sulfone groups make up the PES's molecular structure (Mokarizadeh et al., 2021). PES is widely utilized in many different applications due to its exceptional properties, which include strong resistance to acid-bases, great mechanical strength, and thermal stability. Its remarkable thermal characteristics make it more appropriate for high-temperature applications. PES, however, is an excellent insulator due to its poor heat conductivity (Azhar et al., 2021). PES offers a wide range of applications due to the aforementioned qualities, the most

significant ones being in the biomedical sector. The Polymer PES finds widespread application in medical equipment where resistance to sterilization and biocompatibility are essential features. PES is also utilized in the production of membranes for gas separation and water treatment, including reverse osmosis, nanofiltration, and microfiltration membranes(Al Malek et al., 2012). The polymer does have certain limits, though. Recycling the polymer can be difficult because of its great resistance to heat and pH. Additionally, the filtering process is hampered by its inherent hydrophobicity.

2.15 Polyvinylpyrrolidone

N-vinylpyrrolidone repeating units combine to form polyvinylpyrrolidone, a non-toxic, water-soluble polymer. There are several molecular weights of this polymer, and these weight variations affect its properties (Mireles et al., 2020). Due to its capacity to withstand high temperatures, tolerance to pH changes, and biocompatibility, this polymer finds extensive usage in biological fields. This polymer is utilized to encapsulate lipophilic and hydrophilic medicines in medication delivery systems (Schwarz, 2018). PVP has also been used in tissue engineering, orthopedics, and innovative drug delivery formulations. PVP was used to create hair fixative agents in the hair spray business prior to its use in medicine.

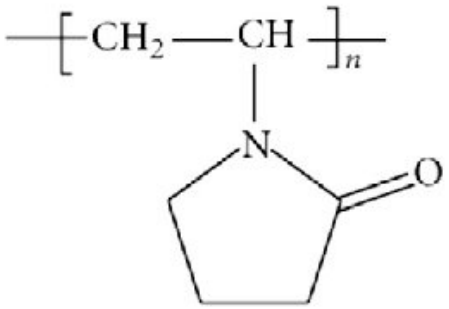


Figure 2.10 PVP chemical structure

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. Silicon powder, Ethanol (C2H6O), Sodium hydroxide (NaOH), and tetraethoxysilane (TEOS) were also purchased from Sigma Aldrich. The base polymer of membrane, polyethersulfone (PES) of molecular weight of 58000 g/mol, was acquired from Solvay advanced material (USA). Polyvinylpyrrolidone (PVP), of molecular weight 40,000 g/mol was purchased from Sigma Aldrich. N-methyl-2-pyrrolidone (NMP) solvent was acquired from Sigma Aldrich, Germany. BSA (purity>97%) and Urea were purchased from Sigma Aldrich, Germany.

3.2 SiO_2 nanoparticles synthesis

A beaker and magnetic stirrer were washed with ethanol and then dried thoroughly. Silicone powder weighing 20g was added to the beaker. 200ml of ethanol was added into the beaker and was vigorously stirred until the silicone powder was completely dispersed. Then 20 ml of 1M NaOH solution was added to the beaker and stirred until the solution is clear. After that 20 ml of TEOS was added dropwise while stirring continuously. Continue stirring for 30 minutes to ensure complete hydrolysis and condensation of TEOS. The sol-gel solution was then poured into a clean glass container and was tightly sealed. The sol gel solution was aged at room temperature for 24 hours. After 24 hours, the sol-gel was heated at 60^{o}C for 2 hours to remove the solvent and form silicone nanoparticles. The solution was then centrifuged at 10,000rpm for 10 minutes to collect nanoparticles. The nanoparticles were then washed with ethanol three times to remove any impurities. The nanoparticles were then dried in vacuum oven at 60^{o}C.

3.3 Characterization of synthesized nanoparticles

3.3.1 FTIR analysis

To assess the chemical structure of the synthesized nanoparticles FTIR analysis was conducted. The sample was then subjected to a spectral resolution within the 400–

4000 cm2 wavenumber range. The Fourier transform infrared (FTIR) spectroscopy approach may be used to detect alterations throughout the whole composition of microorganisms by detecting changes in functional groups in biomolecules. Essentially, it measures the vibration and rotation of molecules that are impacted by infrared light at a specific wavelength. An interferometer is a device that gathers infrared radiation emitted by infrared sources. It consists of a beam splitter, a fixed mirror, and a moving mirror. Accuracy is increased by the interference patterns that the interferometer uses to determine the wavelength of light emitted. An infrared spectrum is created by measuring the amount of radiation that enters a sample at a specific wavenumber after it has been exposed to infrared radiation. The quantity of scans might vary based on the quality requirements for the sample analysis. It is feasible to identify the infrared radiation of chemical groups at a given wavenumber. The spectrum's x-axis indicates wavenumber, while the y-axis displays transmittance or absorbance. Reliable databases and literature were used to compare the detected spectrum peaks.

3.3.2 XRD analysis

An X-ray diffractometer was used to measure the nano-coated drug's X-ray diffraction patterns. The specimens are scanned at 0.4°/min throughout a diffraction angle range of $2\theta = 10°–80°$ while the specimens are at room temperature.

3.4 Membrane fabrication

The membranes were synthesized using a variety of solutions with different levels of nanoparticles 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. Nanoparticles, PVP and PES 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 homogenized. The mixture was then left overnight to release the trapped air bubbles.

Table 3.1 Chemical composition of fabricated membranes along with the codes

Membrane code	PES%	PVP%	SiO_2 nanoparticles %
M1	18	3	1
M2	18	3	2
M3	18	3	3

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 11 Membrane fabrication procedure

3.5 Characterization of fabricated membrane

3.5.1 SEM analysis

The cross-sectional morphology of the fabricated PES membranes was 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.

3.5.2 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 $1cm^2$. The samples were then subjected to a spectral resolution of 2 cm2 within the 400-4000 cm^2 wavenumber range. Reliable databases and literature were used to compare the detected spectrum peaks.

3.5.3 Contact angle analysis

To determine the wettability and hydrophilicity of membranes contact angles were measured. Kruss 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.

3.5.4 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.

3.5.5 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. 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.

$$\varepsilon = \frac{\boldsymbol{Ww-Wd}}{A\times\rho\times\delta} \times 100 \qquad (3.1)$$

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

3.5.6 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.

$$Water\ retention = \frac{\boldsymbol{Ww-Wd}}{Ww} \times 100 \qquad (3.2)$$

3.6 Membrane performance

3.6.1 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 pressurized 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:

$$J = \frac{V}{AT} \quad (3.3)$$

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 $L.m^{-2}h^{-1}$.

3.6.2 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.

$$\text{BSA rejection \%} = \frac{1-Cf}{C_i} \times 100 \quad (3.4)$$

$$FRR\% = \frac{J2}{J1} \times 100 \quad (3.5)$$

Whereas Cf is the concentration of BSA in filtrate while Ci is the concentration of BSA in the feed solution.

3.6.3 Urea clearance %

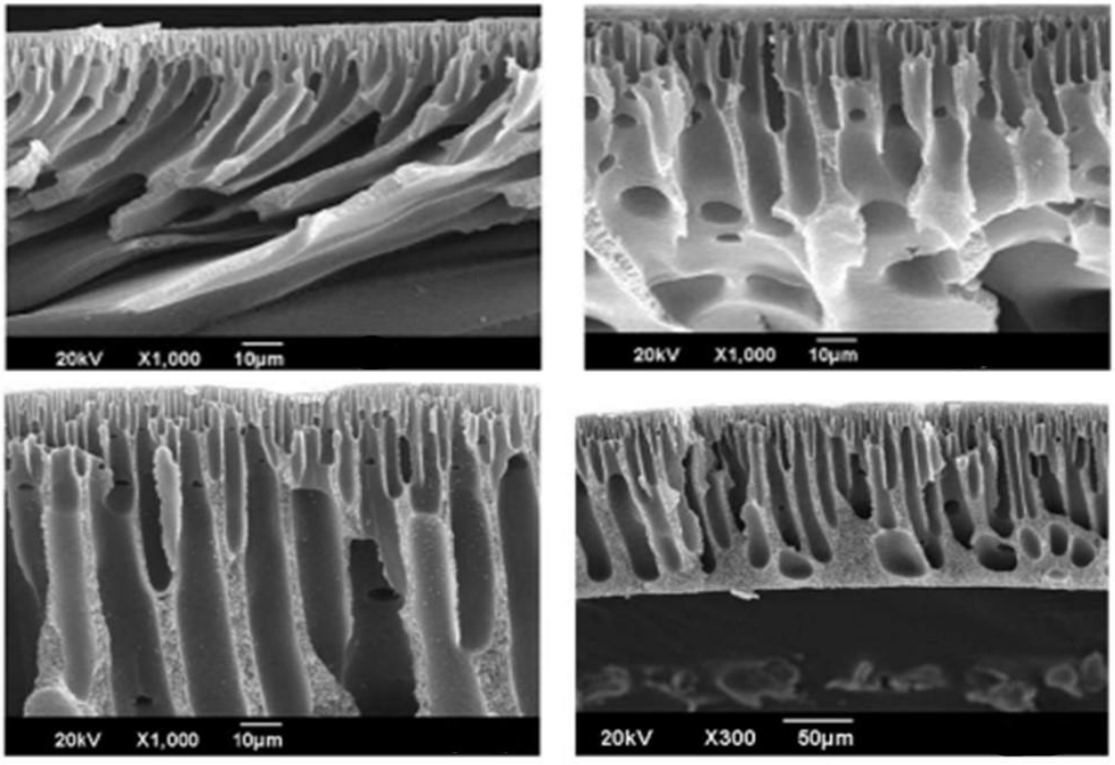
The urea clearance has been found of value in assisting the appraisal of the extent of renal damage, and the course of progress either towards recovery or fatal renal failure. renal damage or disease, when proper allowance is made for the effect of extra-renal influences. Urea clearance is the essential parameter for commercial dialysis membrane. Here, urea concentration was measured using diffusion setup and concentrations were recorded using UV-vis spectroscopy. Membrane M3 was selected for urea clearance performance testing based on its ideal attributes, which

include outstanding hydrophilicity, and best flux. Central composite design (CCD) in Response surface modelling was employed to identify and analyse the ideal combination of properties of the synthesized membrane M3 for urea clearance. For evaluation of the impact of the input factors on the urea clearance was created using the Design Expert software. CCD provided 10 permutations. Pressure and concentration were identified as two main factors influencing the membrane's performance.

CHAPTER 4: RESULTS

4.1 Scanning Electron Microscopy (SEM)

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.



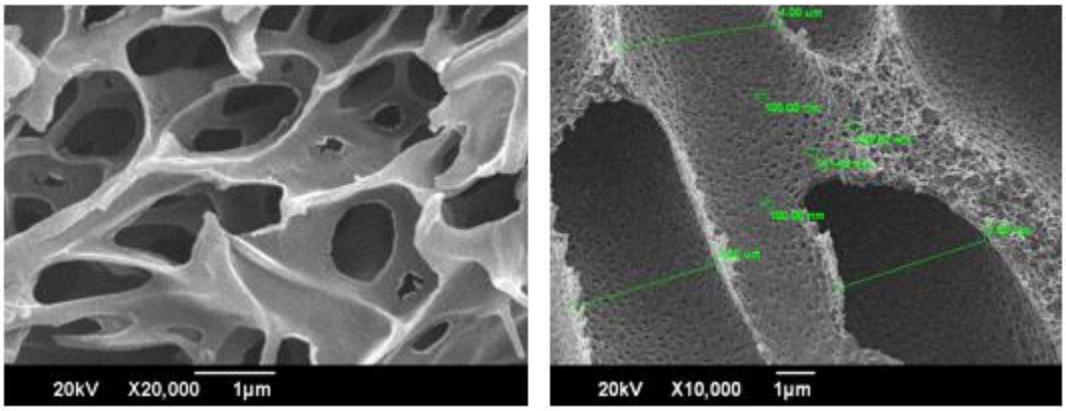


Figure 12 SEM cross-sectional images of fabricated membranes

4.2 XRD nanoparticles

The prepared silica nanoparticles were studied by x-ray diffraction (XRD) measurement and shown in figure.4.2. The XRD pattern shows a typical broad peak which is corresponding to the amorphous phase of prepared silica nanoparticles. This broad XRD reflection peak may be due to the small size and incomplete inner structure of the prepared particles. This demonstrates that a high percentage of these particles are amorphous. No other impurity peak is present which represents the purity of the silica nanoparticles.

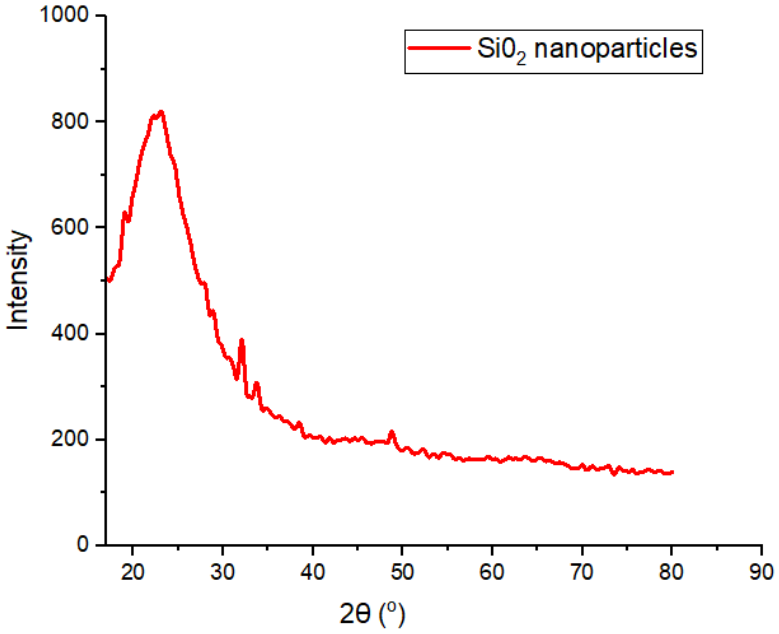


Figure 13 XRD pattern of SiO_2 nanoparticles

4.3 FTIR analysis

4.3.1 FTIR analysis of SiO_2 nanoparticles

SiO_2 nanoparticles peaks are shown at 1000-1200 cm^{-1} (Si-O-Si), 800-950 cm^{-1} (Si-O-H) and 2250-2300 cm^{-1} (Si-H) all of the peaks are for stretching and also the bending vibration of Si-OH at 1630 cm^{-1} (Yusuf, 2023).

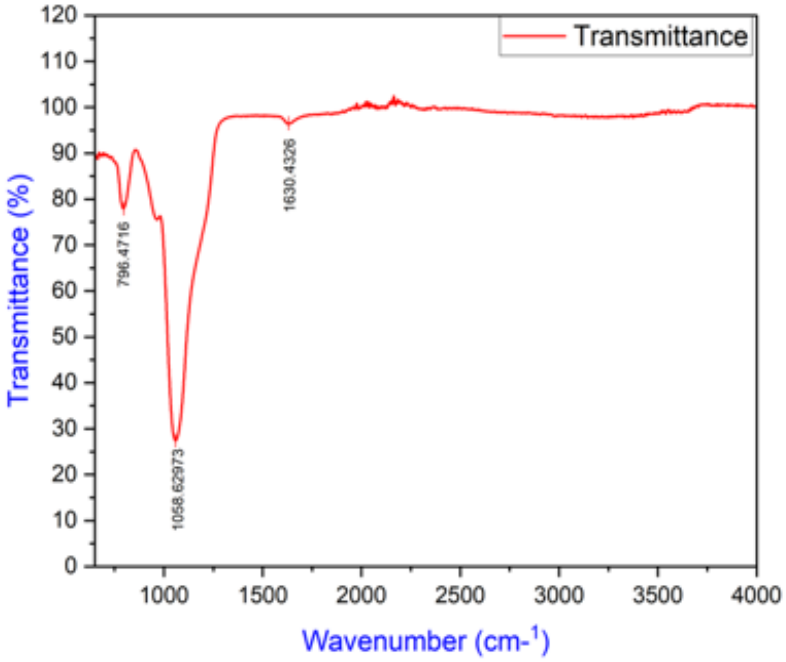


Figure 14 FTIR analysis of SiO2 nanoparticles

4.3.2 FTIR analysis of fabricated membranes

Spectroscopic analysis of hydrophilic blended PES membranes is presented in Figure 4.3. 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 (Sun et al., 2010). CH3 peak at 2820-2920 cm^{-1} is also shown. The appearance of a peak at 1510cm-1 points to the aromatic bond of the benzene ring in PES. The samples 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). Due to presence of SiO_2 nanoparticles peaks are shown at 1000-1200 cm^{-1} (Si-O-Si), 850-950

cm^{-1} (Si-O-H) and 2250-2300 cm^{-1} (Si-H) all of the peaks are for stretching (Yusuf, 2023). Membrane samples had similar compositions with only difference in concentration of SiO_2 nanoparticles, therefore, all the samples showed comparable results. There is a discernible difference in the spectra of all samples since PES is the major polymer with higher concentration with PVP and SiO_2 as additives having low concentration.

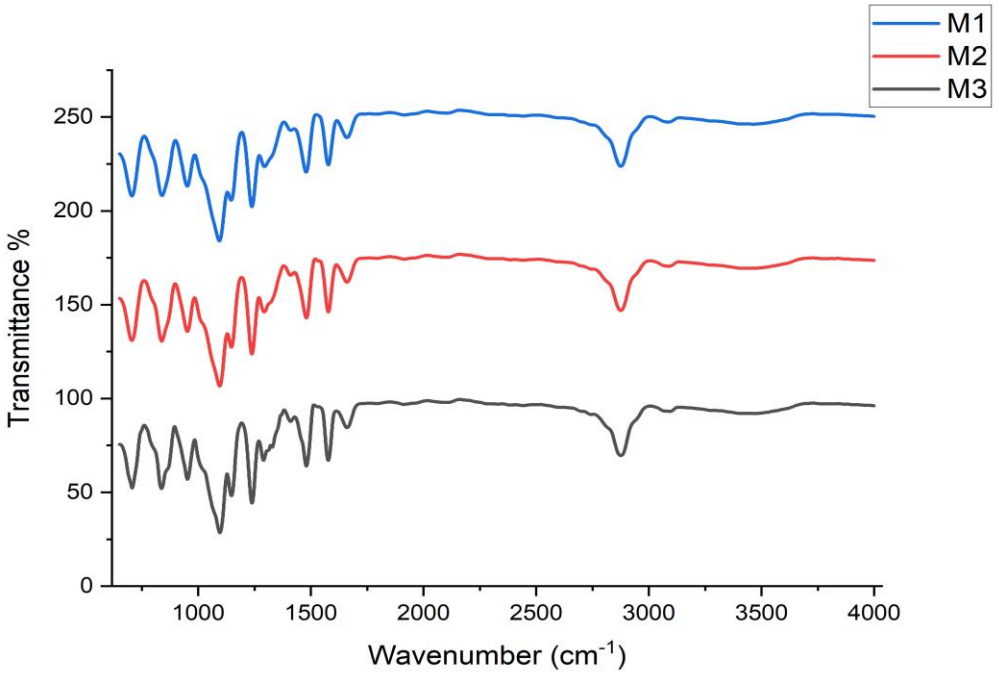


Figure 15 FTIR analysis of fabricated membranes

4.4 Contact angle analysis

Given that polyethersulfone is naturally hydrophobic, have low surface wettability properties. Blending hydrophilic compounds can effectively increase the hydrophilicity. The results show that the addition of SiO_2 nanoparticles significantly improves the wettability of the membranes.

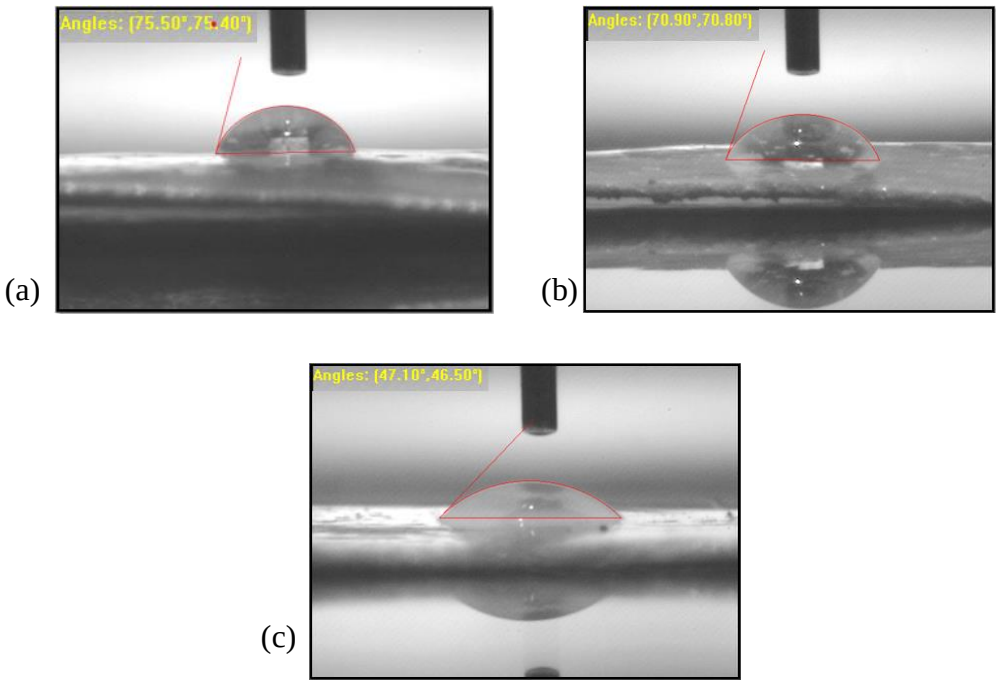


Figure 16 Contact angle analysis of hydrophilic enhanced membranes

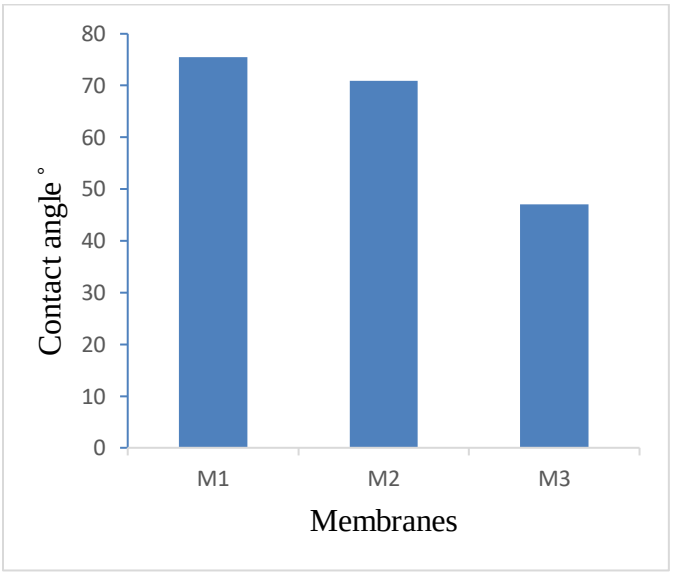


Figure 17 Graphical presentation of the contact angles of the membranes.

As can be seen in figures 4.4 (a) and (b), membrane M1, which has a 1% SiO_2 nanoparticles concentration, has a contact angle of 75°; however, when the concentration in M2 is increased to 2%, this angle decreases to 70°. Comparably, membranes M3 exhibit significant decreases in contact angle with increasing nanoparticles concentration;

they drop from 75° at 1% SiO_2 nanoparticles to 47° at 3%. It was observed that hydrophilicity of membranes increased with the increase in nanoparticles concentration. 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 haemodialysis because they can improve the membrane's blood compatibility and ability to eliminate toxins from the blood (Mokarizadeh et al., 2021).

4.5 Water retention

The ability of the membranes to retain water was assessed, as seen in figure 4.7. Capacity of membrane M1 was only 48.8% but increased to 55.02% when SiO2 nanoparticles content in M2 was increased to 2%. The water retention capacity of membranes M3 measures increased to 63.1% when the SiO2 nanoparticles concentration was raised from 3%. 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.

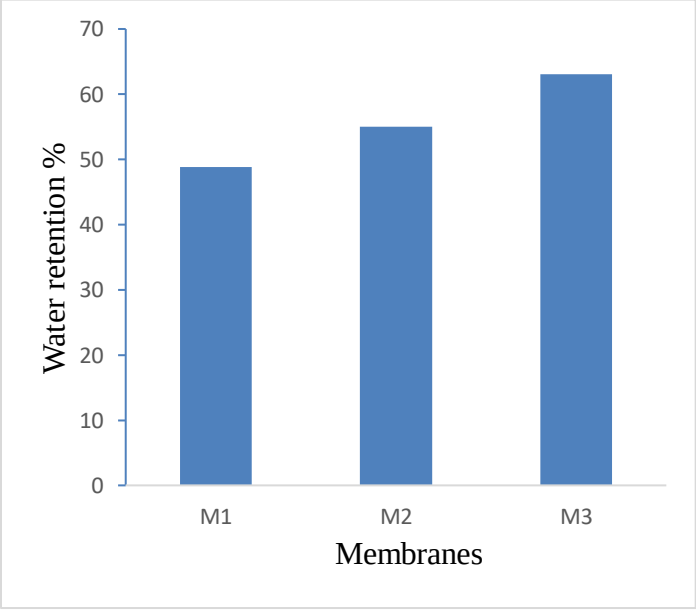


Figure 18 Graphical presentation of water uptake capacity of the fabricated membranes

4.6 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 4.8 presents compelling evidence of a direct relationship between the concentration of concentration of nanoparticles concentration and the resultant porosity %. With 3% additions, membrane M3 had the greatest porosity percentage (56.9%) out of all the membranes evaluated. With 2% SiO_2, M2 exhibits a notable porosity of 49.3%. The porosity of membrane M1 is 41%. 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.

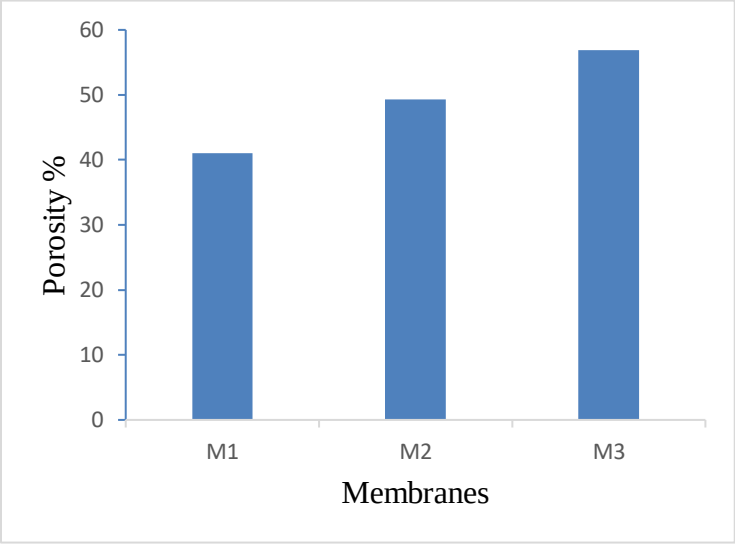


Figure 19 Porosity percentage of the various membranes.

4.7 Tensile strength

When 1% SiO_2 nanoparticles are 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 nanoparticles content, suggesting that increased concentration of SiO_2 nanoparticles has a negative effect on the tensile strength of membranes. It demonstrates that a higher number of nanoparticles 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 3% SiO_2 nanoparticles 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. During the phase inversion, PVP, which is soluble in water, diffuses out and encourages the formation of macro voids. The presence of numerous voids in the membrane structure frequently leads to a reduction in tensile strength. This implies that complex interactions among PVP, SiO_2 nanoparticles and the PES in matrix affect the tensile characteristics. Higher SiO_2 nanoparticles concentration 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).

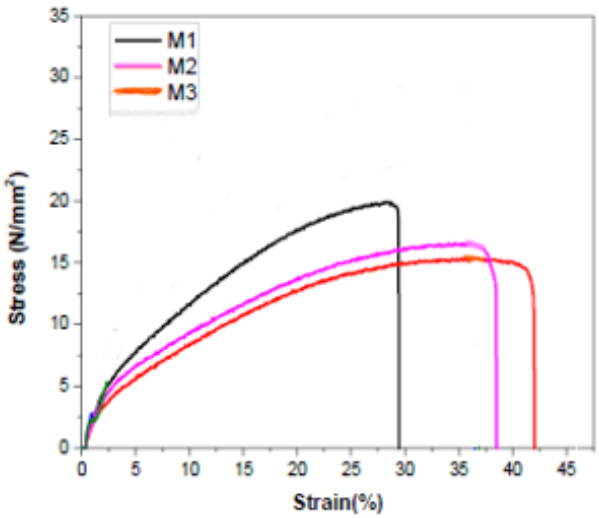


Figure 20: Stress-Strain curve of the membrane

4.8 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 4.10 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 66 L/m²/h was recorded which is improved to 75.25 L/m²/h in M2 when the SiO_2 nanoparticles concentration in the membrane is increased from 1% to 2% respectively. The flux drastically increased to 94% in M3 when a 3% SiO_2 nanoparticles concentration was used. This indicates that increasing the concentration of SiO_2 drastically increases the fluid permeation rate of membranes. As already observed in porosity and contact angle measurements, membrane M3 outperformed all other membranes. A similar trend is evident in flux measurements that show PVP and SiO_2 nanoparticles complements each other to optimize the fluid flow. A delicate balance in porosity, tensile strength, and hydrophilicity facilitates the membrane M3 to perform well in fluid permeation. In addition to that, it can be inferred that pores are well connected, particularly, in membrane M3 which further aids in enhancing the fluid flow (Tufekci et al., 2019).

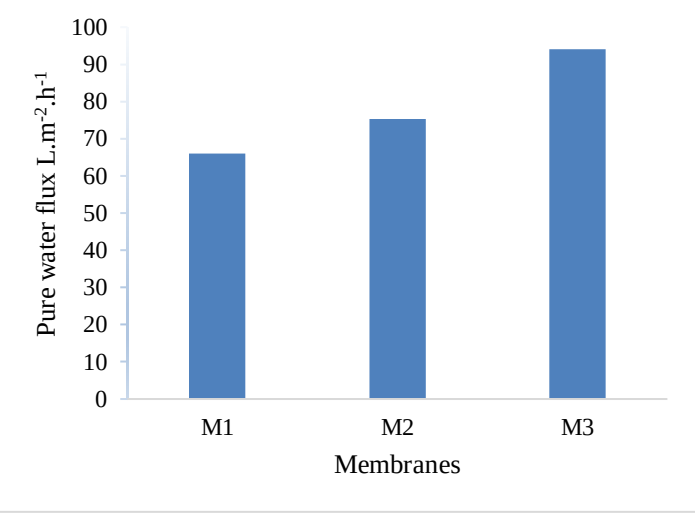


Figure 21 Pure water flux of fabricated membranes

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.

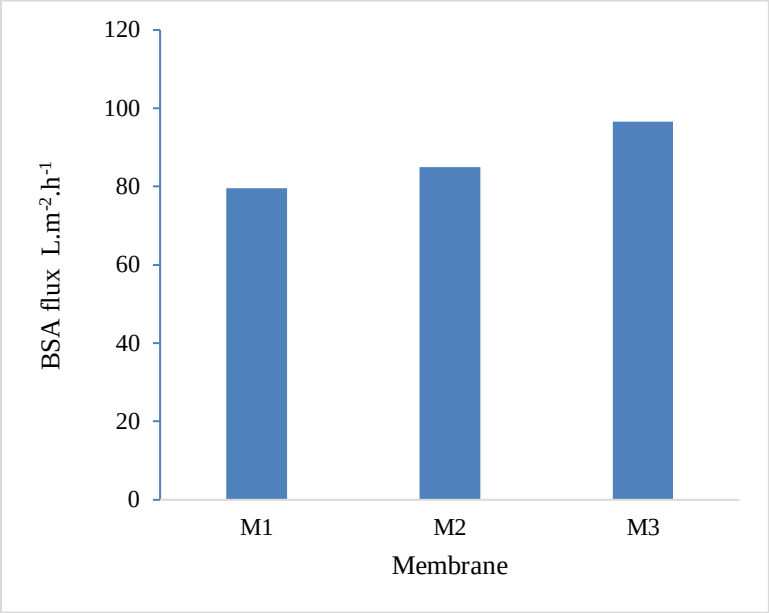


Figure 22 BSA flux of fabricated membrane

Figure 4.11 illustrates how the kind and mix of pore-forming substances used impact the BSA rejection rates for PES-based membranes. PVP has BSA rejection efficiency, as seen in membrane M1 has rejection rate of 79.51% for 1% SiO_2 nanoparticles concentration. However, M2 performs better than M1, because of its greater SiO_2 nanoparticles content, indicating that SiO_2 nanoparticles improves selectivity having flux rate of 85%. M3 has an impressive rejection rate of 96.56%, suggesting that membrane BSA rejection ability is much enhanced by a greater SiO_2 nanoparticles content. 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

Membrane M3 was selected for urea clearance performance testing based on its ideal attributes, which include outstanding hydrophilicity and best flux. Urea clearance has been found of value in assisting the appraisal of the extent of renal damage, and the course of progress either towards recovery or fatal renal failure. renal damage or disease, when proper allowance is made for the effect of extra-renal influences. 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).

Table 4.1 Variables and different responses of urea clearance

	Factor 1	**Factor 2**	**Response**
Run	**Concentration**	**Pressure**	**Urea clearance**
	mg/L	**bar**	**%**
1	730	0.4	71.8
2	800	0.2	74.6
3	800	0.6	75.4
4	1000	0.117	73.2
5	1000	0.2	74.3
6	1000	0. 4	75
7	1000	0. 68	75.6
8	1200	0.4	74.1
9	1200	0.6	76.5
10	1280.84	0.4	72.5

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 M3 outperformed all other membranes. The membrane M3 was the best option for real-world application due to its exceptional porosity, enhanced hydrophilicity, and higher flux. Therefore, only membrane M3 was selected for further assessment of urea clearance. 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 76.5% of urea clearance, as seen in table above.

CHAPTER 5: DISCUSSION

Renal disorders, commonly known as kidney diseases, have a profound impact on global public health, affecting millions of individuals. The kidneys play a crucial role in maintaining the body's internal equilibrium by filtering excess fluids, toxins, and waste products from the bloodstream, and by regulating blood pressure and electrolyte levels (Yang et al., 2020). However, conditions such as hypertension, genetic predisposition, diabetes, and infections can impair kidney function (Lv et al., 2019). Among the various kidney diseases, chronic kidney disease (CKD) is the most prevalent, characterized by a gradual decline in renal function. A recent survey estimates that 800 million people globally are affected by CKD. Those with pre-existing conditions like hypertension, cardiovascular diseases, and diabetes, as well as individuals in low-income regions with limited healthcare access, are particularly vulnerable (Raharjo et al., 2022). CKD often progresses to end-stage renal disease (ESRD), a severe condition where kidney function deteriorates to the point where renal replacement therapy becomes necessary, imposing significant financial, physical, and mental burdens on patients (Gupta et al., 2021). According to the World Health Organization (WHO), renal disorders are a leading cause of mortality and morbidity worldwide. The increase in renal diseases is attributed to factors like diabetes, hypertension, obesity, aging, and exposure to environmental toxins and infections. The asymptomatic nature of early-stage kidney disease complicates timely diagnosis and treatment, often leading to advanced stages before detection (Yang et al., 2020). Consequently, kidney disease not only impacts medical health but also affects patients' overall quality of life, encompassing financial and social challenges.

The X-Ray Diffraction (XRD) analysis of the synthesized silica nanoparticles, illustrated in results above, reveals a characteristic broad peak, indicative of the amorphous nature of the particles. The broadness of this XRD reflection peak is attributed to the high proportion of amorphous content. The absence of any additional impurity peaks in the XRD pattern underscores the purity of the synthesized silica nanoparticles. This finding aligns with the expectation that the synthetic method employed successfully produced silica nanoparticles with minimal contamination

(Cordoba et al., 2024). The amorphous phase is crucial for various applications, including drug delivery and catalysis, where the surface properties and reactivity of the nanoparticles play a significant role.

The cross-sectional microstructure of the membranes was examined using Scanning Electron Microscopy (SEM), as depicted in results. The SEM images revealed that each membrane sample exhibited a distinct bilayer structure characterized by a compact top layer and a macro-void architecture in the lower segment. This structural configuration demonstrates the precise and effective distribution of polymeric components within the membrane. During the casting process, when the solution is initially immersed in deionized (DI) water, the top layer undergoes rapid solidification, resulting in a densely packed surface. Subsequently, as the diffusion rates diminish over time, the lower layer forms finger-like structures. These observations confirm the homogeneous integration of the polymeric materials, ensuring the structural integrity and performance of the membranes.

Fourier Transform Infrared Spectroscopy (FTIR) analysis of the hydrophilic blended PES membranes is shown in results. The FTIR spectra for all membrane samples exhibit a characteristic peak at 1350 cm^{-1}, corresponding to the sulfone functional group (O=S=O) of PES (Sun et al., 2010). Additionally, the CH3 peaks are observed in the range of 2820-2920 cm^{-1}. The peak at 1510 cm^{-1} indicates the presence of the aromatic bond in the benzene ring of PES. The samples also contain PVP, which is identified by the C=O stretching bond of the amide band of the pyrrolidone ring at 1610 cm^{-1} (Mireles et al., 2020). The presence of SiO2 nanoparticles is confirmed by peaks at 1000-1200 cm^{-1} (Si-O-Si), 850-950 cm^{-1} (Si-O-H), and 2250-2300 cm^{-1} (Si-H), all indicative of stretching vibrations (Yusuf, 2023). Since all membrane samples have similar compositions with varying concentrations of SiO_2 nanoparticles, the spectra display comparable results. However, a discernible difference in the spectra is evident due to the dominant presence of PES as the major polymer, with PVP and SiO_2 as additives in lower concentrations.

Contact angle analysis of Polyethersulfone (PES) membranes, inherently hydrophobic, exhibit low surface wettability. The addition of hydrophilic SiO_2 nanoparticles significantly enhances the hydrophilicity. As shown in the results the contact angle of membrane M1 (with 1% SiO_2) is 75°, which decreases to 70° in membrane M2 (with 2% SiO_2). Further increasing the SiO_2 concentration to 3% in membrane M3 results in a substantial reduction in the contact angle to 47°, indicating improved wettability. 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 haemodialysis because they can improve the membrane's blood compatibility and ability to eliminate toxins from the blood (Mokarizadeh et al., 2021).

The water retention capacity of the membranes is depicted in the results above. Membrane M1, with 1% SiO_2, shows a retention capacity of 48.8%, which increases to 55.02% in membrane M2 (2% SiO_2). Membrane M3, with 3% SiO_2, demonstrates the highest water retention capacity at 63.1%, highlighting the role of SiO_2 in enhancing water absorption. 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).

Membrane M1, with 1% SiO_2, has a porosity of 41%. This increases to 49.3% for membrane M2 (2% SiO_2) and reaches the highest value of 56.9% for membrane M3 (3% SiO_2). The direct relationship between SiO_2 concentration and porosity indicates improved structural features essential for ultrafiltration performance. 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.

The tensile strength and elastic modulus are affected by the SiO_2 content. Membrane M1 (1% SiO_2) shows an elastic modulus of 2.15 MPa and an ultimate tensile strength of 19.92 MPa. These values decrease in membrane M2 (2% SiO_2), indicating that higher SiO_2 concentrations negatively impact tensile strength due to the formation of macro voids and a highly porous structure. 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. Higher SiO_2 nanoparticles concentration 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).

Membrane M1 (1% SiO_2) has a moderate flux of 66 L/m²/h, which increases to 75.25 L/m²/h in membrane M2 (2% SiO_2). Membrane M3 (3% SiO_2) exhibits the highest flux rate at 94 L/m²/h, indicating enhanced performance for fluid flow and toxin clearance in hemodialysis (Tufekci et al., 2019).

Membrane M1 (1% SiO_2) has a BSA rejection rate of 79.51%, which increases to 85% in membrane M2 (2% SiO_2). Membrane M3 (3% SiO_2) shows an impressive BSA rejection rate of 96.56%, suggesting that higher SiO_2 content significantly improves membrane selectivity and efficiency in removing high-molecular-weight toxins. The results suggests that the higher amount of hydrophilic additives enhances BSA rejection (Guo et al., 2024).

Based on its superior properties, membrane M3 was selected for urea clearance testing. At an optimal concentration of 1200 mg/L and operating pressure of 0.6 MPa, membrane M3 achieved a urea clearance rate of 76.5%, as shown in results. This performance indicates its potential for real-world applications in renal therapy.

SUMMARY

Summary of various tests of the fabricated ultrafiltration hemodialysis membrane

TESTS	Unit	M1	M2	M3
Contact angle	θ	75.50	70.56	47.10
Porosity	%	41	49.3	56.9
Water retention	%	48.8	55.02	63.1
Pure water flux	$L/m^2/h$	66	75.25	94
BSA rejection	%	79.52	85	96.56
Urea clearance	%	-	-	76.50

CHAPTER 6: 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 PVP and SiO_2 nanoparticles were inspected for their 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 SiO_2 nanoparticles 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 SiO_2 nanoparticles up to 3% can decrease the contact angle as low as 46˚ respectively. Moreover, the porosity percentage can be enhanced up to 56.9% for SiO_2 nanoparticles at 3%. Water retention capacity shows a similar trend of increment with an increase in hydrophilic additive. The contact angle drops to 46˚, porosity upsurges to 56.9%, and water retention capacity increases to 63.1% when 3% of both SiO_2 nanoparticles are added to the membrane simultaneously. The results for tensile testing indicate that higher content of SiO_2 nanoparticles 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 M3, which contains higher SiO_2 nanoparticles concentration had the highest pure water flux values (94 L/m2/h), suggesting that it had the highest flow efficiency out of all the membranes. BSA rejection rates of 96.56% were achieved in M3, indicating the strongest antifouling capabilities measured by flux recovery and BSA rejection. The urea clearance results showed good efficacy (76.5% clearance), particularly at 1200 mg/L concentration

and 0.6 MPa pressure. In summary, using high concentration of SiO_2 nanoparticles during membrane production significantly improves hemodialysis membrane performance. Extend research to explore the potential of optimized membranes beyond hemodialysis, such as drug delivery system and tissue engineering scaffolds, considering their biocompatibility and functional properties. Testing these membranes with real-life blood samples is imperative to bridge the gap between laboratory research and clinical application, ensuring their efficacy and safety in real-world scenarios.

REFERENCES

1. ABE, M., MASAKANE, I., WADA, A., NAKAI, S., NITTA, K. & NAKAMOTO, H. J. F. I. M. 2021. Dialyzer classification and mortality in hemodialysis patients: a 3-year nationwide cohort study. 8**,** 740461.

2. AL AANI, S., MUSTAFA, T. N. & HILAL, N. J. J. O. W. P. E. 2020. Ultrafiltration membranes for wastewater and water process engineering: A comprehensive statistical review over the past decade. 35**,** 101241.

3. AL MALEK, S., SEMAN, M. A., JOHNSON, D. & HILAL, N. J. D. 2012. Formation and characterization of polyethersulfone membranes using different concentrations of polyvinylpyrrolidone. 288**,** 31-39.

4. ALAYANDE, A. B., OBAID, M., YU, H.-W. & KIM, I. S. J. C. 2019. High-flux ultrafiltration membrane with open porous hydrophilic structure using dual pore formers. 227**,** 662-669.

5. ANIS, S. F., HASHAIKEH, R. & HILAL, N. J. J. O. W. P. E. 2019. Microfiltration membrane processes: A review of research trends over the past decade. 32**,** 100941.

6. AREA, D. R. J. I. J. O. N. 2020. Setting up of Hemodialysis Unit. 30**,** 1.

7. ASIF KHAN, R. M., AHMAD, N. M., NASIR, H., MAHMOOD, A., IQBAL, M. & JANJUA, H. A. J. P. 2023. Antifouling and Water Flux Enhancement in Polyethersulfone Ultrafiltration Membranes by Incorporating Water-Soluble Cationic Polymer of Poly [2-(Dimethyl amino) ethyl Methacrylate]. 15**,** 2868.

8. AZHAR, O., JAHAN, Z., SHER, F., NIAZI, M. B. K., KAKAR, S. J., SHAHID, M. J. M. S. & C, E. 2021. Cellulose acetate-polyvinyl alcohol blend hemodialysis membranes integrated with dialysis performance and high biocompatibility. 126**,** 112127.

9. BANERJEE, I., PANGULE, R. C. & KANE, R. S. J. A. M. 2011. Antifouling coatings: recent developments in the design of surfaces that prevent fouling by proteins, bacteria, and marine organisms. 23**,** 690-718.

10. BILAD, M. R., VANDAMME, D., FOUBERT, I., MUYLAERT, K. & VANKELECOM, I. F. J. B. T. 2012. Harvesting microalgal biomass using submerged microfiltration membranes. 111**,** 343-352.

11. CLARK, W. R., DEHGHANI, N. L., NARSIMHAN, V. & RONCO, C. J. B. P. 2019. Uremic toxins and their relation to dialysis efficacy. 48**,** 299-314.

12. CLAUDEL, S. E., MILES, L. A. & MUREA, M. Anticoagulation in hemodialysis: a narrative review. Seminars in Dialysis, 2021. Wiley Online Library, 103-115.

13. CORDOBA, A., CAUICH-RODRÍGUEZ, J. V., VARGAS-CORONADO, R. F., VELÁZQUEZ-CASTILLO, R. & ESQUIVEL, K. J. P. 2024. A Novel In Situ Sol-Gel Synthesis Method for PDMS Composites Reinforced with Silica Nanoparticles. 16**,** 1125.

14. DONG, X., LU, D., HARRIS, T. A. & ESCOBAR, I. C. J. M. 2021. Polymers and solvents used in membrane fabrication: a review focusing on sustainable membrane development. 11**,** 309.

15. DURMAZ, E. N. & ÇULFAZ-EMECEN, P. Z. J. C. E. S. 2018. Cellulose-based membranes via phase inversion using [EMIM] OAc-DMSO mixtures as solvent. 178**,** 93-103.

16. ELELE, E., SHEN, Y., TANG, J., LEI, Q., KHUSID, B., TKACIK, G. & CARBRELLO, C. J. J. O. M. S. 2019. Mechanical properties of polymeric microfiltration membranes. 591**,** 117351.

17. FAHRINA, A., YUSUF, M., MUCHTAR, S., FITRIANI, F., MULYATI, S., APRILIA, S., ROSNELLY, C. M., BILAD, M. R., ISMAIL, A. F. & TAKAGI, R. J. J. O. T. T. I. O. C. E. 2021. Development of anti-microbial polyvinylidene fluoride (PVDF) membrane using bio-based ginger extract-silica nanoparticles (GE-SiNPs) for bovine serum albumin (BSA) filtration. 125**,** 323-331.

18. GUO, D., YIN, Z., ZHANG, M., HADI, M. K., SUN, Z., YAO, T. & RAN, F. J. N. J. O. C. 2024. A high flux ultrafiltration membrane with a multi-hydrophilic particle additive and controlled self-assembly of micellar particles. 48**,** 8386-8401.

19. GUPTA, R., WOO, K. & JENIANN, A. Y. Epidemiology of end-stage kidney disease. Seminars in vascular surgery, 2021. Elsevier, 71-78.

20. HAILEMARIAM, R. H., WOO, Y. C., DAMTIE, M. M., KIM, B. C., PARK, K.-D., CHOI, J.-S. J. A. I. C. & SCIENCE, I. 2020. Reverse osmosis membrane fabrication and modification technologies and future trends: A review. 276**,** 102100.

21. HALL, J. E. & HALL, M. E. 2020. *Guyton and Hall Textbook of Medical Physiology E-Book: Guyton and Hall Textbook of Medical Physiology E-Book*, Elsevier Health Sciences.

22. HEIDARI, A., ABDOLLAHI, E., MOHAMMADI, T., ASADI, A. A. J. S. & TECHNOLOGY, P. 2021. Improving permeability, hydrophilicity and antifouling characteristic of PES hollow fiber UF membrane using carboxylic PES: A promising substrate to fabricate NF layer. 270**,** 118811.

23. HOŁDA, A. K. & VANKELECOM, I. F. J. J. O. A. P. S. 2015. Understanding and guiding the phase inversion process for synthesis of solvent resistant nanofiltration membranes. 132.

24. HOWE, K. J., CLARK, M. M. J. E. S. & TECHNOLOGY 2002. Fouling of microfiltration and ultrafiltration membranes by natural waters. 36**,** 3571-3576.

25. IRFAN, M., IDRIS, A. J. M. S. & C, E. 2015. Overview of PES biocompatible/hemodialysis membranes: PES–blood interactions and modification techniques. 56**,** 574-592.

26. IRFAN, M., IRFAN, M., SHAH, S. M., BAIG, N., SALEH, T. A., AHMED, M., NAZ, G., AKHTAR, N., MUHAMMAD, N., IDRIS, A. J. M. S. & C, E. 2019. Hemodialysis performance and anticoagulant activities of PVP-k25 and carboxylic-multiwall nanotube composite blended Polyethersulfone membrane. 103**,** 109769.

27. KADANYO, S., GUMBI, N. N., MATINDI, C. N., DLAMINI, D. S., HU, Y., CUI, Z., WANG, H., HU, M., LI, J. J. S. & TECHNOLOGY, P. 2022. Enhancing compatibility and hydrophilicity of polysulfone/poly (ethylene-co-vinyl alcohol) copolymer blend ultrafiltration membranes using polyethylene glycol as hydrophilic additive and compatibilizer. 287**,** 120523.

28. KHAN, B., HAIDER, S., KHURRAM, R., WANG, Z. & WANG, X. J. M. 2020. Preparation of an ultrafiltration (UF) membrane with narrow and uniform pore size distribution via etching of SiO2 nano-particles in a membrane matrix. 10**,** 150.

29. KOHLOVÁ, M., AMORIM, C. G., ARAÚJO, A., SANTOS-SILVA, A., SOLICH, P. & MONTENEGRO, M. C. B. J. J. O. A. O. 2019. The biocompatibility and bioactivity of hemodialysis membranes: their impact in end-stage renal disease. 22**,** 14-28.

30. LV, J.-C., ZHANG, L.-X. J. R. F. M. & THERAPIES 2019. Prevalence and disease burden of chronic kidney disease. 3-15.

31. LV, J., ZHANG, G., ZHANG, H., ZHAO, C. & YANG, F. J. A. S. S. 2018. Improvement of antifouling performances for modified PVDF ultrafiltration membrane with hydrophilic cellulose nanocrystal. 440**,** 1091-1100.

32. MA, Y., SHI, F., MA, J., WU, M., ZHANG, J. & GAO, C. J. D. 2011. Effect of PEG additive on the morphology and performance of polysulfone ultrafiltration membranes. 272**,** 51-58.

33. MAGNANI, S. & ATTI, M. J. T. 2021. Uremic toxins and blood purification: a review of current evidence and future perspectives. 13**,** 246.

34. MEHTA, R. L., KELLUM, J. A., SHAH, S. V., MOLITORIS, B. A., RONCO, C., WARNOCK, D. G., LEVIN, A. & CARE, A. K. I. N. J. C. 2007. Acute Kidney

Injury Network: report of an initiative to improve outcomes in acute kidney injury. 11**,** 1-8.

35. MIRELES, L. K., WU, M.-R., SAADEH, N., YAHIA, L. H. & SACHER, E. J. A. O. 2020. Physicochemical characterization of polyvinyl pyrrolidone: A tale of two polyvinyl pyrrolidones. 5**,** 30461-30467.

36. MOHAMMAD, A. W., TEOW, Y., ANG, W., CHUNG, Y., OATLEY-RADCLIFFE, D. & HILAL, N. J. D. 2015. Nanofiltration membranes review: Recent advances and future prospects. 356**,** 226-254.

37. MOKARIZADEH, H., RAISI, A. J. E. T. & INNOVATION 2021. Industrial wastewater treatment using PES UF membranes containing hydrophilic additives: Experimental and modeling of fouling mechanism. 23**,** 101701.

38. MOLLAHOSSEINI, A., ABDELRASOUL, A., SHOKER, A. J. M. C. & PHYSICS 2020. A critical review of recent advances in hemodialysis membranes hemocompatibility and guidelines for future development. 248**,** 122911.

39. NALEZINKOVÁ, M. J. T. R. 2020. In vitro hemocompatibility testing of medical devices. 195**,** 146-150.

40. OATLEY-RADCLIFFE, D. L., WALTERS, M., AINSCOUGH, T. J., WILLIAMS, P. M., MOHAMMAD, A. W. & HILAL, N. J. J. O. W. P. E. 2017. Nanofiltration membranes and processes: A review of research trends over the past decade. 19**,** 164-171.

41. OTITOJU, T. A., AHMAD, A. L. & OOI, B. S. J. R. A. 2018. Recent advances in hydrophilic modification and performance of polyethersulfone (PES) membrane via additive blending. 8**,** 22710-22728.

42. PSTRAS, L., RONCO, C. & TATTERSALL, J. Basic physics of hemodiafiltration. Seminars in Dialysis, 2022. Wiley Online Library, 390-404.

43. RAHARJO, Y., ZAINOL ABIDIN, M. N., ISMAIL, A. F., FAHMI, M. Z., SAIFUL, ELMA, M., SANTOSO, D., HAULA', H. & HABIBI, A. R. J. M. 2022. Dialysis membranes for acute kidney injury. 12**,** 325.

44. RONCO, C. & CLARK, W. R. J. N. R. N. 2018. Haemodialysis membranes. 14**,** 394-410.

45. ROSNER, M. H., REIS, T., HUSAIN-SYED, F., VANHOLDER, R., HUTCHISON, C., STENVINKEL, P., BLANKESTIJN, P. J., COZZOLINO, M., JUILLARD, L. & KASHANI, K. J. C. J. O. T. A. S. O. N. 2021. Classification of uremic toxins and their role in kidney failure. 16**,** 1918-1928.

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

47. SHI, X., TAL, G., HANKINS, N. P. & GITIS, V. J. J. O. W. P. E. 2014. Fouling and cleaning of ultrafiltration membranes: A review. 1**,** 121-138.

48. SONG, X., JI, H., ZHAO, W., SUN, S. & ZHAO, C. J. A. M. 2021. Hemocompatibility enhancement of polyethersulfone membranes: Strategies and challenges. 1**,** 100013.

49. SPECIFICATIONS, H. M. J. I. J. O. N. 2020. Selection and Use of Machine, Dialyzer and Dialysis Fluid for Maintenance Hemodialysis. 30**,** 1.

50. SUN, M., SU, Y., MU, C., JIANG, Z. J. I. & RESEARCH, E. C. 2010. Improved antifouling property of PES ultrafiltration membranes using additive of silica− PVP nanocomposite. 49**,** 790-796.

51. SUN, W., LIU, J., CHU, H. & DONG, B. J. M. 2013. Pretreatment and membrane hydrophilic modification to reduce membrane fouling. 3**,** 226-241.

52. TUFEKCI, M., GUNES-DURAK, S., ORMANCI-ACAR, T. & TUFEKCI, N. J. J. O. A. P. S. 2019. Effects of geometry and PVP addition on mechanical behavior of PEI membranes for use in wastewater treatment. 136**,** 47073.

53. WANG, A. Y., NINOMIYA, T., AL-KAHWA, A., PERKOVIC, V., GALLAGHER, M. P., HAWLEY, C. & JARDINE, M. J. J. A. J. O. K. D. 2014. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. 63**,** 968-978.

54. WANG, C., LIN, B., QIU, Y. J. C. & BIOINTERFACES, S. B. 2022. Enhanced hydrophilicity and anticoagulation of polysulfone materials modified via dihydroxypropyl, sulfonic groups and chitosan. 210**,** 112243.

55. WARSINGER, D. M., CHAKRABORTY, S., TOW, E. W., PLUMLEE, M. H., BELLONA, C., LOUTATIDOU, S., KARIMI, L., MIKELONIS, A. M., ACHILLI, A. & GHASSEMI, A. J. P. I. P. S. 2018. A review of polymeric membranes and processes for potable water reuse. 81**,** 209-237.

56. WEI, Q., FENG, S., ZHANG, Z., LIU, L., WU, L. J. C. & BIOINTERFACES, S. B. 2022. A high-protein retained PES hemodialysis membrane with tannic acid as a multifunctional modifier. 220**,** 112921.

57. WESTPHALEN, H., SAADATI, S., EDUOK, U., ABDELRASOUL, A., SHOKER, A., CHOI, P., DOAN, H. & EIN-MOZAFFARI, F. J. S. R. 2020. Case studies of clinical hemodialysis membranes: Influences of membrane morphology and biocompatibility on uremic blood-membrane interactions and inflammatory biomarkers. 10**,** 14808.

58. YAMAMOTO, K.-I., HIWATARI, M., KOHORI, F., SAKAI, K., FUKUDA, M. & HIYOSHI, T. J. J. O. A. O. 2005. Membrane fouling and dialysate flow pattern in an internal filtration-enhancing dialyzer. 8**,** 198-205.

59. YANG, C.-W., HARRIS, D. C., LUYCKX, V. A., NANGAKU, M., HOU, F. F., GARCIA, G. G., ABU-AISHA, H., NIANG, A., SOLA, L. & BUNNAG, S. J. K. I. S. 2020. Global case studies for chronic kidney disease/end-stage kidney disease care. 10**,** e24-e48.

60. YIN, J. & ZHANG, H.-F. J. P. 2021. A combined physical blending and surface grafting strategy for hydrophilic modification of polyethersulfone membrane toward oil/water separation. 233**,** 124177.

61. YOUNG, T.-H. & CHEN, L.-W. J. D. 1995. Pore formation mechanism of membranes from phase inversion process. 103**,** 233-247.

62. YUSUF, M. O. J. A. S. 2023. Bond characterization in cementitious material binders using Fourier-transform infrared spectroscopy. 13**,** 3353.

63. ZAINOL ABIDIN, M. N., NASEF, M. M. & MATSUURA, T. J. P. 2022. Fouling prevention in polymeric membranes by radiation induced graft copolymerization. 14**,** 197.