Biocompatible Sulfonated Penta-block Copolymeric Membrane for Hemodialysis

By

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Biocompatible Sulfonated Penta-block Copolymeric Membrane for Hemodialysis

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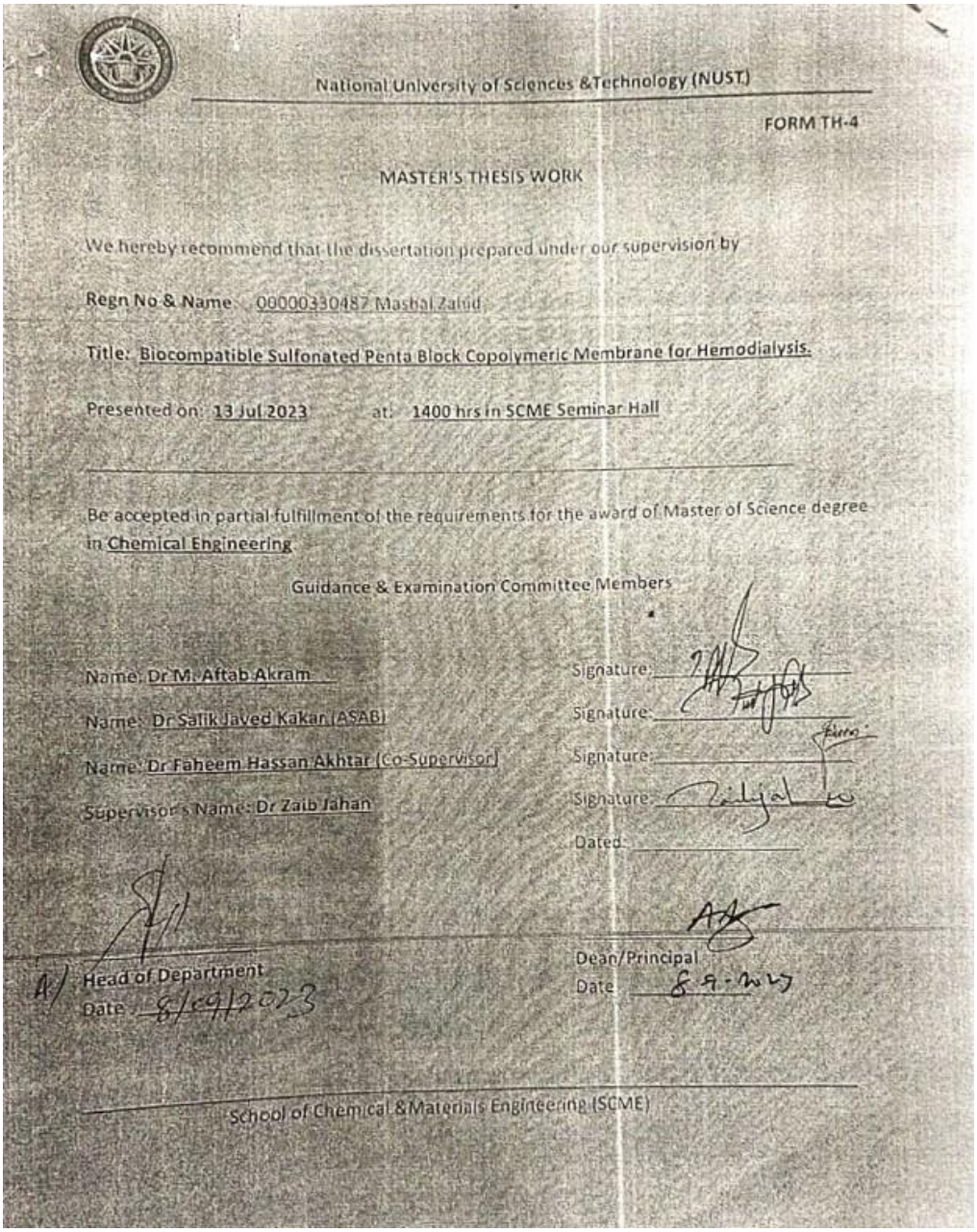

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Dedication

Dedicated to my amazing parents, whose unfailing help and collaboration helped me achieve this outstanding goal.

Acknowledgement

I'm grateful to Allah Almighty for guiding me through this project. Anyone who assisted me with my thesis, whether it was my parents or someone else, did so at Your command, so only You are deserving of praise.

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Abstract

Chronic kidney disease is a potential threat for patient's wellbeing due to high morbidity and imposes a financial burden on the patient. Hemodialysis is the best economical option for end stage renal diseases. The blood is filtered during hemodialysis using a semi-permeable membrane and the diffusion principle. Effective removal of uremic toxins can drastically improve the time required and efficiency of the hemodialysis membrane. Therefore, in this work novel interconnected self-assembled membranes are devised to ensure improved separation, better transport, and mechanical strength. Nexar^{TM} is an amphiphilic Penta block sulfonated copolymer with rigid end blocks that provides mechanical stability to the membrane. Nexar^{TM} can form a long range of self-assembled and ordered nanoscale morphologies that can be altered by the choice of polar or non-polar solvent. The membrane is cast by using a solution casting method that is economical and easy to handle followed by slow evaporation. Polar solvent form ordered hydrophilic structure of width about 20nm that helps in the clearance of urea and creatinine, while nonpolar solvent offers random hydrophobic arrangement. SEM results show that both the membranes are dense so, the filtration is completely diffusion based. The membranes are tested on dead-end filtration cells for flux measurement and then for hemocompatibility via biocompatibility testing. The experiment reveals that in case of polar solvent the creatinine and urea clearance are increased to 97% and 89.2% respectively, while BSA rejection is 79%. The hemolysis ratio is 3.7%, and the plasma recalcification time is 497 s. In the case of non-polar solvent, the creatinine and urea clearance are 67% and 87.5% respectively and for BSA rejection 72.8%. The biocompatibility results of non-polar solvent shows that the hemolysis ratio is 3.84%, while the plasma recalcification time is 477 s. Comparison of the results shows that the polar solvent is more suitable for hemodialysis as its ordered structure and assembly facilitates the clearance process. The membranes can further be improved by the addition of additives that can enhance the rejection of BSA or facilitate the clearance of urea and creatinine.

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List of Abbreviations

BCP	Block co-Polymer
CKD	Chronic Kidney Disease
CRF	Chronic Kidney Failure
DT	Degree Of Thrombus Formation
FTIR	Fourier Transform Infrared Spectroscopy
HR	Hemolysis Ratio
IPA/Tol	Isopropanol Alcohol and Toluene Blend
PBS	Phosphate Buffer Solution
PPP	Plasma Poor Plasma
PRP	Plasma Rich Plasma
PRT	Plasma Recalcification Time
RBCs	Red Blood Cells
SEM	Scanning Electron Microscope
THF	Tetrahydrofuran

Chapter: 1

Introduction

1 Background

Globally, the prevalence of kidney disorders is progressively rising, although the south Asian nations are particularly affected. Chronic Kidney Disease (CKD) jumped to the 18th spot in 2010 from 27th place in 1990's list of causes of all deaths globally [1]. Now, Pakistan is on the 8^{th} rank in CKD. This renal illness is responsible for the death of 20,000 people and reports 220,000 to 275,000 new patients yearly in Pakistan. This leads to 13% of all instances of reflux nephropathy, 11% of all cases of chronic glomerulonephritis, and 22% of cases of obstructive uropathy impact children. It is the commonly comorbid cause of End-Stage Renal Disease (ESRD) [2]. The possible treatments for CKD are kidney transplant, peritoneal dialysis, or hemodialysis. Evidently, kidney transplant is the best cure for CKD but because of the risky surgical procedure, difficulty in finding match and being expensive makes this treatment unfavorable for patient [1]. The best available treatment is hemodialysis, but it is still in the developing phase, in terms of membrane efficiency and time required. Some uremic solute compounds, such as indoxyl sulphate and p-cresol, still need to be resolved clinically. Hemodialysis should be improved to make it more affordable. According to a 2018 research, there are about 7 million persons in Pakistan who have renal failure [3] .The typical cost of hemodialysis in Pakistan is between Rs 3,000 and Rs 8,000 every session, or Rs 550,000 to Rs 700,000 per year, but the country's claimed average annual income is just about Rs 320,000 [4]. More than 2 million people worldwide are undergoing renal replacement therapy to stay alive, even though this only represents 10% of those who require it. Hemodialysis is the only affordable form of treatment available after renal failure to keep the patient healthy and breathing. To exclude uremic toxins and extra water from blood to the glucose solution known as dialysate, semi-permeable membranes are utilized. In Pakistan, conventional hemodialysis is used by 42% of patients with CKD, while 71% of patients in the USA receiving conventional hemodialysis [5].

1.1 Scope

The hemodialysis process works on the principle of convection and diffusion. The high and low flux rate of the dialyzer helps in the clearance of the solute. However, the hemodialysis process is not effective enough for the toxins bounded by protein such as creatinine, p-cresol and indoxyl sulfate. These protein bound toxins increase the mortality rate [2]. The removal percentage of prominent toxins are mentioned below [6].

Table 1: Removal percentage of uremic toxins through hemodialysis

Toxins	Removal Percentage %
Urea	75-87
Indoxyl sulphate	35
3-cardoxy-4methyl-5-propyl-2-furanopropanic acid	32
p-cresol	29
β2-microglobulin	0.7-6.8

According to the literature, removing water-soluble toxins significantly affects renal disease patients' short- and medium-term survival, measured in days and months, respectively. However, maximizing the removal of protein bound toxins can add years or decades to the patients' life [6, 7]. These proteins bound toxins, if not removed effectively, can increase death risk in the patients. In a five-year, randomized clinical study, Eknoyan et al. examined patients receiving hemodialysis three times per week. This study found that even while employing high-flux membranes for short-term hemodialysis, no deaths or illnesses occurred. However, they advised using high-flux membranes for individuals receiving hemodialysis for 3.7 years [7]. Hence, the primary objective of this research is to fabricate a membrane that can remove all types of toxins during hemodialysis so that kidney disease patients can avoid developing CKF.

1.2 Motivation

The main driving force behind this research is to synthesize a membrane that can eliminate all types of uremic toxins, especially protein bound toxins, much more effectively than the current hemodialysis membranes. The motivation is to develop efficient polymeric membrane for hemodialysis that reduces the hemodialysis time as well, which presently takes three to four hours, by removing toxins more quickly. Only 30% of the protein bound

toxins can be removed through hemodialysis because they are attached with the albumin protein. However, more than 60% of urea and creatinine can be filtered through hemodialysis [8]. Creatinine, if not removed properly, damages the kidney, and causes uremic cardiovascular diseases. Therefore, the main motivation is to fabricate a membrane that can effectively remove uremic toxins and the production cost is lesser than the existing membranes. This will enhance the performance efficiency of the process and offer economic benefits to the patients.

1.3 Kidney

One of the body's most crucial organs is the kidney. It regulates waste elimination and regulates the level of water and salt in the body through osmoregulation. The normal kidney's role is to regulate the blood through detoxification, maintains blood pressure, regulates the production of erythropoietin to stimulate the creation of red blood cells (RBCs) and urine production [9]. To keep the kidney healthy and to maintain proper functioning it is important to have a balanced diet along with plenty of water. This will not only keep the kidney healthy but also reduce the amount of uremic toxins. Normal glomerular filtration rate (GFR) in the age group of men and women below 40 is 100-130 ml/min and 90-120 ml/min, respectively [10].

Table 2: Daily waste production by human kidney [11]

Component	Concentration (g/day)
Urea	30
Creatinine	0.6
Uric acid	0.9
Water	1500
Sodium	5
Potassium	22
Calcium	0.2
Phosphates	3.7

When the GFR gets lower than 16 ml/min then kidney failure occurs. The main reasons that results in kidney failure are excessive use of high potency medicines, hypertension, infection and diabetes [11]. In case of kidney collapse one of the possible solutions is dialysis as a life support for the patients. Dialysis helps in separating excessive uremic toxins, salts and fluid from the blood through a dialysis machine usually called dialyzer [12]. This is the best suited option for Chronic Kidney Failure (CKF) patients.

1.3.1 Structure

Kidneys are bean shaped organs on both sides of spine. They are 11 cm long, about 6 cm in diameter and 4 cm in thickness. The approximate weight of kidneys in male is in the range of 125-170 g and that for females it is 115-155 g [2]. Each of the renal capsules is surrounded by tough fiber. The main functioning unit of the kidney is nephron. Furthermore, there are more than one million nephrons in each kidney. Inside nephron is glomerulus that is surrounded by complex network of capillaries. This whole arrangement is called Bowman's capsule. The capillaries have micro voids inside the walls that filters waste from the blood through difference in pressure [12].

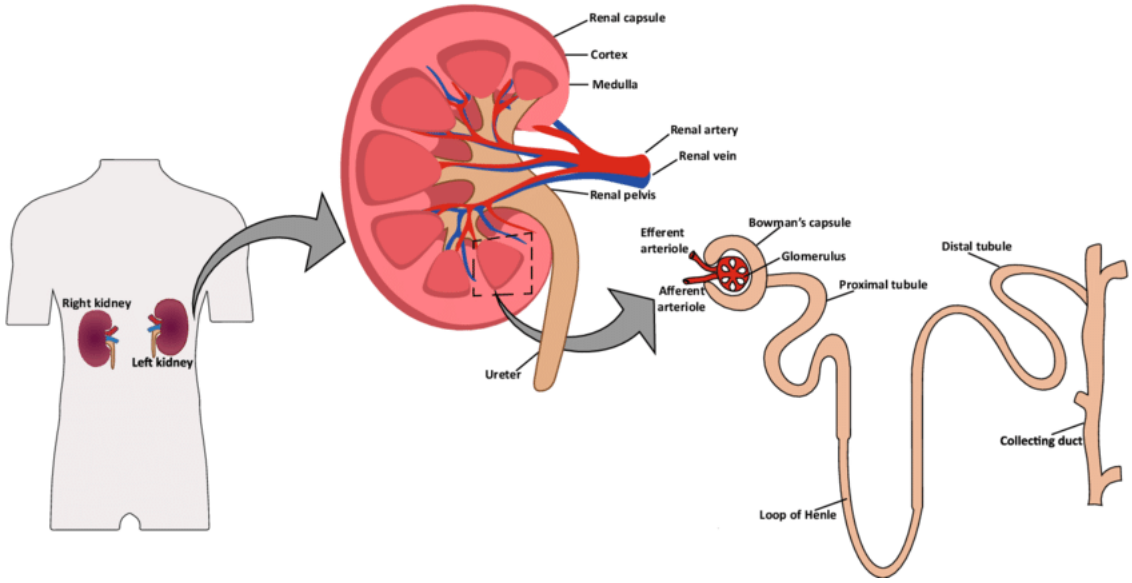


Figure 1: Structure and working of kidney [13]

1.3.2 Function

The important kidney functions are [14]as following;

- Regulated the acid and base level of the body.
- Erythropoietin is the hormone produced by the kidney that helps in the production of RBCs.
- Production of urine.
- Maintains vitamin D and calcium level in body to ensure bone stability.
- Regulates blood pressure.
- Removes excessive toxins from the blood.

1.4 Uremic Toxins

Inorganic or organic substances that accumulate in the body fluid of the patient suffering CKF are uremic toxins. These uremic toxins are responsible for CKF [15]. All these toxins have different molecular weights, serum cytotoxicity and some bounded with Albumin or other protein. There are different types of uremic toxins such as water-soluble toxins, high molecular weight toxins and protein bound toxins. All these toxins are explained below:

Table 3: Common uremic toxins in human blood [16]

Toxins	Molecular weight (g/mol)	Toxin type
Urea	60	Water soluble toxins
Creatinine	113	
Uric acid	168	
β2-microglobulin	<500 Da	High molecular weight toxins
Indoxyl sulfate	251	Protein bound toxins
p-cresol	108	

Table 4: Comparison of toxins concentration in normal person and CKD patient [17]

Solute	Healthy person	CKD patient	Maximum range
Urea	< 6700	38,333 18,333	76,667
Urea acid	< 400	496 265	873
Creatinine	< 106	1204 407	2124
p-cresol	< 5.6 9	186 41	377
Indoxyl sulfate	< 2.4 22	211 365	940

1.4.1.1 Water soluble toxins

The toxins that weigh less than 500 Da are categorized as water soluble toxins i.e. urea and creatinine [18]. As the name suggests, these toxins are easily soluble in water, and do not bound with the protein (Albumin). These characteristics make separation easy through hemodialysis [19]. As the marker for renal function, creatinine is used as the reference. The increase in the concentration of creatinine is either because of uremic build up or muscle breakdown. Hike in creatinine serum level in CKF patients causes infection, organ damage and in some cases death [20].

1.4.1.2 High molecular weight toxins

Toxins that weigh greater than 500 Da are high molecular weight toxins or large toxins [21]. The prominent high molecular weight toxin is β2-microglobulin. The accumulation of these toxins in blood is associated with an increased risk of death [22].

1.4.1.3 Protein bound toxins

The toxins that linked themselves with the Albumin protein are protein bound toxins uremic toxins, examples are indoxyl sulfate and p-cresol. They are frequently disregarded since the effectiveness of hemodialysis is typically assessed by urea elimination. The increase in the amount of protein bound uremic toxins causes coronary diseases along with chronic kidney diseases (CKD) [23, 24]. P-cresol sulphate is consequent of tyrosine and phenylalanine. Whereas indoxyl sulphate is the result of tryptophan in dietary proteins. Consequently, the urine excreted from the kidney has this protein bound toxins. Their increased serum levels point to deteriorating renal functions [25].

1.5 Kidney failure

Partial or complete absence of normal kidney functions is known as renal failure. Kidney failure is evident by the body's inability to excrete extra water and metabolic waste products. Blood pressure, blood volume, and blood content are eventually affected by this. According to the underlying cause, kidney damage is divided into acute kidney injury (AKI) and chronic renal failure (CRF) [26]. This occurs because of the 0.3 mg/ML rise in serum creatinine, which is roughly less than or equal to 26.4 mol/L. The reduction in the

urine production (oliguria less than 0.5 mL/kg per hour recorded for more than 6 hours) and the increase in creatinine $\geq 50\%$ (1.5 times higher than the baseline) both are the symptoms of acute kidney failure (AKF) [9, 27]. The main symptom of CRF is when the filtration rate is below $60\ mlmin^{-1}/_{1.73m^2}$ of body's surface area for at least three months [10].

Table 5:Stages of acute kidney failure [28]

Stage	**Description**	**Glomerulus filtration rate (GFR)** $\left(\mathbf{60\ mLmin^{-1}}/_{\mathbf{1.73m^2}}\right)$
1	Kidney damage with normal or increase GFR	≥ 90
2	Kidney damage with mild decrease GFR	60-89
3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney failure	< 15 or dialysis

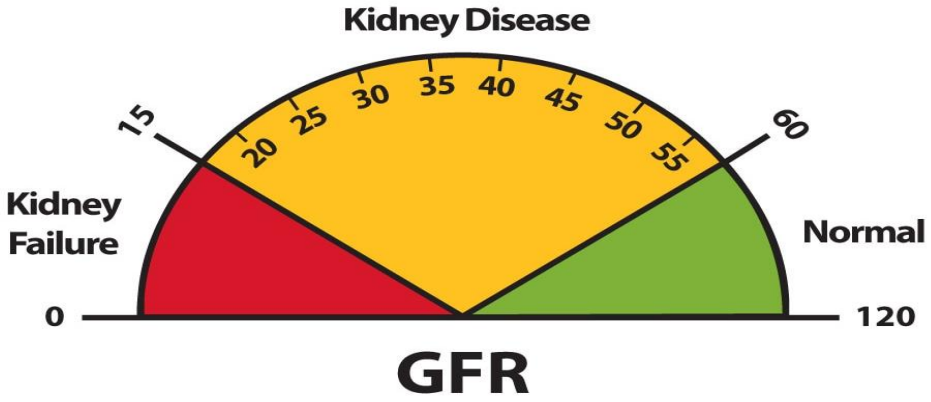


Figure 2: Glomerulus filtration range mL/min [29]

1.5.1 Solution

The following are some alternate solutions after kidney failure:

1.5.1.1 Kidney transplant

In kidney transplant, a healthy kidney is implanted within the body to replace a failing kidney. With the help of this therapy, the patient's health and vitality can be preserved, and they can resume living their normal lives. Significant disadvantages and hazards accompany kidney transplant surgery. For as long as the new kidney's function causes major adverse effects, the patient will also require anti-rejection medications. Following therapy, the patient faces a high risk of developing cancer[16]. Furthermore, a donor is needed, with a proper kidney match. Even after the surgery, the expense of the drug and the procedure itself for the therapy is very high [30].

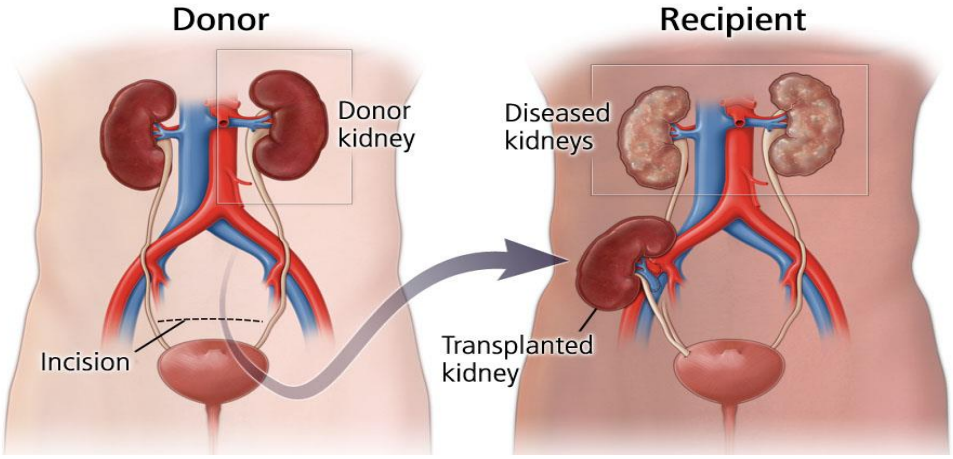


Figure 3:Kidney transplant procedure [31]

1.5.1.2 Peritoneal dialysis

Peritoneal dialysis is a modified kind of renal replacement treatment. Since patient survival is now comparable to that of hemodialysis, many patients prefer to receive this form of treatment. Fluid exchange occurs in this procedure via peritoneal membrane diffusion [32]. A few weeks are given for the incision to heal before a permanent tiny tube known as a catheter is placed into it. It's painful and challenging to have the catheter linked to the patient's abdomen permanently. The peritonitis and weekly loss of bovine serum albumin (BSA) close to 21-42g/1.73m^2 are the major drawbacks of this treatment [33]. Hemodialysis is a better option than this treatment because peritoneal dialysis results in infecting the body [34].

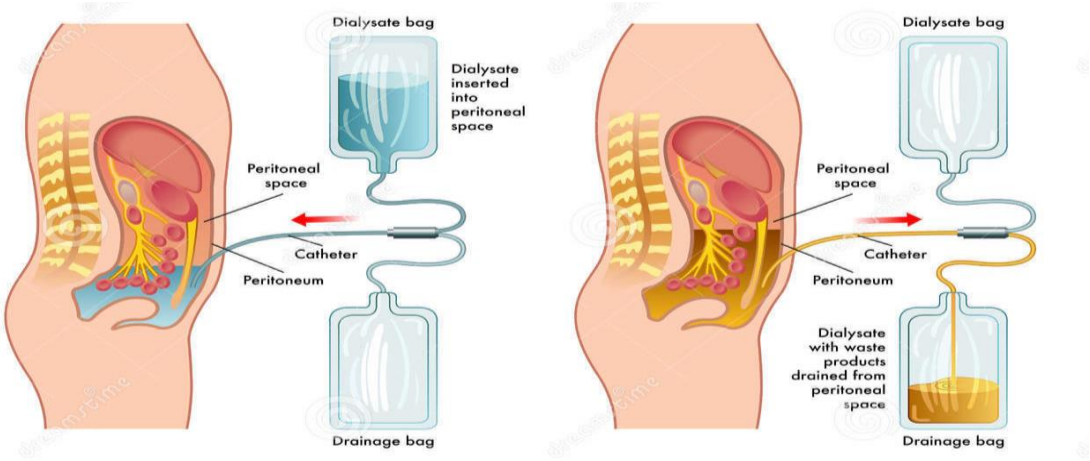


Figure 4: Peritoneal dialysis [35]

1.5.1.3 Hemodialysis

Hemodialysis is the most used type of dialysis. It is a synthetic kidney procedure. The blood is sent to dialyzer by keeping the blood pressure up. To prevent coagulation, heparin is administered into the blood stream as it enters the dialyzer. When blood comes into touch with the dialyzer's membrane, extra bodily waste is transferred to the dialysate through convection, diffusion, or ultrafiltration mechanisms. As the level of minerals must remain constant, the dialysis solution is changed frequently. After this the clean blood enters patient's body [36]. The membrane is a crucial component of the entire process, and its structure and pore size determine how molecules are filtered. Dialysate is the fluid responsible for removing toxins from the blood.

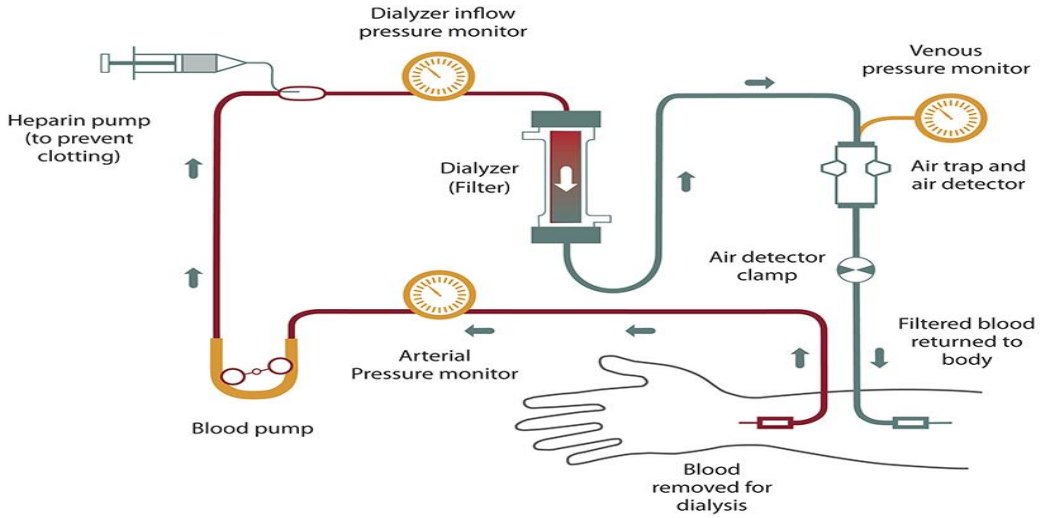


Figure 5: Typical hemodialysis circuit [37]

Dialysate's main components are sodium chloride, magnesium chloride, calcium chloride, potassium chloride, and sodium bicarbonate. Dialysis is typically performed three times a week for a duration of roughly four hours, however recent study has found that dialysis performed six times a week yields better outcomes [38].

1.5.1.4 Hemoperfusion

In the 1940s, the hemoperfusion (HP) technique was introduced. It is used to treat drug overdoses and poisoning [39]. It was modified in clinics for the treatment of acute intoxication in the 1970s and 1980s. Figure 6 shows the typical hemoperfusion system. It consists of a blood circuit with blood pumps like hemodialysis, pressure monitors, and a cartridge with adsorbents like charcoal, resin, or activated carbon. The anticoagulated blood is pumped out of the cartridge. The adsorption procedure eliminates the uremic toxins [40].

Table 6: Different absorption cartridges for hemoperfusion [41]

Manufacturer	Device	Solvent type
Clark	Biocompatible system	Carbon
Gambro	Adsorba	Norit carbon
Nextron medical	Hemosorba Ch-350	Petroleum bead carbon

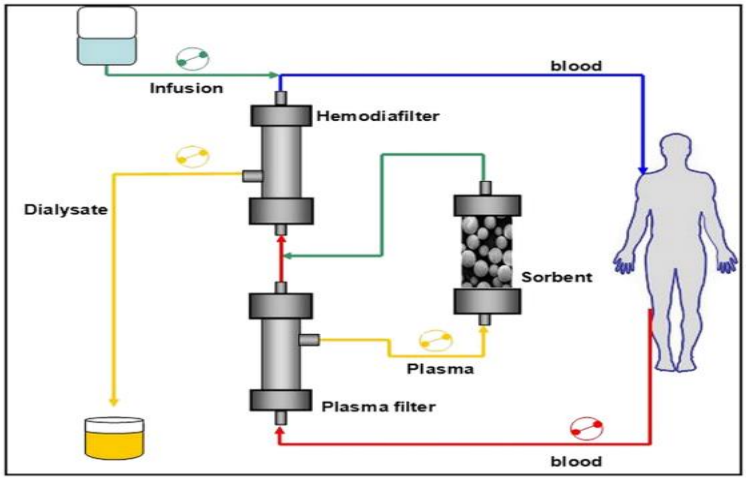


Figure 6: Typical hemoperfusion setup [42]

Hemoperfusion can cause thrombocytopenia, leukopenia, hypocalcemia, and hypoglycemia, among other complex medical conditions. The development of high flux

hemodialysis has eliminated the need for such a mechanism. As high flux hemodialysis is less expensive and has far fewer health issues. However, hemoperfusion is still a viable alternative for the low concentrated toxin dispersion and high degree of protein binding [43].

1.5.1.5 Wearable kidney

In the current hemodialysis procedure, a sizable part of dialysate, the hemodialysis fluid, travelled through the system in a single pass. The size of the hemodialysis system can be significantly lowered if the amount of fluid is decreased during a single hemodialysis procedure. This can be done by using an adsorbent system to regenerate the dialysate [18, 44].

Wearable artificial kidneys (WAK) are a small-scale hemodialysis device that the patient can wear around his belly and move around with. A WAK would be a huge help in combining effective toxin clearances with progressive fluid drainage, while still enabling the patient mobility. In contrast to conventional dialysis, which uses vast quantities of dialysis fluid in a single pass configuration, the idea behind a micro dialysis device is to continuously regenerate and reuse a little amount of dialysis fluid in a closed-loop system [45]. Therefore, the dialyzer is the most important part of the hemodialysis. However, WAK types can differ from one another. Yoshida, Henne, Davankov, Granger, and Gura are among the renowned WAK designs that predominantly use adsorbents to create dialysate [18].

Willem Kolff, the father of modern hemodialysis therapy, started the long-running hunt for a WAK. He created a 3.5 kg WAK unit including a circuit for blood and dialysate, pumps, batteries, tubing, and a module for charcoal regeneration. With the use of the gadget, uremic toxins like creatinine, salt, and water could all be continuously removed. The patients also need to be occasionally connected to a dialysate batch to eliminate urea and potassium, therefore this device could not properly be termed wearable [46]. In 1986, a more comprehensive regeneration module built on sorbent and enzyme technology was suggested. Urease was employed to remove urea from the recirculated dialysis fluid, charcoal to absorb non-urea organic toxins, zirconium phosphate to get rid of potassium

and ammonium generated by urease, and zirconium oxide to get rid of phosphate from the sorbent cartridge [47].

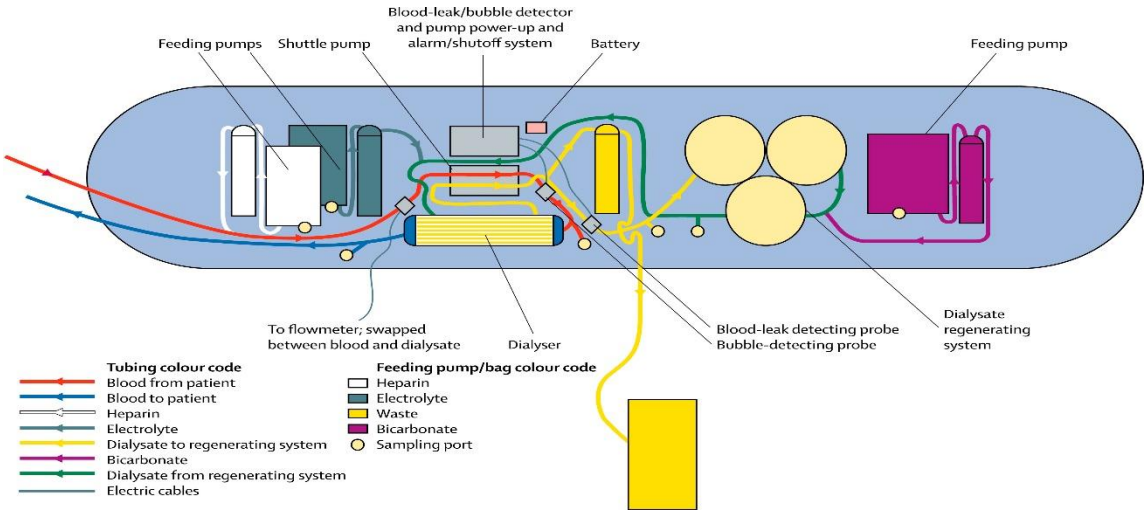


Figure 7: Layout of typical wearable kidney [48]

Table 7: Comparison of hemoperfusion, hemodialysis and wearable kidney

	hemoperfusion	**hemodialysis**	**Wearable kidney**
Working mechanism	Absorption	Diffusion convection	Diffusion
Usage	Poisoning and overdose	Kidney failure	Kidney failure
Key component	Adsorption cartridge	Dialyzer or dialysate	Dialyzer or adsorption cartridge

1.6 Hemodialysis

1.6.1 Process

Hemodialysis is primarily utilized as an artificial replacement for kidney function in people with renal failure. It can remove surplus water and waste products from the blood. Figure 8 illustrates the hemodialysis procedure. Hemodialysis involves transferring patient blood into a dialyzer's blood section, which is made up of semi-permeable hollow fiber or flat membranes. Dialysate is currently flowing in the area around the hollow fibers while the blood passes through the membrane. Thus, the dialysate receives the waste products from the blood through convection and diffusion. The patient would then receive

freshly purified blood. Membrane is the key component of dialysis machine, as the membrane decides the flow of different molecules depending on its selectivity. Dialysate is a critical element in this stage to eliminate toxic substances from blood. Most of the membrane inside our body works on the same principles, such as cell membranes, skin membranes and peritoneal membranes. Extracorporeal membranes are used to treat many diseases, such as those caused by artificial transplanted organs. For the extraction of both exogenous and endogenous toxins from the blood during hemodialysis, plasmapheresis, hemofiltration, blood oxygenation, and hemodiafiltration, membrane technology is strongly advocated [49].

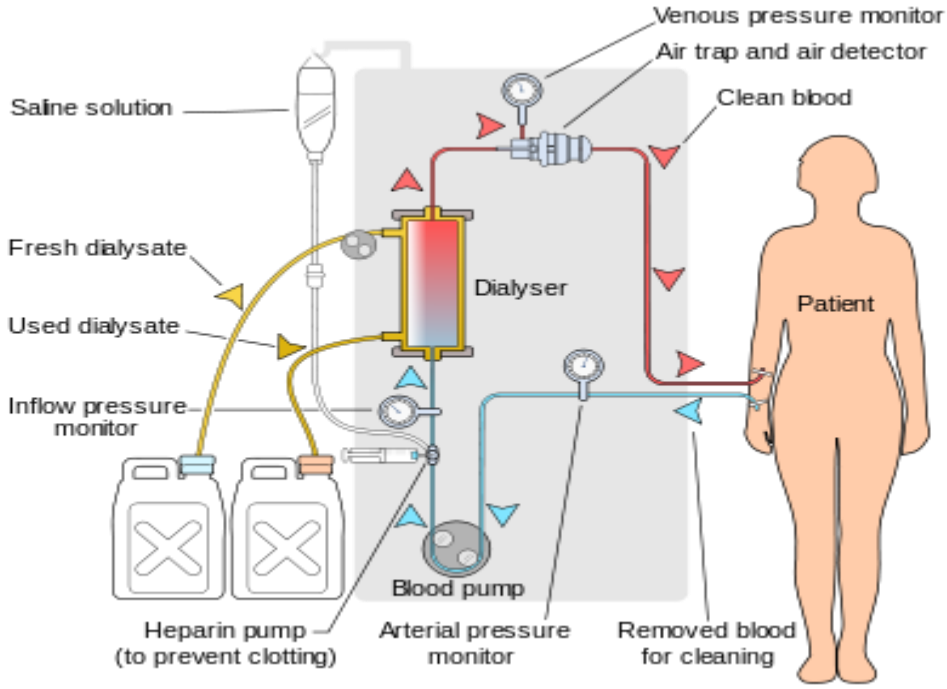


Figure 8: Hemodialysis process [50]

1.6.2 Setup

1.6.2.1 Dialysis machine

Dialysis machine is the main equipment that operates and regulates the entire setup. It regulates the body's temperature and blood flow to enhance hemodynamic stability. The quantity control system helps in regulating blood circulation. To improve treatment efficiency, online urea clearance is determined simultaneously.

1.6.2.2 Dialyzer

In the United States, dialyzer has been used since the early 1960s [51]. High flux dialyzers are economically friendly and clear large amounts of uremic toxins. The major advantages of using a dialyzer facility are budget friendliness, reduction in biological waste and being able to withstand high pressure. It also goes by the name artificial kidney since it cleanses extra fluid and waste from human blood. Semi-permeable membranes, which allow for the passage of fluids and tiny solutes, make up dialysis machines. Human blood enters the dialyzer from one side while fresh dialysate enters from the other. By using a diffusion gradient, wastes from the blood percolate into the dialysate. Waste-containing dialysate is removed from the dialyzer and flushed out [24]. The human body then receives clean blood. Permeability, membrane composition, biocompatibility, geometric design, and surface area are used to classify them [24, 52].

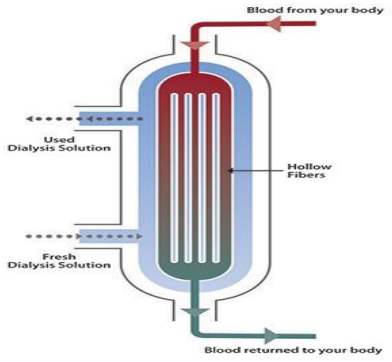


Figure 9: Typical dialyzer setup [53]

1.6.2.3 Dialysate

Dialysis fluid, solution, or bath is a mixture of purified water, electrolytes, salts like sodium, and bicarbonates. Utilizing the diffusion mechanism, the dialysate's objective is to remove toxic wastes from the blood. The concentration gradient causes uremic waste to migrate from the blood to the fluid. Additionally, the electrolytes in the fluid are used to maintain the patient's electrolyte balance. The toxins in the dialysate solution are then drained from the renal patient's body. The hemodialysis patient was treated with more than 300 liters of water [54, 55].

1.6.2.4 Hemodialysis circuit

Blood is divided into the blood circuit with the aid of an arterial needle. It is then pumped through the dialyzer with peristaltic pumps and returned to the body by needle venous. Heparin is introduced into the system to stop blood from coagulating. Fistula is guarded by arterial pressure monitoring by looking into high negative pressure. When the fistula is misplaced, blood loss from the circuit can be detected using a veno-pressure monitor. Through artery needles, air can potentially enter the circulatory system from the outside environment. By using an air bubble trap, it can be checked for air and, if found, the pump can be turned off. Dialysis flow rate, blood flow rate, fluid removal rate, and treatment duration are a few variables that should be modified based on the patient's requirements at the time of the procedure [55].

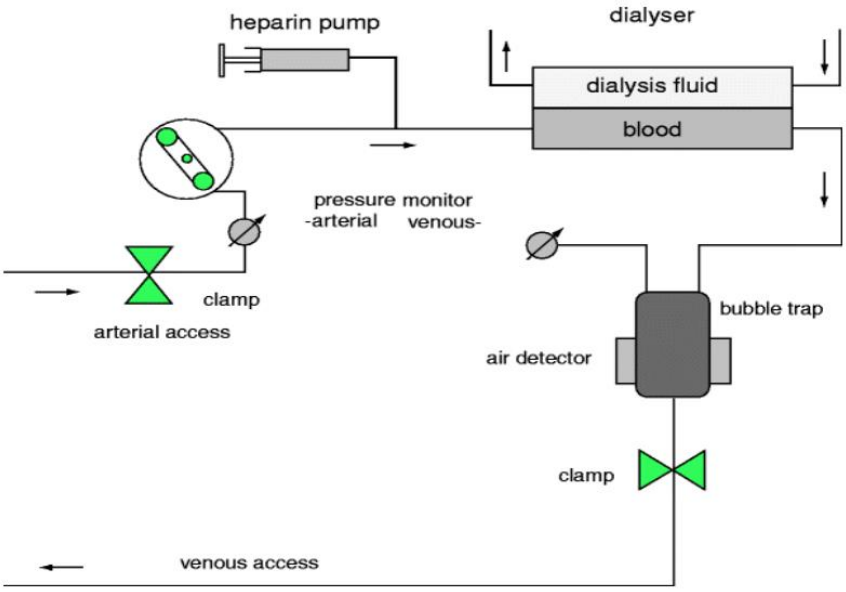


Figure 10: The flow circuit of hemodialysis setup [56]

1.6.3 Principle of Hemodialysis membranes

Hemodialysis uses a semipermeable membrane to exchange blood with a range of uremic toxins while performing dialysis to maintain the balance of the blood's electrolytes. Convection and diffusion are the transport methods used in the most contemporary hemodialysis. Adsorption mechanisms are crucial to osmosis, ultra-filtration, and hemodialysis treatment. The following explains each of them.

1.6.3.1 Diffusion

The Brownian process of diffusion primarily eliminates the tiny molecules [57]. The concentration of the solutes shifts from higher to lower. The fundamental procedure is described in Figure 11. Urea diffuses from blood to dialysate due to concentration gradient, while the dialysate travels in the opposite direction to enhance toxin elimination [22, 28]. Blood-dialysate concentration, flow rates, thickness, temperature, conductivity, and the membrane's surface area or shape are all factors that affect diffusion. While maintaining every other element constant during the operation, diffusion is heavily depended on the gradient of concentration between the fluids [9]. The framework for diffusion is also drafted by the Fick's Law [58].

$$J = -cD\left(\frac{\partial c}{\partial X}\right) \qquad 1.1$$

Here, J represents the diffusion rate in $flux\ m^{-2}s^{-1}$, D is the coefficient of diffusion in ms^{-1}, c is the molar density in kmol. ∂c and ∂X is the concentration gradient in gm^{-3} and distance in m^{-2} respectively.

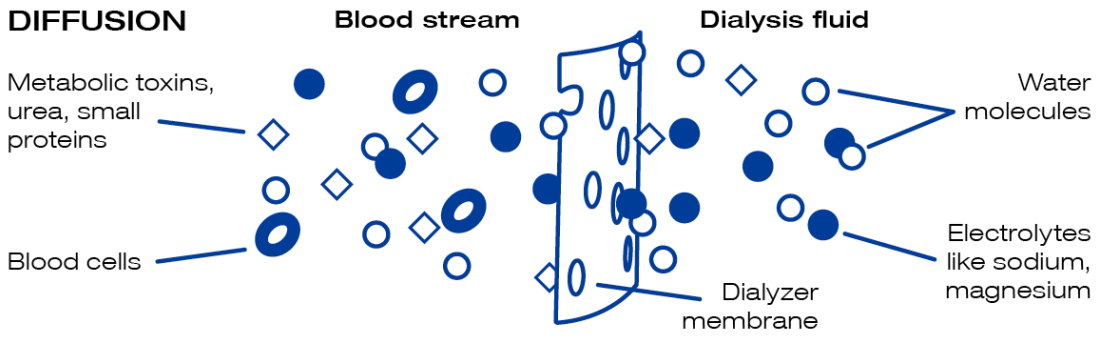


Figure 11:Basic diffusion mechanism [59]

1.6.3.2 Convection

Convection is the process by which waste and toxins from the blood are transferred to the dialysate across the membrane due to a pressure gradient. Convection is the term used to describe the flow of fluid from a denser layer to a lighter zone because of temperature. The main goal was to distinguish middle-sized molecules from all other toxins that were transported through semi-permeable membranes during high flux dialysis. The convection phase of hemodialysis involves the simultaneous transport of a solute and water from

blood to membranes due to the differential pressure. Convection depends on several key variables, including membrane surface area, sieving coefficient, toxin concentration, pressure gradient and hydraulic permeability through the membrane [60].

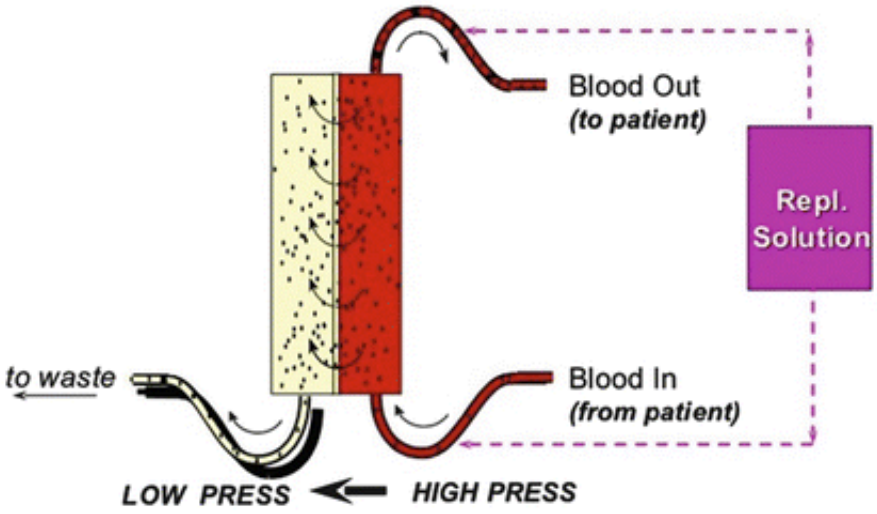


Figure 12: Mechanism of convection process [61]

1.6.3.3 Osmosis

The concentration gradient is necessary for osmosis. Through a semipermeable barrier, the net migration of solvent molecules into the region of high solute concentration occurs in this process to balance the concentration. Osmosis in hemodialysis is the process by which water is transferred from a liquid or blood plasma through a hemodialysis membrane [62]. The entire process is depicted in full in Figure 13.

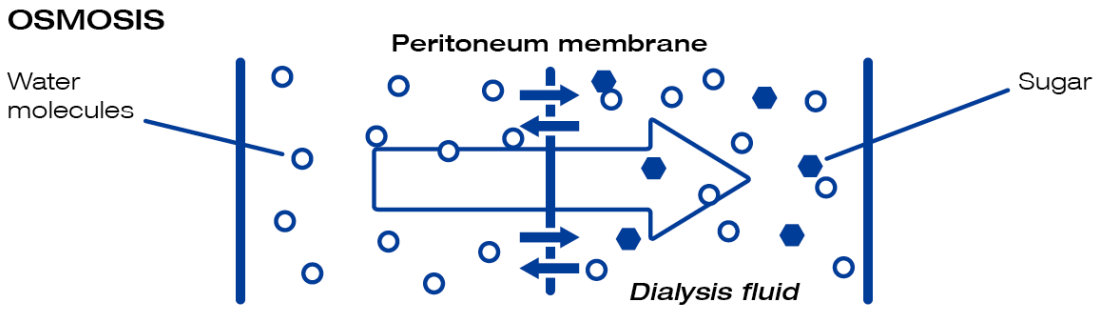


Figure 13: Mechanism of osmosis [59]

1.6.3.4 Ultrafiltration

As shown in figure 14, ultrafiltration essentially involves the removal of extra water from the body. The change in pressure causes the water to migrate from the blood plasma to the dialysate. The water travels toward the dialysate because it has a lower pressure than the blood side, which has a higher pressure. The water travels toward the dialysate because it has a lower pressure than the blood side, which has a higher pressure. The blood pressure and membrane porosity both affect ultrafiltration. Prior to and after the procedure, the patients are weighted. In order to calculate the membrane's efficiency, the patient's weight difference must be taken into account [63]. This procedure was designed to get rid of medium-sized toxins. However, ultrafiltration results in uremia.

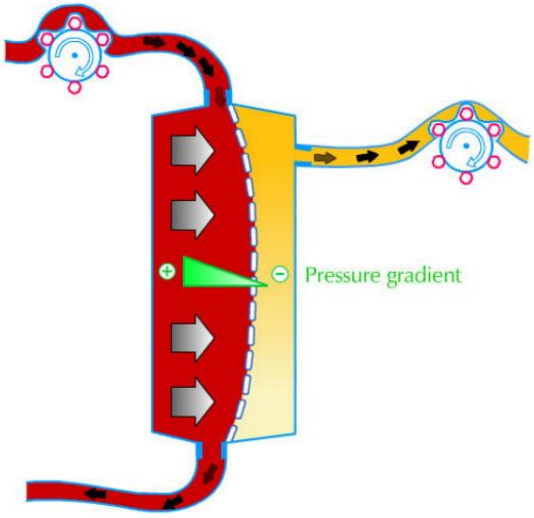


Figure 14: Mechanism of ultrafiltration [64]

1.6.3.5 Adsorption

Adsorption is the process whereby the solutes create bonds with the membrane surface. Through this process solutes create bonds with the membrane's surface. In this process, liquid, solid or gas adhere to other surfaces by electrons, particles, and molecules. The toxic solutes adhere to the membrane's surface or the adsorbent within the membrane follows the hemodialysis principle of adsorption. Uremic toxins bind to or adhere to the adsorbents present in the membranes on the surface of the semi-permeable hemodialysis membrane, causing hemodialysis adsorption to take place. P-cresol, indoxyl sulphate, and peptides are three toxins that are challenging to separate [65]. The best way to get rid of

them is to absorb them onto the membrane's surface or to attach an adhesive to the adsorbent inside the membrane. A specific protein that is important for the body is also absorbed from the membrane surface. They could be preserved by back flushing. The drawback is that toxins can easily clog membrane pores, decreasing their efficiency. Since the surface area affects the removal of toxins, it can be strengthened by the membrane's capacity for adsorption [66].

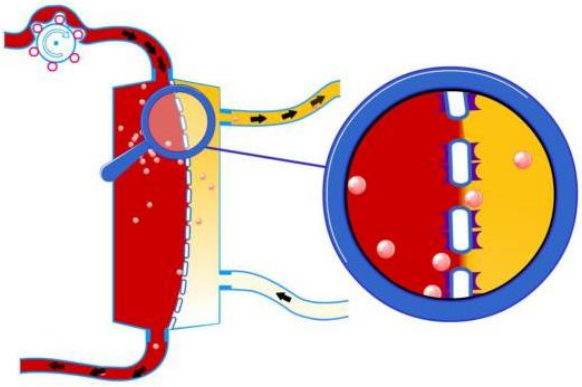


Figure 15: Adsorption mechanism [64]

1.6.4 Types of Hemodialysis

1.6.4.1 Convectional hemodialysis

Dialyzers that used acetate dialysate were regarded as the standard kind of hemodialysis in the 1980s. The dialysis machines without volume control used low flux ultrafiltration coefficient membranes. Middle-sized uremic toxins are eliminated while separation rates are low. The main flaw of this method was that it used a dialysis pump to remove a lot of water and an equivalent amount of blood from the patient's body. For the separation, the diffusion principle was applied across the membrane. Synthetic high flux dialyzers and bicarbonate dialysate overcame the traditional hemodialysis method in the 1990s [67].

1.6.4.2 Hemofiltration

Hemofiltration was cited in 1977 as a practical method for removing extracellular fluid from a patient's body. To eliminate intermediate molecules more effectively than small molecules, the convective treatment principle was applied. This technology cleared a significant amount of toxins from the body by using highly permeable membranes [68]. This method's clearance rates are independent of the sample substance's molecular weight

and flow of filtrate. Renal replacement therapy is also known as continuous hemofiltration. Hemodialysis and hemofiltration both used comparable mechanisms for their processes. However, as this method solely concentrates on the elimination of intermediate molecules, it is not appropriate for ESRD. Additionally, only the bare minimum of tiny molecules is separated. However, it offers patients with acute renal failure better outcomes [69, 70].

1.6.4.3 High flux dialysis

Compound fluid balance develops inside the system in the high flux dialysis (HFD). Although real filtration rates in the dialyzer are equalized by back filtration, net filtration rate is controlled volumetrically. Eliminating the middle-sized molecules using a convective transport mechanism, it is regarded as being significantly superior to standard hemodialysis. However, hemodiafiltration is more efficient. Toxins of intermediate size are separated by a convective mechanism, typically through internal filtering [71]. Internal filtration in this method is dependent on osmatic forces. The membrane's hydraulic permeability is tested along the length of the dialyzer [72]. The filter resistance controls blood flow filtration and back filtration that results in pressure drop. The dialyzer's two compartments experience a pressure gradient, also known as transmembrane pressure (TMP). Water molecules leave the blood when the TMP is positive and migrate in the direction of the dialysate. In the case where its value is negative, back filtration occurs. Following is the link between TMP and filtration rate:

$$Kuf = \frac{U_f}{TMP} \qquad 1.2$$

Where, Kuf, in mL/h/mmHg, is the membrane ultrafiltration coefficient. TMP is expressed in mmHg, while ultrafiltration (U_f) is expressed in mL. Currently, the separation of small molecules and some intermediate solutes works well using high flux membranes. This method's disadvantage is that it leaves the other compounds in the present renal therapy in place [60].

1.6.4.4 Hemodiafiltration

Hemodiafiltration (HDF) is a novel method that increases the high flux dialyzer's removal potential by introducing convective transport. Convection is a natural phenomenon that considerably improves the separation of middle and large molecule toxins that are otherwise difficult to eliminate through diffusion. For conventional solute transport in traditional HDF, a rate of more than 70 mL/min ultrafiltration is employed [73]. The

ultrafiltration exceeds the patients' intended weight loss, allowing the sterile fluid to be injected into their bodies. This technique requires sophisticated equipment and a sizable amount of exchange fluid. The net ultrafiltration rate in the system is defined as the difference between the overall ultrafiltration rates and the reinfusion rates in the patient's body. The machine continuously maintains strong internal filtration on the dialyzer's neighboring side and low net ultrafiltration rates [74]. The final fluid's balance was maintained by back filtration in the dialyzer's lateral section. The quantity of net filtration rate was managed by the dialysis system [75]. In contrast, the true and back filtration was properly established by the dialyzer's structural geometry, osmotic pressure or hydrostatic forces, hydraulic permeability, and morphology [76].

In the long run, it is thought that middle-sized molecules like leptin, β2-microglobulin, and insulin play a significant role in the development of amyloidosis. Therefore, the elimination of these middle-sized solutes is the present problem for hemodialysis therapy. The clearance of middle-sized molecules performed best using this method [77].

The cost of the process is increased when the amount of substitution fluid is increased. Therefore, the system's complexity is what makes it expensive [78]. In this system, sterile dialysate is advised due to renal health difficulties brought on by the back filtration. As a result, these dialyzers yield significant ultrafiltration rates that should be utilized with care [79]. Hemodiafiltration uses hydrophobic membranes, whereas hemodialysis uses dense hydrophilic membranes [80].

1.6.5 Hemodialysis membranes

1.6.5.1 Symmetric membranes

Two different types of fiber structures, symmetric and asymmetric, make up the polymeric membranes. Symmetric membranes have a single layer of polymer and are uniform, non-porous, and dense. They are created without using any polymer-derived additives. These membranes have modest fluxes and are significantly thicker than asymmetric membranes [81, 82]. Cellulose or any artificial polymer that aids in creating pores of a similar size can be used to create the outer and inner layers of the membrane wall for hollow fiber membranes [82].

1.6.5.2 Asymmetric membranes

Asymmetric membranes are those that are dense porous and have a high flux. Asymmetric membranes have two primary layers, the top layer of which is quite thin while the bottom layer is relatively dense. Numerous qualities, including permeability, shape, selectivity, and mechanical strength that can withstand high pressure, are present in these two layered membranes [81]. These membrane types are typically employed in the processes of ultrafiltration, gas separation and reverse osmosis. Small water-bound toxins encounter diffusive resistance because the wall has thickened, while the membrane's porosity makes it easier for toxins to get through the membrane. They can be used for things like high permeability, selectivity, and high pressure because of their mechanical strength. Triple layers asymmetric membranes are created to boost the flux, with the outer layer serving as the support [82].

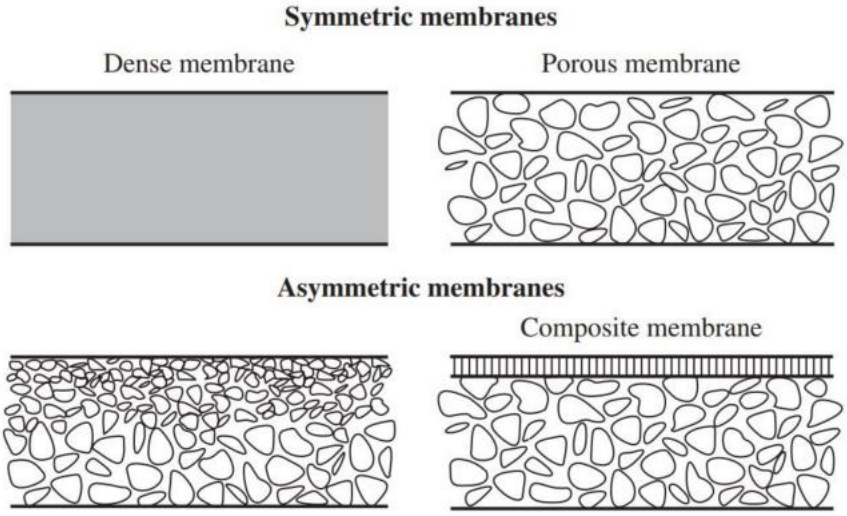


Figure 16: Symmetric and Asymmetric membrane structure [83]

1.6.5.3 High flux membranes

High flux membranes are porous membranes with fixed pores that are between 2 and 100 nm in size for ultrafiltration and between 0.1 and 10 m in size for microfiltration. High flux membranes offer some benefits to the treatment. The high flux membranes had ultrafiltration rates of more than 20 ml/mmHg and a sieving coefficient of only 33.90 ±2.94 mg/dL for β2-microglubulin [43, 84]. This improves lessens the requirement for erythropoietin, anemia control, and reduces cardiovascular diseases [41]. The size of the

pores determines selectivity. Toxins with medium and large molecular sizes, such as β2-microglubulin and phosphoric molecules, which accumulate during chronic kidney illness, were more easily separated into high flux membranes. Additionally, it lessens hemodialysis's long-term negative effects. High flux membranes eliminate more of the toxins that lead to uremia and lessen the chance of producing cytokines. In compared to low flux membranes, it also lessens the body's inflammatory responses [17]. High flux membranes are compatible with the hemodiafiltration, hemofiltration and hemofiltration processes and provide the necessary penetration.

Moreover, if a patient has serum albumin less than 40 g/l, using high flux membranes reduces the chance of death [85]. The amount of serum albumin is inversely correlated with the patient's mortality risk rate. Observed that the membrane material had no bearing on the patient's mortality [8, 85, 86]. High performance membranes have the disadvantage of having large pore sizes that extract albumin along with other substances. Large amounts of albumin lost could have detrimental effects on the kidney's patients. It is believed to be beneficial to a certain subgroup of patients rather than all patient types. Patients must convert to conventional dialysis membranes or low-flux membranes if they cannot tolerate protein deprivation [8, 87]. The cellulose membrane is typically utilized in high flux membranes because it has a higher permeability than low flux membranes. Conversely, high flux membranes have more useful characteristics than low flux membranes, such as high adsorption capacity, high molecular and high porosity weight are these characteristics.

1.6.6 Low flux membranes

Non-porous membranes with low flux are typically used for liquid and gas separation. The intrinsic qualities of the materials affect how well the membrane performs. Due to their small average pore size and low porosity, low flux membranes can be utilized for the removal of small compounds in hemodialysis patients. The key difference between them is that the ultrafiltration rate is even lower than 20 ml/mmHg and the sieving coefficient of low flux membranes for β2-microglubulin is equal to 0. Since these membranes' surface adsorption capability is limited, they lose protein at a higher rate than other membranes do. Low flux dialyzers' primary flaw is their inability to

eliminate toxins effectively, which leads to adverse consequences on many physiological systems over time [17].

1.7 Classification of hemodialysis membranes

The typical hemodialysis membrane has been classified into the following parameters that affect its ability to work properly.

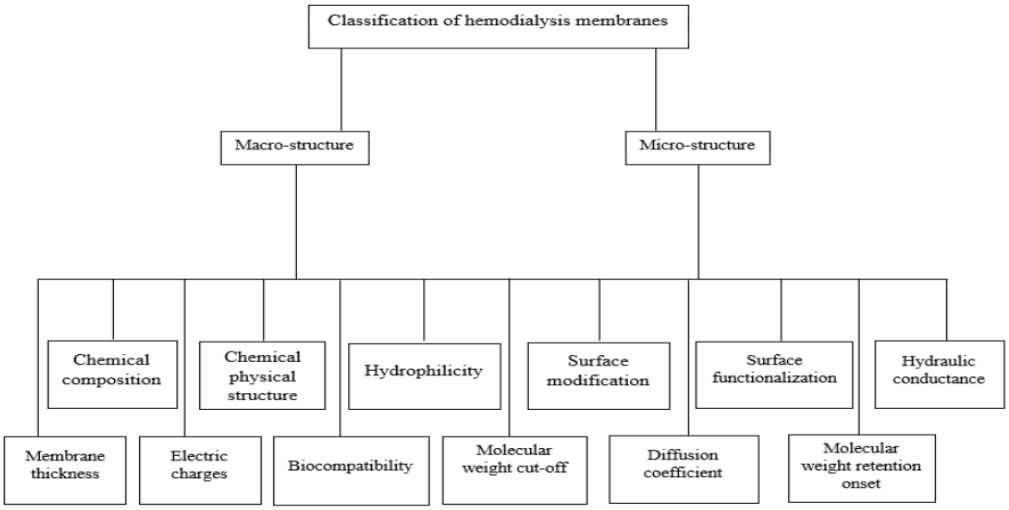


Figure 17: Multidimensional parametric classification of hemodialysis membrane [88]

1.8 Challenges for hemodialysis membranes

Death rates are still noted to be high despite all the advancements in blood purification biocompatible membranes [89]. Even more so, it illustrates how traditional hemodialysis can simply prolong a patient's life and not help them live a healthy life. For surface alterations, several modified approaches have been introduced. Additionally, not all the examined membranes took hemocompatibility testing into account [90]. In other words, there aren't many research articles that discuss hemocompatibility issues. While studies reported hemocompatibility tests using a limited number of variables. The rejection, flux, and solute clearance elements of hemodialysis are improved by technology. The need for hemodialysis in hospitals and at home has increased due to material improvements, pore size adjustments, and surface modifications for blood purification. For hemodialysis patients, quality of life continues to be a primary concern. The surface morphology must therefore be improved to boost the flux, rejection of proteins, solute clearance, and the membrane's biocompatibility are all necessary smeared in blood [91].

Chapter:2

Literature Review

2 Literature Survey

2.1 History of hemodialysis membranes

In Philadelphia, Prof. Abel performed the first dialysis using a celloidin tube in 1996 [92]. He used these tubes to examine the mass separation between two fluid phases. Thirty years ago, Professor Alwall of Lund university conducted an experiment on the blood purification of his first artificial kidney. These experiments paved the path for the researchers to create artificial hemodialysis [93]. Willem Kolff created a useful artificial kidney with revolving drums in 1942 [94]. That was the ESRD's initial application in the UK and the US. Arteriovenous Teflon shunt was created in Seattle by Belding Scribner in 1960, but it wasn't commercialized until then. James Haviland and Scribner founded the artificial kidney center after the start of this therapy. In 1962, it served as the first nonprofit kidney facility. Their next task was to treat ESRD patients and further develop the approach [51]. By that point, cutting the duration of the procedure from 12 to 4 hours improved process efficiency. The blood flow was kept at 400-500 mL/min and effectively removed the urea. After a few years, hemodialysis at home became a therapy option. It is less expensive with lower hepatitis risk [94]. The effectiveness of hemodialysis treatment depends on the blood's uremic toxins' ability to permeate from blood to dialysate. Even though urea and creatinine are thought to be the most toxic uremic solutes, they are necessary for treatment [95].

Dialysis machines were unable to accurately quantify the amount of urea removed from the blood, due to the buildup of medium and large size toxins. After this treatment, several issues still exist, leading to diabetes, hypertension, carpal tunnel syndrome, skeletal anomalies, and anemia [96]. The membrane, which is the process's core element, determines how well it will operate. Specific molecules flow through the membrane when pressure is applied, while the membrane prevents the flow of others. The membrane module's effluent is the feed stream. The liquid that permeates from the semipermeable membrane is known as the permeate, while the liquid containing the retained elements is

known as the retained phase. The primary characteristics of membrane that increase its appeal are higher efficiency, compactness, ease of operation, energy sustainability, and higher selectivity [60]. Numerous end uses of this technique exist, including dialysis procedure, gas separation, pharmaceuticals, chemical production, beverages production, food production, and water treatment [52]. The importance of membranes has expanded for drinking water filtration and in the biological field since the commencement of World War II [97]. The membranes are now used as biomaterials, coming in touch with cells, organs, and tissues as well as biological fluids. Membranes have also demonstrated their value as components of artificial organs, tissue engineering, diagnostic tests, bioreactor systems, and other medical devices and implants [98].

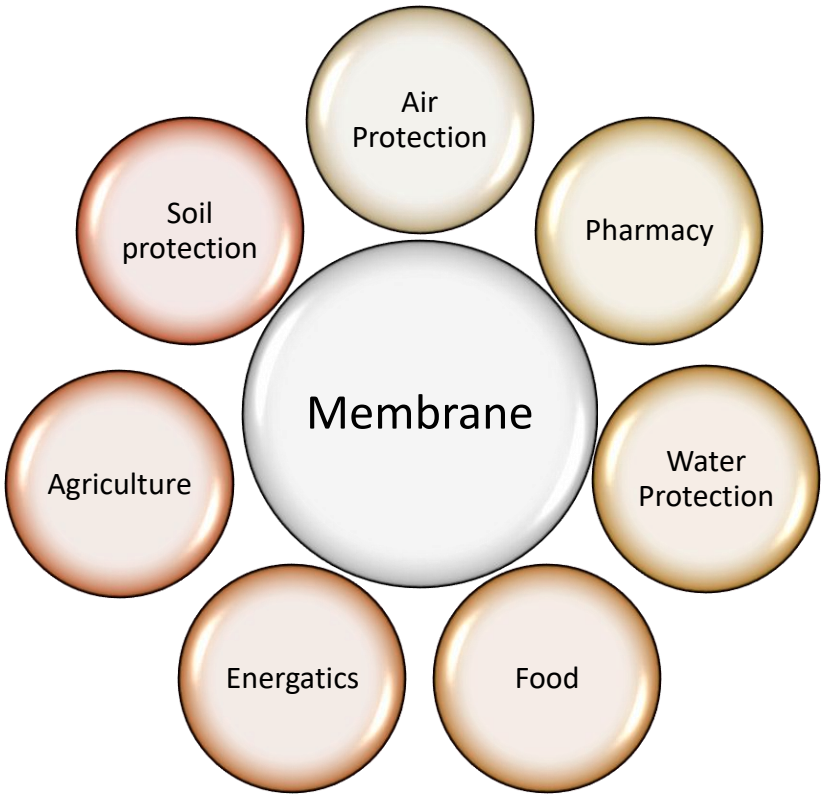


Figure 18: Different applications of membrane technology [99]

Membrane technology is strongly advised for hemodialysis, plasmapheresis, hemofiltration, blood oxygenation and hemodiafiltration for the removal of endogenous and exogenous toxins from blood [49]. To comprehend the membrane transport phenomenon through the capillary network, Kedem-Katchalsky proposed a frictional

approach. A concentration difference causes passive transport to develop in the membrane system. Additionally, it is stated that the main components received as permeate and retentate, are the blood flow and the dialysate flux, respectively. The hydrostatic pressure difference and osmotic pressure gradient both affect the membrane's flux [63]. The analysis of processes in which the boundary layers played a significant role may be done using the derived KK equation [19]. The number of patients who are willing to undergo hemodialysis is used to measure the societal impact of this treatment. Compared to only 8.5% of patients who had peritoneal dialysis in 2008, more than 90% of patients received hemodialysis treatment [100]. It has been noted that the number of dialysis clinics and equipment has been steadily rising since 2009. Patients receiving hemodialysis experience psychological issues as the treatment progresses. The main problems are suicide, depression, poor quality of life, inflammation, and starvation. Both pharmaceutical and non-pharmacological methods are used to treat these issues [101].

Hemodialysis membrane expenses worldwide were $1400 million USD in 1994, while the profit margin from the hemodialysis process was about $20,000 USD annually [102]. Therefore, the demand for hemodialysis membranes is increasing and will rise more in the future. Dialyzer and tubing can be produced locally, which will lower the cost of hemodialysis. Non-governmental organizations (NGOs) can play a bigger part in Pakistan’s finance by raising money to develop hemodialysis centers [103]. In conclusion, hemodialysis is preferred because it is less painful and has an increased mortality rate compared to other treatments. The development of this treatment has, however, been slowed down by genuine patient-centered developments. Millions of deaths are reported annually, and many people are still unable to receive this treatment [104].

2.2 Development in hemodialysis membranes

Membrane technology is becoming more and more significant worldwide. The phenomenon of membrane technology was first examined in the mid-1700s [52]. The important development of synthetic membranes for industrial applications began in the 1960s. Enhancing the restructure processes, safeguarding the environment, and promoting public health for continuous growth [105]. In the hemodialysis industry, membrane

technology advanced significantly, much like other applications such as gas separation, water purification, medicine, etc.

Semipermeable membranes, the most basic type of membrane made of biological and synthetic material to remove undesired components from blood by concentration difference, are the foundation of hemodialysis technology. Over the century, people play with different materials in different concentrations to achieve best membranes. However, it results in several issues throughout the dialyzing process, including decreased effectiveness, increased cost, and decreased biocompatibility. The collodion tube membranes, which allow for the crossflow mechanism between dialysate and blood, replace the semi-permeable membranes [106]. The collodion tube membrane's primary issue is the lengthy cleaning procedure, which causes physical and psychological issues for individuals who are dealing with kidney disease. In the rotating drum dialyzer, where blood and dialysate revolve in a drum-like structure, membranes were utilized [107]. It was more efficient than a collodion tube, but because of the complicated fabrication, and the increased cost, making it prohibitive for dialysis facilities. For the fabrication of flat sheet membranes, solution coating and dip coating techniques were used in the 1980s [108]. It represented a turning point for the hemodialysis industry. Modifications were made to the surface of the flat membranes, such as the addition of additives, the integration of nanoparticles and zeolites, etc., to boost the effectiveness of the membranes. Coil or tube membranes were created to reduce the membrane's surface area. Parallel blood and dialysate flow patterns improve the membrane's capabilities in the dialyzer, resulting in a modified hollow fiber membrane that is effective in removing solutes and rejecting proteins [109].

2.3 Commonly used hemodialysis membranes

In 2000, Chuang et al. [110] studied polyvinyl alcohol (PVA) membranes. Acetic acid affects the membrane's structural and filtering capabilities which is used as an additive. Increasing the amount of acetic acid improves the influx rate of coagulant medium by acid base equilibrium. Results provide a deeper knowledge of the interactions between the constructed membrane and the structure of the skin.

In 2004, M. Hayama et al. [111] created hemodialysis membranes by combining PS and PVP. The improvement of biocompatibility was the goal of this study. This study demonstrated that good biocompatibility may be achieved by adding both large and small amounts of PVP utilizing the AC approach and the - method. Changing the wet/dry ratio of the polymer surface allowed researchers to study polymer particle swelling.

In 2005, Ye et al. [112] created CA hollow fiber membranes using water-soluble amphiphilic 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymer. This study showed that the membrane biocompatibility was improved. They observed less fouling, great permeability, and protein adsorption.

In 2006, Li et al. [113] created CA membranes by Liquid-Liquid de-mixing of solvents such as N-methyl pyrrolidone and -butyrolactone (GBL). Through regulating the amount of GBL, the membrane's clearance capabilities were enhanced. The macro voids were turned into sponge like structures that resulted in increasing the membranes' permeability and flux.

In 2007, Chou et al. [114] created a CA asymmetric hollow fiber membrane to measure the pure water flux and protein retention. PEG was added as a filler. As PEG dextran dosage increased, rejection and PWF increased. Additionally, it reduced macro voids, and changes in coagulation temperature enhanced permeability performance.

In 2008, Saljoughi et al. [115] used polyvinyl pyrrolidone (PVP) as an additive for casting CA membranes. While investigating PVP concentration and coagulation bath temperature (CBT) were altered. By varying the concentration of PVP, micro voids formed which enhanced the pure water flux (PWF). On the other hand, in the case of CBT, it lessens the macro void formation, lowering the membrane's PWF and hydrophilicity.

In 2009, Ani Idris et al. [116], published another study on CA dialysis membranes. In that research, D-glucose monohydrate was used as an additive and CA membrane was fabricated using phase inversion method. The main purpose of this study was to examine how D-glucose monohydrate affected the elimination of toxins from the blood. This additive increased the production of macro voids, which improved the elimination of

creatinine and urea by 19.54% and 49.77%, respectively. The results showed that 96.78% of the BSA was retained. D-glucose monohydrate is suitable for dialysis membranes.

In 2010, E. Saljoughi et al. [117] fabricated asymmetric cellulose acetate (CA) membranes by using the phase inversion technique. The membranes were created using 1-methyl-2-pyrrolidone (NMP) as the solvent and polyethylene glycol (PEG) as the additive. Pure water permeability (PWP), thermal and chemical stability of the membranes, and human serum albumin were all the subjects of the investigation (HSA). The thermal and chemical stability was shown to increase with higher CA/PEG concentrations and lower coagulation bath temperatures (CBT). PWP and HSA were increased because of increasing CBT and decreasing CA/PEG.

In 2011, G. J. Dahe et al. [118] investigated that when PSF/PSFgTPG was utilized, the biocompatibility and separation efficiency of the antioxidant polysulfone/vitamin E TPGS composite hollow fiber membranes was 0.53 percent (59a).

In 2012, M. Uz et al. [119] studied that most of the hemodialysis membranes today are hydrophobic. As a result, protein was adsorbed to the membrane's surface. It might be analyzed using several methods, including mass spectroscopy, surface Plasmon resonance, and X-ray photoelectron spectroscopy. AFM was used to investigate how the BSA and PSF membrane interacted.

In 2013, S. Yu et al. [120] manufactured a hollow fiber membrane made of CA base polymer. The semi-permeable cellulose triacetate membrane was then modified using hydrolysis and carboxy methylation. SEM and FTIR were used to assess the effects of modification. Hydrolysis increased membrane pore size and surface hydrophilicity. The membrane's porosity and negative charge were both affected by carboxymethylation. This study concluded that CA modified membrane performed better than CA pure membrane.

In 2014, Ahn et al. [121] created a CA flat sheet membrane with a PVA cover. This changes the surface's permeability, hydrophilicity, and water flux. He also observed that when the average membrane pore size is reduced, it increased permeability.

In 2015, Lijing Zhu et al. [122] used block copolymer (polylactic acid-block poly (2-hydroxyethyl methacrylate copolymers) as blending additive in polylactic acid membrane. The copolymer addition improves the antifouling ability and hemocompatibility of the hemodialysis membrane. The resultant membrane cleared more than 0.70 mL/min of urea and more than 0.70 mL/min of creatinine, roughly 0.50 mL/min of lysozyme, and as little as 0.31 mL/min of BSA.

In 2016, Hizba Waheed [123] studied polyethylene glycol (PEG) 400 and glycerol as additives in CA flat sheet membranes. The phase inversion technique was used to create the CA/PEG400/glycerol membrane. After creating the CA/PEG membrane, it was modified by adding glycerol while still using the same amount of PEG 400. This alteration led to an improvement in the clearance of urea. The rate of elimination dropped once the glycerol reached 10.1 weight percent. Hemodialysis membranes that included PEG and glycerol also produced better glucose separation outcomes.

In 2017, Maria J. Sandker et al. [124] they explore the use of biodegradable poly (DL-lactide)-PEG-poly (DL-lactide)-b-poly(L-lactide) multiblock copolymer microspheres with a limited particle size distribution. It may be appropriate for articular joints' local sustained medication release. Using a micro-sieve membrane emulsification technique, mono spheres with diameters of 5, 15, and 30m and a tight particle size distribution were created.

In 2018, Carlos E. de Castro et al. [125] investigated the synthesis, characterization and cellular uptake of block copolymer assemblies made of a pH-responsive poly(2-di-isopropyl-amino ethyl methacrylate) core balanced by three different biocompatible hydrophilic shells, including a zwitterionic type poly(2-methacryloyloxy ethyl phosphorylcholine) layer, a highly hydrated polyethylene-oxide layer that has a furtive effect as well as a poly(N-(2-hydroxypropyl methacrylamide) layer that has been shown to be nontoxic and immunogenic.

In 2019, Jiemei Zhou et al. [126] studied the block copolymer (BCP) of PSF and PEG. The constant production of BCP membranes via melt extrusion combined with microwave-boosted selective swelling and the large-scale, economical synthesis of

polysulfone-based BCPs. Our PSF-b-PEG membranes are anticipated to successfully address this issue because none of the additives are employed in the selective swelling procedure and the PEG blocks are attached via covalent bonds to the PSF framework, and thus strengthened to the exterior of the membrane to improve its hydrophilicity during swelling but will never wear off to pollute the blood. The PSF-b-PEG membranes are another intriguing option for lithium battery separators because of the PSF's exceptional thermal stability, high attraction for lithium ions, and wettability to the ions of the PEG blocks. Research on hemodialysis has made use of these PSF-b-PEG membranes.

In 2020, Jing Wand et al. [127] created the highly perm-selective and anti-fouling ultrafiltration membranes using PSF-b-PEG block copolymers with various PEG concentrations. According to their findings, the PSf-b-PEG block copolymer and PSf/PEG blend system with increased PEG content were advantageous for forming more pores and a thinner top skin layer with the slightly larger pore size and the higher MWCO of the manufactured membranes. However, due to the microphase separation of the PSf block and PEG block, PEG in the block copolymer may contribute to the generation of more pores with a comparable pore size than PEG in the blend system under the same content.

In 2021, Dinglei Zhong et al. [128] fabricated additive free block co-polymeric membrane for hemodialysis. Platelet adhesion, protein adsorption, solute rejection, hemolysis, ultrafiltration coefficient and toxin clearance were evaluated in addition to the PSF-b-PEG membranes' compatibility and performance in in-vitro tests. The PSF-b-PEG membranes demonstrated superior hemodialysis performances than conventional membranes. This was made possible by the inherent presence of hydrophilic and biocompatible PEG on the surface.

In 2022, Jian Ren et al. [129] investigated the compatibility of mPEG-b-PES-b-mPEG and PES for dialysis and the sieving flux of intermediate molecular weight toxins in 2022. Therefore, in flux, sieving, and hemocompatibility, the membranes of BCP mPEG-b-PES-b-mPEG have shown superior balance than the mix membranes. With mPEG-b-PES-b-mPEG's growing collaboration, the blend membranes have demonstrated a rising flow, hemocompatibility, and separation of lysozyme.

Chapter: 3

Research Methodology

3 Methodology

3.1 Selection of Material

3.1.1 Nexar™

Nexar™ is the commercially available amphiphilic sulfonated penta-block copolymer. The polymers morphology can be tempered by the solvent choice. The polymer has a remarkable balance of mechanical properties and membrane performance [130]. The middle block is sulfonated styrene that creates water selective channels and the end blocks, tert-butyl styrene, and ethylene co-propylene, are responsible for the flexibility in the polymeric chain and good mechanical stability. Nexar™ maintains integrated in hydrated state due to high degree of sulfonation [131, 132]. The center block is hydrophilic and the end blocks are hydrophobic. The membrane hydrophilic or hydrophobic nature depends on the choice of solvent [131].

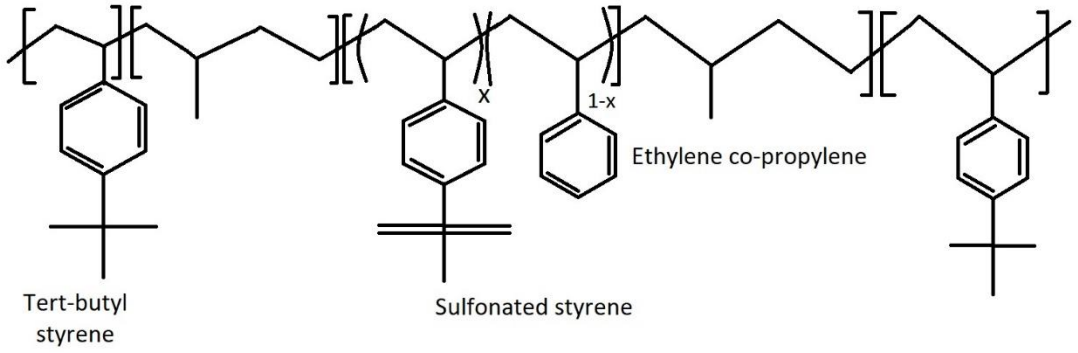


Figure 19: Structure of NexarTM polymer

3.1.2 Tetrahydrofuran

Tetrahydrofuran is a polar organic solvent. The compound is heterocyclic and is specifically cyclic ether. The low viscosity and the water miscible organic compound are used as a precursor to polymers. It is mainly used as the solvent [133]. The dielectric constant of THF is 7.6. As THF is polar solvent, the morphology of the polymer will be highly organized and self-assembled.

3.1.3 Isopropanol and Toluene

Isopropanol (IPA) and toluene both are non-polar organic solvents. Blend of both non-polar solvents is used in 15 wt.% and 85 wt.% ratio, respectively as solvent. Toluene has a dielectric constant of 2.4 and 19.9 in the case of IPA. Toluene is used as a solvent widely. As IPA has major pharmaceutical applications, it will aid in improving the biocompatibility of the membrane [134].

3.2 Materials and Method

3.2.1 Materials

The block co-polymer used for the formation of the membrane was sulfonated Penta block copolymer (Nexar^{TM} MD9200) provided in the forms of films by Kraton Polymers (Houston, TX). The solvents Toluene, Tetrahydrofuran (THF) and Isopropanol (IPA) were purchased from Sigma Aldrich. All the solvents were used as received. The hemodialysis tests were performed on urea with molecular weight 60.06, creatinine and Bovine Serum Albumin (BSA) of purity > 97%. All of these were purchased from Sigma Aldrich. Biocompatibility tests were performed on human blood donated by volunteers.

3.2.2 Method

3.2.2.1 Solution Preparation and Casting

The membrane was fabricated using different solvents mentioned in table 8, as the morphology of the membrane is very much dependent on the type of solvent used. The membranes were fabricated by casting by 2 wt. % polymer solution in two different solvents.

Table 8: Composition of Nexar membranes

Sr no.	Membrane	Polymer (wt.%)	Solvent
1	Nexar-THF	2	THF
2	Nexar-IPA+Tol	2	IPA (15 wt.%) +Tol (85 wt.%) blend

The first solvent was polar tetrahydrofuran (THF) and in the second case blend of non-polar solvents, toluene (85 wt.%) and isopropanol (15 wt.%), was used to dissolve the polymer. The homogenous mixture was prepared by stirring the solution at 300 rpm, 25℃ for 1 hr. The solution was then sonicated for 30 mins to release the trapped air. The solution was then cast in Teflon dish. Slow evaporation was ensured to obtain the desired morphology. The Teflon dish is covered with glass beaker, to control the rate of evaporation. The membrane was then vacuum dried to remove any leftover solvent at 25℃ for 24 hrs. The obtained membrane had area of 0.00146 cm^2 and thickness 23µm and 17µm for Nexar-IPA+Tol and Nexar-THF, respectively.

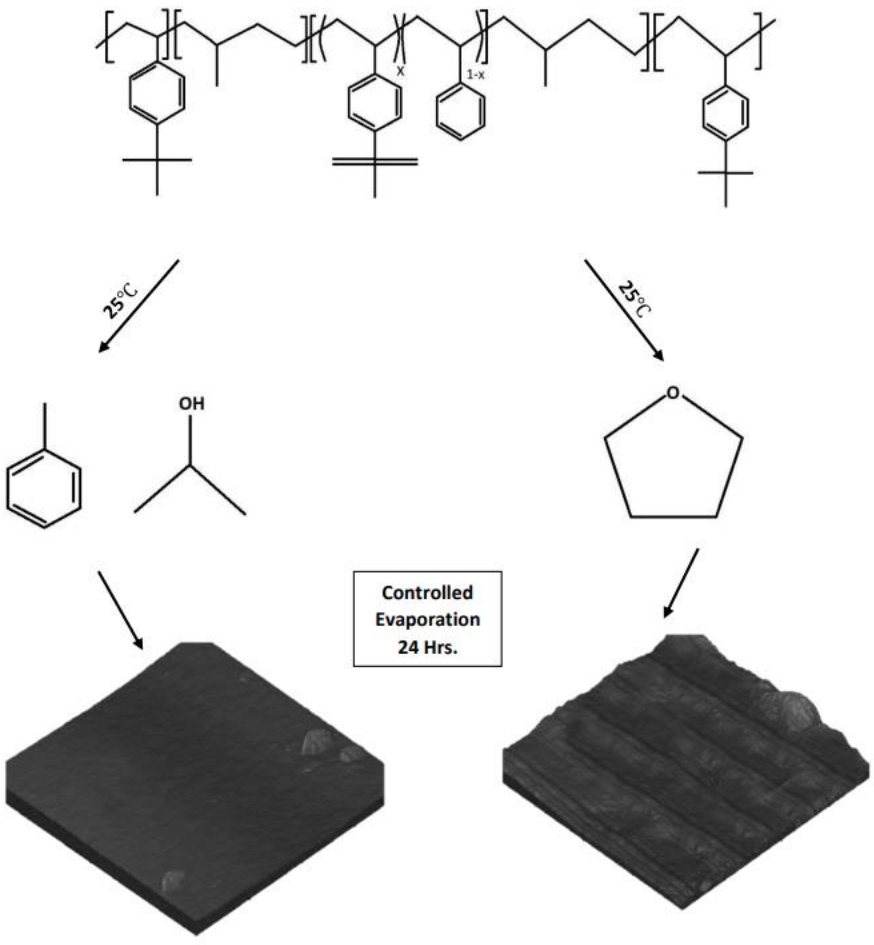


Figure 20: Experimental scheme of Nexar-THF and Nexar-IPA+Tol membrane fabrication and filtration test.

3.3 Characterization Techniques

3.3.1 Scanning Electron Microscope

Scanning Electron Microscope (SEM) technique helps to study the morphology and thickness of the fabricated membranes. In SEM analysis, a beam of electrons is created using a thermionic process employing resistive heat. When the electron beam interacts with the material, subordinate electrons, backscattered electrons, and X-rays are produced which create the spitting image of the membrane's surface and its cross-section.

Once detected, an image is displayed on the monitor. Magnifications of X250, X500, X1000, X2000, X5000, X10,000, and X15,000 are recorded using a 10 kV voltage. Dual-sided bondable tapes were used to shatter the membrane sample in liquid nitrogen while it was placed on brass plates. SEM model JSM 6409A, made by JOEL, Japan, was used to detect the morphology of the surface and cross-section of pure and blended membranes. Three samples of each mixture were evaluated in most studies for accurate results.

Figure 21: Scanning electron microscope [135]

3.3.2 Atomic Force Microscope

The Atomic Force Microscope (AFM) is used to inspect the roughness of the surface of pure and blended membranes.

AFM was performed using JSPM-5200, Japan, with 3D micrographs instrument. Tapping mode was used. A membrane area of around 10µm x 10µm was used for the scanning. From AFM images, the AFM software program calculated the roughness parameters of sample membranes. The average roughness (R_a) and the root mean square roughness of the membrane surface are both used in roughness data.

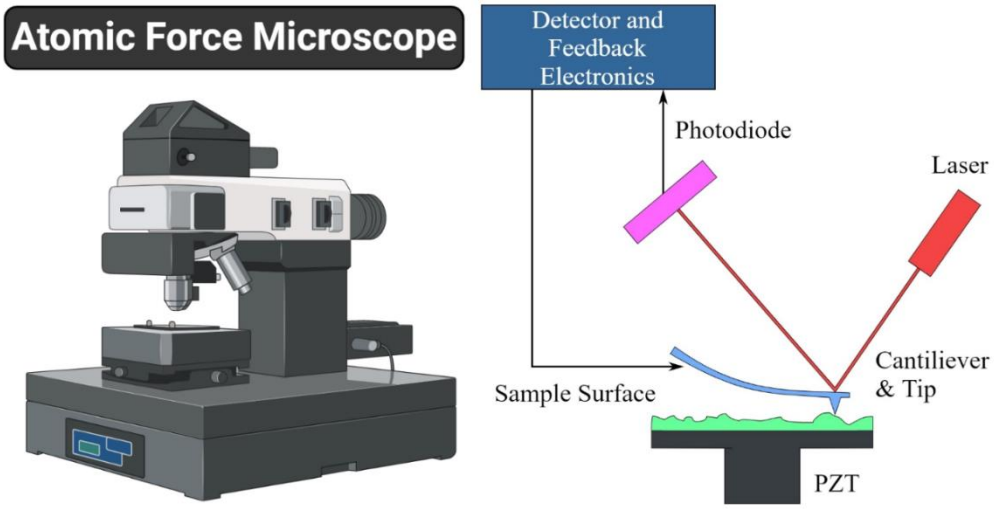


Figure 22: Atomic force microscope [136]

3.3.3 Fourier Transform Infrared Spectroscopy

The characterization method known as Fourier Transform Infrared Spectroscopy (FTIR) provides extensive information on covalent bonding and can demonstrate changes that have occurred in functional groups and elemental chains of polymers. It measures over a large range in a short amount of time and has a high spectral resolution. The FTIR measurements of the membrane samples were performed using a 100 PerkinElmer, MID-IR FTIR Spectrum analyzer.

The pieces of all membranes were cut and stored in a sample holder. The holding was then installed in the aforementioned apparatus. Transmission mode in 1 cm^{-1} was used in the 500–4000 cm^{-1} wave number range at 25°C. To assure accuracy, three samples of each membrane composition were evaluated.

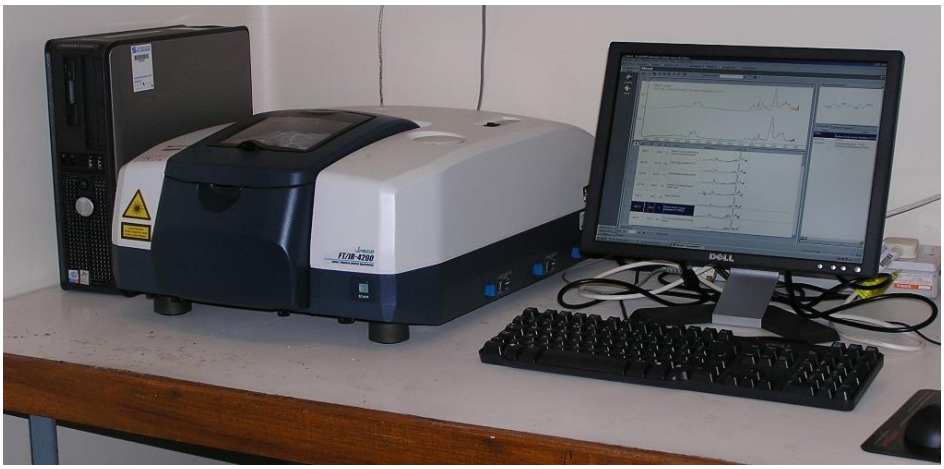


Figure 23: Fourier transform infrared spectroscopy [137]

3.4 Membrane Testing

3.4.1 Porosity of Membrane

The porosity was measured using 1×1 cm^2 area for all formulated membranes. The membrane was oven dried for 1 hr. at 25 ℃ and weighed afterwards. Then the sample was immersed in distilled water for 24 hrs. and weighed again [138]. The porosity (ϵ) of the membrane was then calculated by following equation:

$$\text{porosity } (\epsilon) = \frac{\frac{W_{wet} - W_{dry}}{\delta_w}}{\frac{W_{wet} - W_{dry}}{\delta_w} + \frac{W_{dry}}{\delta_p}} \qquad 3.1$$

Where, W_{wet} and W_{dry} are the weight of wet and dry membrane in grams (g), respectively. δ_w is the density of water in $\frac{g}{cm^3}$ and δ_p is the density of the polymer.

3.4.2 Water Uptake

To determine hydrophilicity, water uptake is particularly important. For the calculation of water uptake, three sets of 1×1 cm^2 membrane area was taken, and oven dried for 1 hr. at 25℃ to remove any trapped moisture and weighed. The samples were then immersed in distilled water for 24 hrs. and weighed again. Then the water uptake was estimated using the subsequent equation [139].

$$water\ uptake\ (\%) = \frac{W_{wet} - W_{dry}}{W_{dry}} \times 100 \qquad 3.2$$

where W_{wet} and W_{dry} are the weight of wet and dry membrane in grams (g), respectively [139].

3.4.3 Water Contact Angle

The angle formed between a liquid droplet and the active top layer surface of a membrane is known as the water contact angle. At the three-phase boundary, liquid molecules generate angles and interact with molecules of solid, liquid, and gas. It is the wetting ability of the polymer helps to determine the hydrophilic or hydrophobic nature of the membrane [140]. If the angle formed between the active top layer surface of membrane and a liquid droplet is less than 90, the membrane is hydrophilic. However, if it is greater than 90 degrees, the membrane is hydrophobic. The test was run with the contact angle system OCA (Data physics, USA). Sessile contact angle was used to assess the static contact angle after cutting the sample membranes into stripes. The distilled water dosage rate was changed to 0.1 L/s with a consistent dosing rate of 0.2 L with the help of the micro syringe. The water droplet was recorded on the membrane surface. The angle was measured on average three times on membrane surface.

3.4.4 Pure Water Flux

The flux of pure water through the membrane is the most typical test that is conducted on a membrane before usage. The dead-end filtration cell HP4750-Sterlitech was used for a hydraulic permeability experiment [141].

The main components of the experimental setup were:

- nitrogen cylinder to maintain the required pressure.
- feed container where the feed was added.
- membrane filtration cell
- membrane piece
- container to collect permeate after membrane filtration.

The feed stream for this experiment was distilled water. The entire system was run for almost 10 minutes to fill the volume of the module and stabilize its flow and pressure. The sample membranes of area 0.00146 m^2 were used and Nitrogen gas was used to maintain 2 bar pressure. To achieve the constant flux, experiments were conducted for 1 hour and

50 minutes at room temperature. Permeate was collected in beaker for every 10 minutes. The pure water flux was calculated by using the following equation [138].

$$j = \frac{V}{A \times T} \qquad 3.3$$

Where, J is the flux, L/m^2 h, T is the time in hours (hr.), A is the total area of the membrane in m^2, and V is the Volume of the permeated water in Liters (L).

The permeability (L/m^{2}hbar) was calculated by the following equation.

$$Permeability = \frac{Flux}{Pressure} \qquad 3.4$$

3.4.5 Mechanical Properties

A mechanical test called tensile strength is used to assess the stress and strain on membrane samples [142]. To determine the ultimate tensile strength of 50 kN, SHIMADZU, AGS-X was used. Using ASTM Standard D-8802-02, a strain rate of 0.5mm/min was maintained for all samples. The strain sate was maintained until the membrane was broken. This method was used to determine the stress and strain of all the samples individually.

3.5 Dialysis Experiment

Dead end stirred batch cells were used to measure the BSA rejection through the formulated membranes. Furthermore, it was utilized to calculate the clearance of urea and creatinine from blood samples.

3.5.1 BSA Rejection

A unit HP4750- Sterlitech with an operative membrane area of 0.00146 m^2 calculated the BSA rejection. BSA solution of 1 mg/mL was prepared in distilled water at room temperature. Experiment was performed at room temperature and at the pressure of 2 bar. Feed stream was the BSA solution and permeate was collected. Stirring at 600 rpm was maintained during the whole experiment for the homogeneity of solution [128]. The experiment lasted for 210 minutes. BSA was detected using spectrophotometer (Shidmazu

UV 1240) at the wavelength of 278 nm. The BSA rejection by the membrane samples was calculated by equation [141].

$$BSA\ \%\ rejection = 1 - \frac{C_p}{C_r} \times 100 \qquad 3.5$$

Where, Cp is the solution concentration (gL^{-1}) in the permeate and Cr is the solution concentration (gL^{-1}) in retentate.

3.5.2 Urea and Creatinine Clearance

Toxin clearance was used to determine the effectiveness and performance of the hemodialysis membrane. For the determination of membrane performance, 1 mg/mL urea and creatinine solutions were prepared in distilled water at 25℃, which is almost equal to the toxin concentration level of kidney failure patients [143]. Experiment was performed at room temperature and at the pressure of 2 bar. Stirring at 600 rpm was maintained during the whole experiment to avoid concentration polarization. The experiment was performed for 210 minutes for toxin removal and readings were taken after every 15 mins. For both urea and creatinine, the UV spectrophotometer (Shidmazu UV 1240) at wavelength 190 nm was used to measure the variation in concentration at permeate and retentate side. The clearance was determined using the following equation [116].

$$Clearance\ \% = \frac{C_i - C_f}{C_i} \times 100 \qquad 3.6$$

Where, C_i is the initial concentration (gL^{-1}) and C_f is the final concentration (gL^{-1}).

3.6 Biocompatibility Test

3.6.1 Thrombus Formation

In this experiment, 1×1 cm^2 membrane samples were submerged in 1.5 mL of blood and heated at 37 °C in an incubator with 5% CO_2. The phosphate buffer solution (PBS) was then used to wash the samples. After that, graded ethanol was used to dehydrate the samples. Next, the degree of thrombus development was calculated [144].

$$DT = \frac{W_f - W_i}{W_i} \times 100 \quad (3.7)$$

Where, DT is Degree of thrombus, W_f is the weight of the blood coagulated membranes in mg and W_i is the initial weight of the dried membrane.

3.6.2 Platelet Adhesion

Platelet Rich plasma was extracted from the blood. Membrane samples measuring 1 x 1 cm^2 were placed on the 12-well plate after being washed with phosphate buffer solution (PBS). Each sample had 100 L PRP, which was then kept at 37°C for an hour. The membrane samples were then twice rinsed in PBS to eliminate unstable platelets. For 24 hours, 2.5 wt.% of glutaraldehyde was added to the mixture to adhere the adsorbed platelets. The samples were then dried with graded ethanol over the course of 10 minutes. SEM was used to observe platelet adhesion on membranes [145].

3.6.3 Hemolysis Ratio

To perform this test three sets of each membrane of area 1×1 cm^2 were taken. The samples were washed with deionized water thrice. Then 0.9 wt.% NaCl solution was used to wash the samples. Then incubated at 37℃ for 30 mins in water bath. 200µL of human blood was added in the solution and again kept in incubation for 1 hr. at 37℃. After the incubation, the samples were centrifuged at 1500 rpm for 10 mins to separate the red blood cells (RBCs). The released RBCs were measured through UV spectrophotometry in the supernatant at 545 nm wavelength. In this process the 0.9 wt. % NaCl is negative control and pure water is positive control. The hemolysis ratio was calculated through the following equation [145]

$$Hemolysis\ ratio\ \% = \frac{AS - AN}{AP - AN} \times 100 \quad (3.8)$$

Here AS is the absorbance of the sample, AN is the absorbance of negative control and AP is for the positive control.

3.6.4 Plasma Recalcification t\Time

This test was carried out by centrifuging 10 mL of anticoagulated blood for 15 minutes at 3000 rpm in a centrifuge tube. As supernatant, plasma poor plasma (PPP) was used. In a 12-well plate, 1×1 cm^2 sample area was taken, and 200 L of PPP was dropped into it. The culture plate should next be incubated for 10 minutes at 37°C in a water bath. 100 L of the prepared 0.025 mol/L $CaCl_2$ aqueous solution was then added to the sample. The creation of fibrin thread was used to calculate the time. For each sample, the experiment was run three times, and the average value was calculated [146].

Chapter:4

Results and Discussions

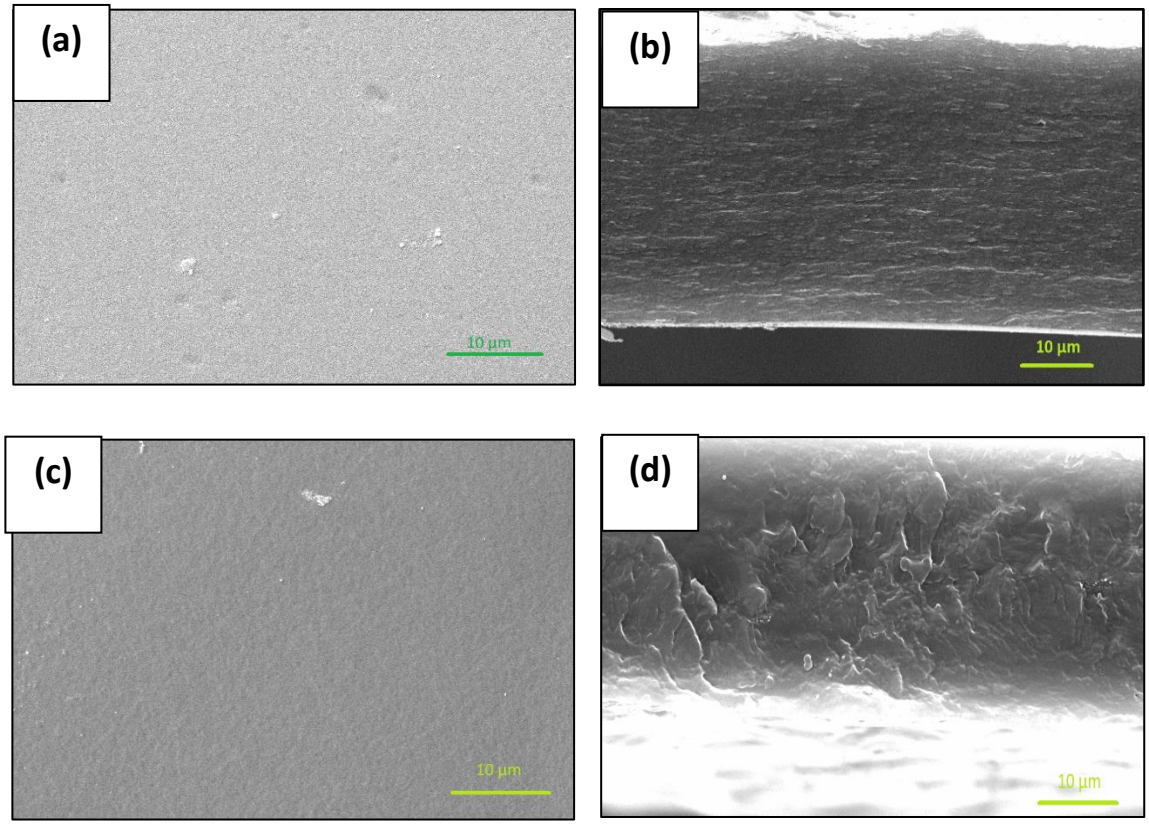
4 Results

4.1 Morphology and Surface Chemistry of Membrane

SEM is the analytical technique that explains the surface and cross-sectional morphology of the membrane. Figure 24 shows the surface morphology as well as the cross-sectional image of both membranes. In Figure 24 (a) the top active layer of Nexar-IPA+Tol having 2 wt.% Nexar^{TM} is shown. The membrane exhibits a regular surface without pores [147]. The cross-sectional image of the same membrane (figure 24 (b)) illustrates the internal dense structure of the membrane. The width of membrane is measured 23.12 ± 0.17µm. The width is 18.05 ± 0.13 µm (figure 24 (d)) in the case of Nexar-THF membrane having 2 wt.% Nexar^{TM}. The variation in width is because of the ordered structured arrangement formed by polar solvent. The surface morphology of Nexar-THF membrane as shown by SEM in figure (c) is almost same as that of Nexar-IPA+Tol membrane. The Nexar^{TM} polymer employes slow and controlled evaporation process so, the membranes formed are dense. The only difference in the membranes is the formation of assembled organized channels in the presence of polar THF solvent. These channels help in the clearance of urea and creatinine. In the case of non-polar solvent blend, IPA+Tol, these channels are highly unorganized and causes hinderance in the clearance of uremic toxins. However, SEM cannot capture the assembly of the membranes. Therefore, the membrane under SEM appears to be dense and smooth. The dense membranes are previously employed in hemodialysis, having no visible pores or channels [147, 148]. As both membrane's surfaces are dense, so all the solute transportation will be because of diffusion.

The AFM explains the membrane surface pattern depicted in figure 24 (e) and (f). The surface roughness of all sample was investigated and measured using an AFM in tapping mode having frequency range 76–263 kHz. The scan size of the membranes was 1 by 1 µm, 3D AFM photos of the top surfaces of all the membranes were acquired as 3D images. The 3D images can facilitate to show the roughness of the surface is. On the surface topography, the light parts defined the heights while the dark regions revealed depths

[149]. The AFM image of Nexar-IPA+Tol shows the surface if smooth (figure 24 (e)). The surface roughness is 3.245±0.265. The BCP has irregular arrangement assembly with non-polar solvent such as IPA+Tol blend [150]. In the case of THF prepared membrane, the AFM image (figure 24 (f)) shows orderly arrangement of BCP. The membrane has roughness 5.5± 0.4 in case of polar solvent (THF). The increase in the roughness of the membrane is due to random arrangement of the membrane. The unorganized surface morphology increases the roughness of the membrane and causes hindrance in the clearance of the uremic toxins. However, on the other hand the self-assembly arrangement of the BCP facilities the transportation process [151]. Similar material was used before for dehumidification with similar membrane morphology [152].The surface roughness contributes towards the platelet adsorption as less rough surface adsorbs less platelets. As the IPA+Tol membrane surface is rough due to the randomly arranged surface morphology. Therefore, the non-polar membrane is more prone to fouling due to roughness.



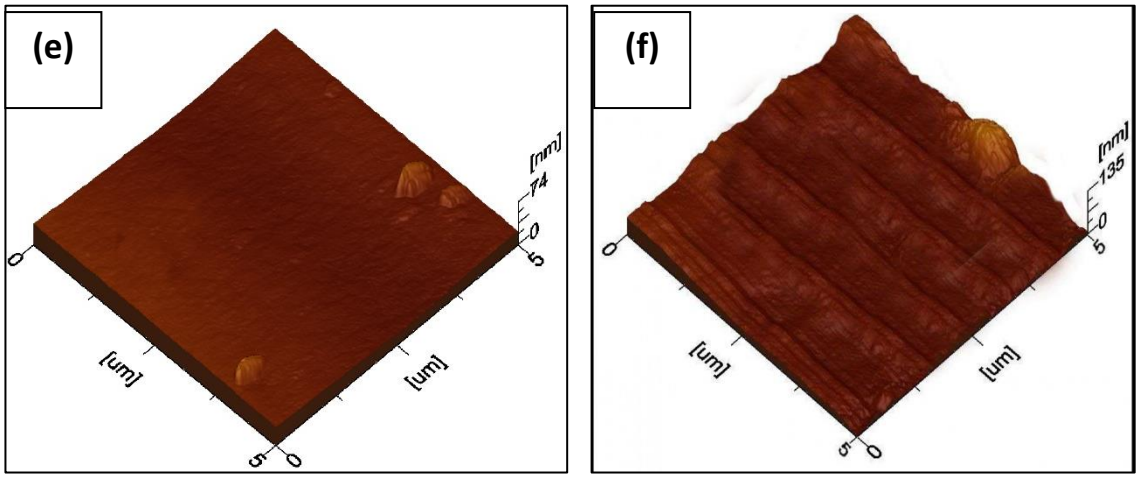


Figure 24: (a) SEM image of IPA+Tol membrane, (b) Thickness of IPA+Tol membrane, (c) SEM image of THF membrane, (d) Thickness of Nexar-THF membrane, (e) AFM image of IPA+Tol membrane, and (f) AFM image of Nexar-THF membrane.

FTIR is a key tool for qualitative investigation of chemical structures on polymeric membrane surfaces. Figure 25 shows the FTIR spectrum of both membranes. The spectrum shows strong peak in the range of 1026.59-1241.80 cm^{-1} in both membranes resulting from the symmetrical and asymmetrical stretching of SO_3^-. This band confirms the Nexar^{TM} presence in the membranes. C-S styrene band can be observed in the range of 586.12-836.45 cm^{-1} [153]. The medium peak of C-H bending for aromatic compound is observed at 1635.62 and 1656.30 cm^{-1} in Nexar-THF and Nexar-IPA+Tol blend membrane respectively. At 2921.78 and 2920.26 cm^{-1} C-H bond peak is observed in THF and Nexar-IPA+Tol blend membrane respectively [154]. The ethylene (C=C) presence in the BCP is confirmed by the small peak in the range of 2200.31- 2368.92 cm^{-1} in both membranes. A sharp peak of OH at 3426.11 cm^{-1} in case of THF and at 3429.43 for Nexar-IPA+Tol membrane is observed. The sulfonic group in the BCP has attached water molecules and some moisture from the environment is responsible for this peak. The water uptake of BCP is also high due to these attached water molecules. This shows that Nexar^{TM} is hydrophilic, the characteristic required in biocompatibility and also responsible for antifouling of membrane [139, 155].

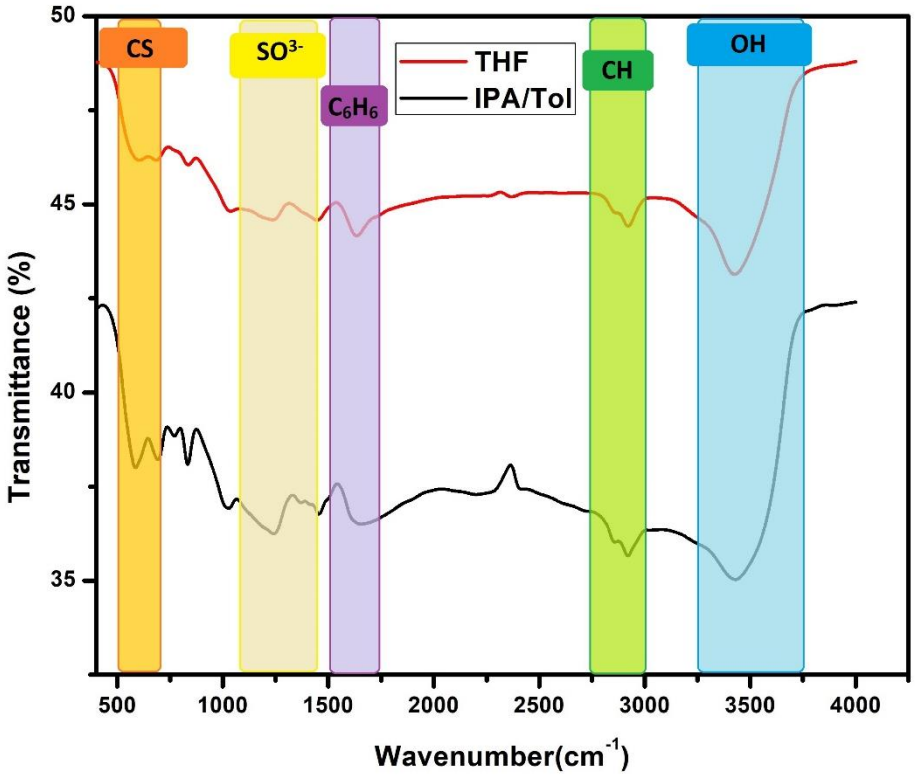


Figure 25: FTIR Spectrum of Nexar-THF membrane and Nexar-IPA+Tol membrane

4.2 Water Uptake and Water Contact Angle

Water contact angle and water uptake both help in determining the nature of the membrane. Either the membrane is hydrophilic or hydrophobic, depending on the amount of water absorbed by the membrane. The increase in the water uptake and decrease in the water contact angle indicates the hydrophilic nature of the membrane. The contact angle less than 90˚ shows the hydrophilic nature of the membrane [140]. Figure 26 shows the comparison of water uptake and contact angle of the membrane and the angle measured on the active layer of the membrane surface. Nexar-IPA+Tol membrane has dense surface morphology is responsible for the angle of 91.45± 1.05°. The increment in the contact angle in the case of non-polar solvent is because of random arrangement of the polymer and the compactness of the membrane. However, the water uptake is less due to this arrangement. The hydrophobic sides of the BCP are in contact with water in this arrangement, hence decreases the water uptake for Nexar-IPA+Tol membrane. These properties make this membrane less promising for hemodialysis process. In the case of polar solvent, THF membrane, the surface contact angle formed is 74.3 ± 0.6°. The

contact angle results shows the Nexar-THF membrane is hydrophilic [156]. The water uptake of the membrane (figure 26) increases as the hydrophilic block sulfonated styrene creates hydrophilic water selective organized channels in the presence of polar solvent (THF). Figures 26 justify the hydrophilic behavior of the THF membrane, that is the main requirement for the hemodialysis process. The hydrophilic membranes exhibit the best biocompatible results [118]. The Nexar-THF membrane is more hydrophilic than the Nexar-IPA+Tol membrane due to the self-assembled organized arrangement, that also contributes toward the contact angle measurement.

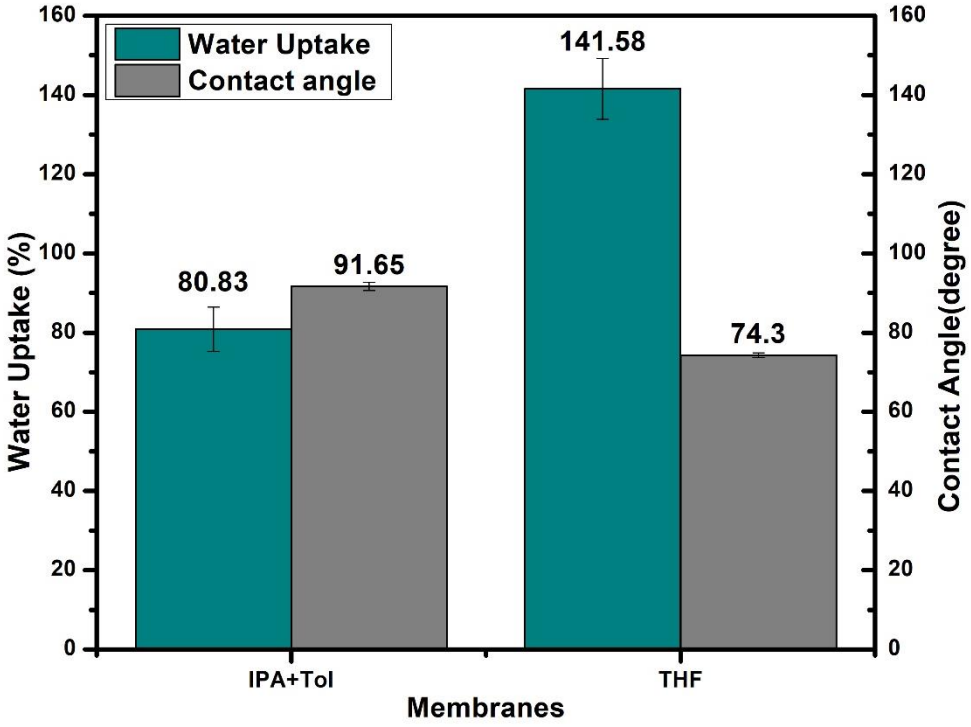


Figure 26: Water uptake and contact angle measurement of the membranes

The Nexar™ (BCP) exhibits unique self-assembling behavior. The morphology of the BCP is dependent on the choice of the solvent [157]. As mentioned before Nexar™ is an amphiphilic BCP. The non-polar solvent, IPA+Tol blend, creates randomly arranged morphology, the hydrophobic end block surrounds the hydrophilic middle block and creates hydrophobic membrane. In the case of the THF solvent, polar, the morphology of the membrane alters completely. The hydrophilic middle block surrounds the hydrophobic end blocks and creates water selective channels as shown in figure 24 (f). These channels are responsible for the hydrophilic nature of the membrane as well as the increase in the

water uptake. The increase in water uptake and decrease in water contact angle confirmsthe formation of hydrophilic water selective organized channels. This increase in water uptake corresponds with the clearance ratio of urea and creatinine [152].

4.3 Effect of Mechanical Strength of Membranes on Hydrophilicity

During the dialysis process the membrane must be able to withstand the applied pressure. The membrane's tensile strength and elongation break should be according to the supplied pressure inside the dialyzer. Figure 27 shows the stress and strain of the membranes. The stress of Nexar-THF membrane is less as compared to IPA+Tol membrane. However, the strain of both the membranes are almost similar. The hydrophilicity of the membranes results in the decrease of mechanical properties [158]. As Nexar-THF membrane is more hydrophilic the mechanical properties of the membrane decrease.

Polyether sulfone membrane has generally the stress of 3.31 ± 0.45 and strain of 3.3 ± 0.007 and this stress over strain ratio is doubled by the incorporation of graphene oxide [148]. The CA/PVA blend membrane has comparatively low mechanical strength depending on the amount of PVA added [159]. The hemodialysis setup runs at very low pressure here stress over strain ratio has less significance.

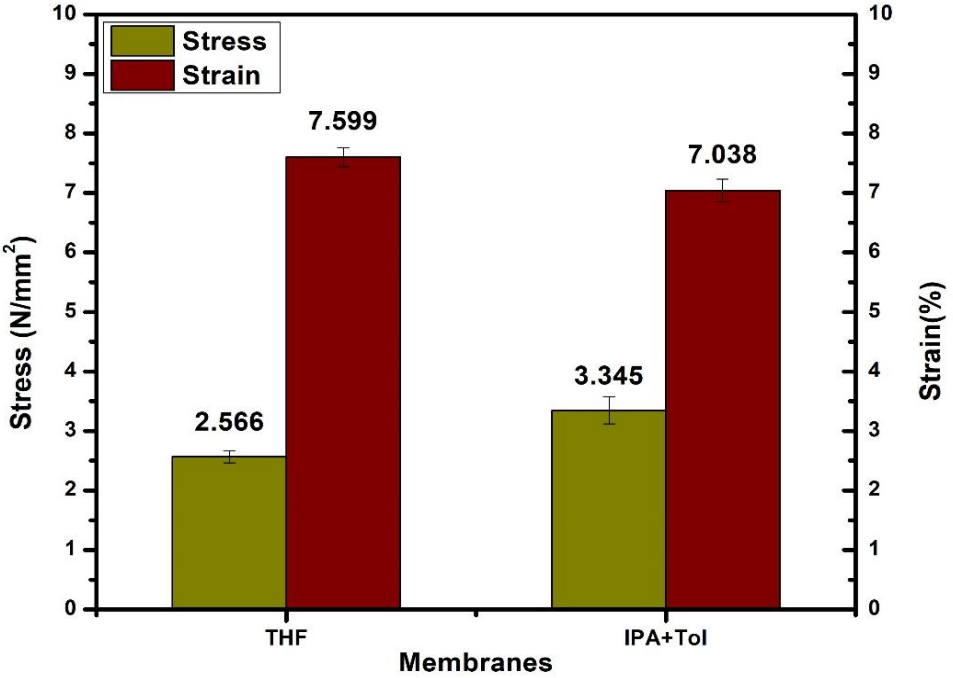
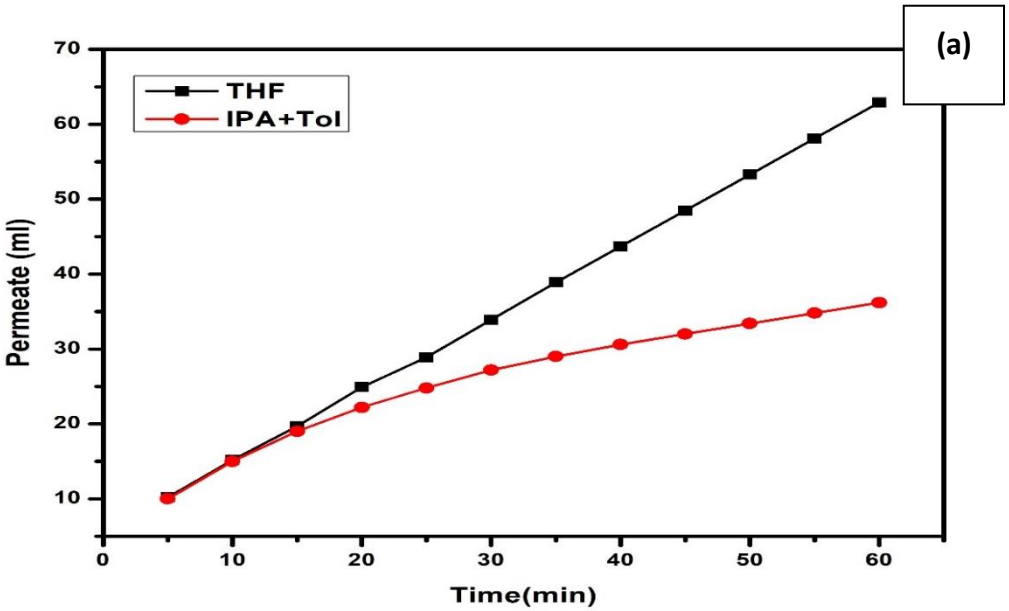


Figure 27: Tensile Stress and Strain of the membranes

4.4 Effect Of Membrane Morphology on Flux

The efficiency of the membranes can be evaluated by pure water permeability test. The deionized water was used as the solvent on both membranes to understand the behavior of the membranes (figure 28(a)). After that, the flux was calculated from the permeate and the graph was plated as figure 28(b). The permeation and flux both increases in case of Nexar-THF membrane because of the organized structured pathway [160]. The following graphs show permeate and flux over a period of 1 hr. The flux and permeate was measured after every 15 mins at constant pressure of 2 bars. As the time proceeds the permeate increases [161]. The permeate in case of Nexar-THF membrane is more as compared to Nexar-IPA+Tol membrane because of the hydrophilic nature of former and the organized water channel also facilitates the permeation rate [152, 162]. As the permeate increases the flux decreases and eventually became constant. The water flux is 24.79 $\pm$ 2 L/m^{2}h for Nexar-IPA+Tol membrane and that is 43.08 $\pm$ 1.26 L/m^{2}h for THF membrane. The decrease in flux is sharper in Nexar-IPA+Tol membrane as compared to the THF membrane. This decrease is because of the fouling of the membrane as the membrane is hydrophobic and more prone to fouling. The dense surface and random morphology of the non-polar membrane is also responsible for the decrease in the flux [159]. For ideal hemodialysis moderate water flux is favorable, as the removal of excess or wastewater is required only. The moderate flux is obtained from the THF membrane, making it favorable for hemodialysis [163, 164].



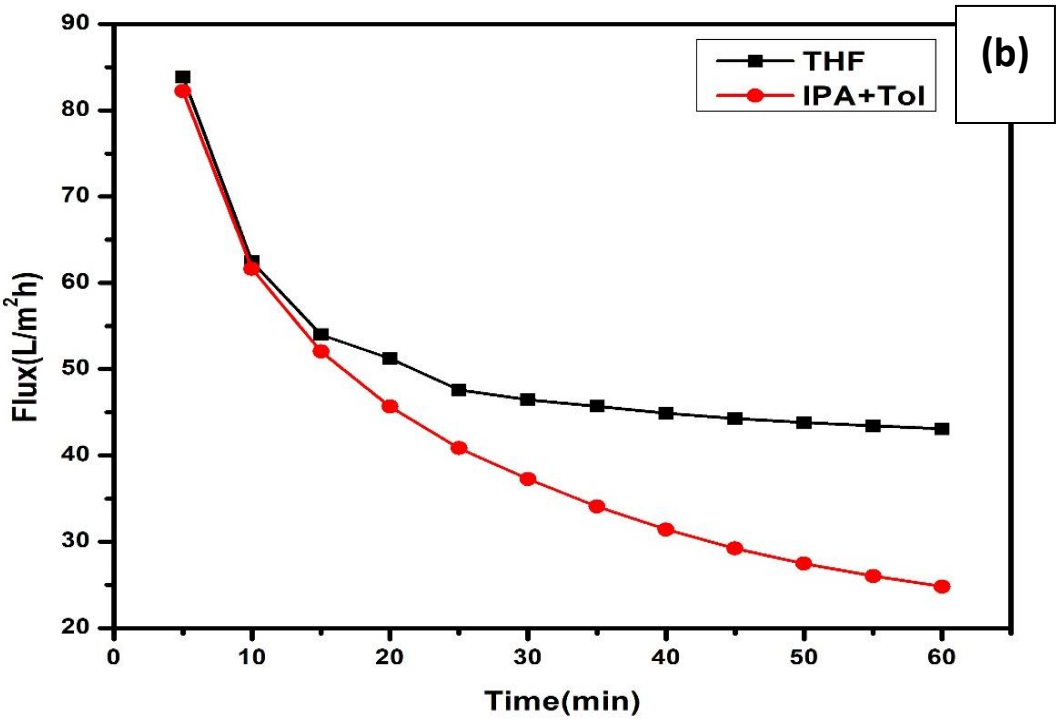


Figure 28: (a) Permeate vs time (b) flux vs time graph for both membranes

4.5 Dialysis Performance

4.5.1 Urea and Creatinine Clearance

Nexar^{TM} membranes are subjected to hemodialysis test performed on dead end filtration cells. The solution of urea and creatinine were prepared and used as a mimic of blood. The hemodialysis membrane must remove 60% of the uremic toxins [165]. The urea and creatinine clearance for the Nexar-IPA+Tol membrane is 87.5 $\pm$ 0.87 % and 67$\pm$ 1.2% respectively. The maximum clearance for urea and creatinine is achieved by Nexar-THF membrane, 89.2 $\pm$ 1.1 % and 97 $\pm$ 0.96% respectively. The main reason behind the high clearance ratio is more water uptake. The increase in water uptake also increases the clearance ratio [166]. The polar membrane also has well defined, organized, and structured channels, that passes the uremic toxins easily [167]. This orderly structure is absent in the non-polar membrane. Hence decreasing the water uptake and eventually lowering the filtration rate. Figure 29 shows that the Nexar-THF membrane fulfils the clearance requirements for the hemodialysis.

Previously, block co-polymers PES-b-PEG were employed in hemodialysis process. The clearance of urea was achieved up to 69.9% [128]. CA is a commonly used hemodialysis membrane polymer. Urea clearance of 93% can be achieved by the incorporation of PEG in CA membranes [159].

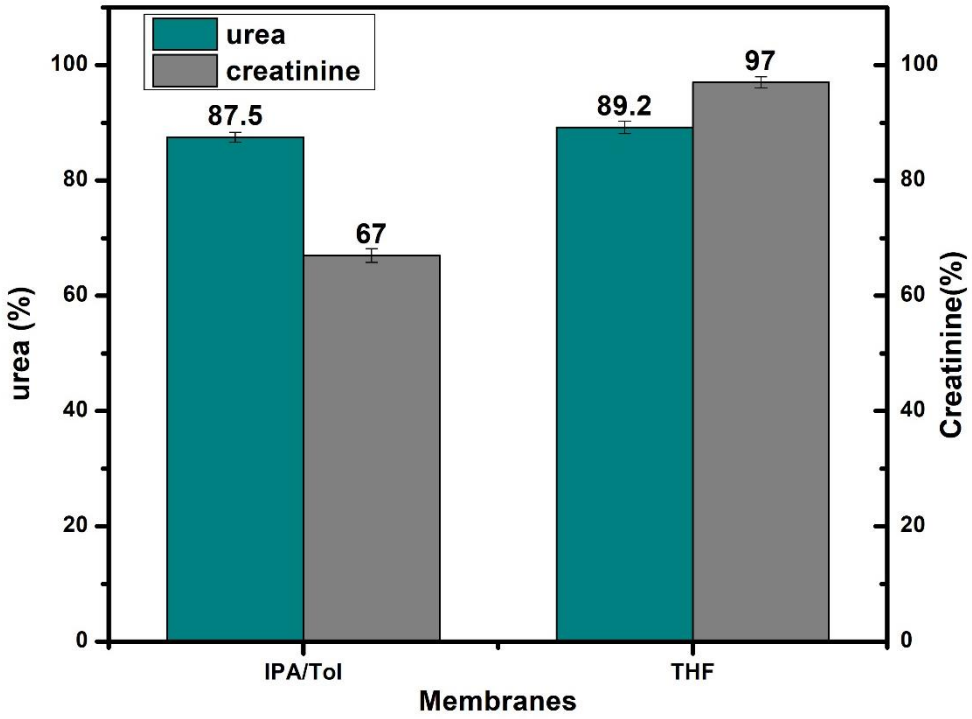


Figure 29: Clearance ratio for uremic toxins of Nexar membranes

4.5.2 BSA Rejection

Albumin is the required protein in the human body and must not be lost during the hemodialysis process. When the patient goes through dialysis treatment Albumin loss occurs. The hemodialysis is considered best if the Albumin rejection should not be less than 75% [168]. This albumin loss can be controlled by altering the morphology of the membrane [164, 168]. Figure 30 shows that the BSA rejection by the Nexar-IPA+Tol membrane is 72.8 $\pm$ 1.73%, the rejection rate lies below the favorable range due to the random arrangement and dense surface. As the Nexar-IPA+Tol membrane is hydrophobic and hydrophobic membranes act as an active site for the adhesion of protein [138]. However, Nexar-THF membrane has rejection of 79$\pm$1.86%. the membrane is hydrophilic

rejecting the protein and hence the loss is minimum and making the membrane best fit for hemodialysis [169].

Hydrophilic membranes reject BSA the most. Polymeric membrane of PSF/CA have the rejection compatibility the most and rejected 79% of protein [170]. Polymers like polyether sulfone/ sulfonated poly ether sulfone rejected BSA up to 78% [171]. The BSA rejection zeolite was added in PSF/PEG membrane, the rejection rate was improved to 93.5% [163].

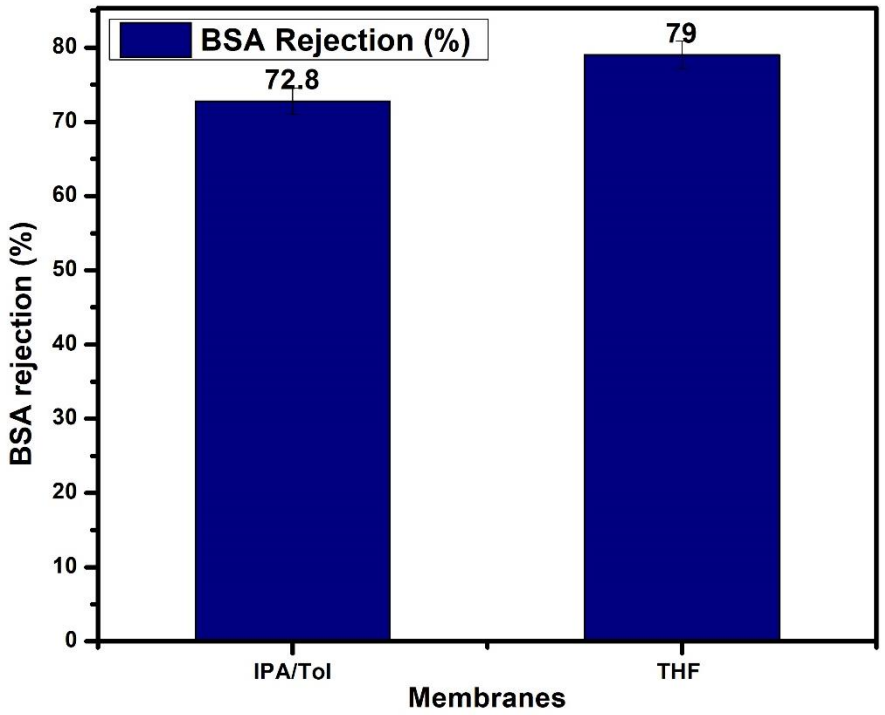


Figure 30: BSA rejection for Nexar-IPA+Tol and Nexar-THF membrane

4.6 Biocompatibility Study

The objective of the research is to reduce the platelet adhesion on the membrane. The platelet activation causes fibrinogen adhesion on the membrane surface. The adhesion causes fouling on the membrane surface and affects the clearance efficiency of the membrane. Protein adhesion can be observed through SEM images shown in figure 32. The large amount of protein adheres to the hydrophobic site and causes fouling [144]. The Nexar-IPA+Tol membrane is hydrophobic, it's more prone to platelet activation and eventually protein adhesion (Figure 31a). However, in the Nexar-THF membrane the ether

bond coupled with the water molecule through hydrogen bonding and forms a hydration layer around the membrane surface, this act as physical barrier for the bio-component to adhere the membrane surface (Figure 31b) [145].

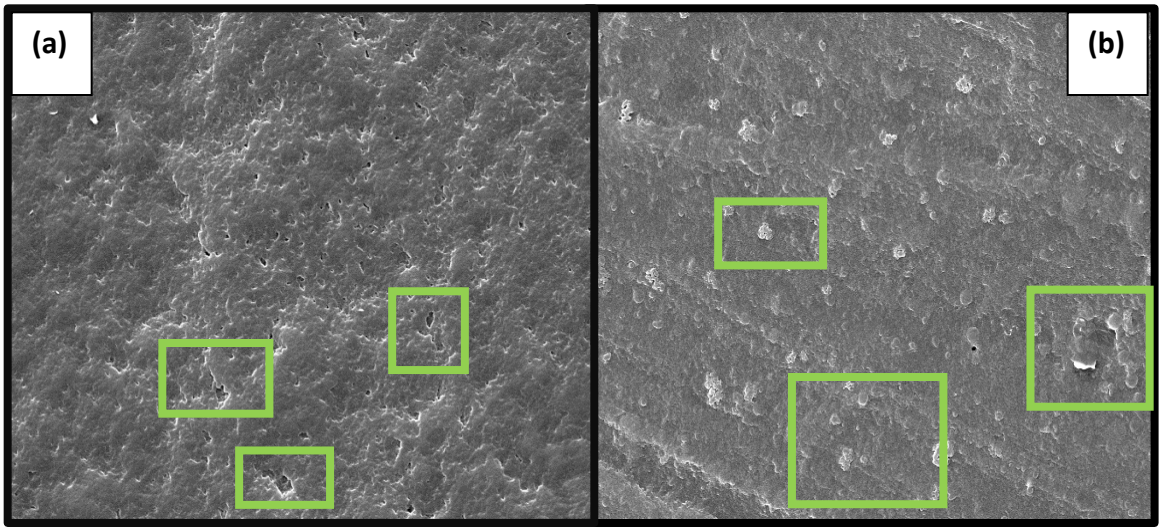


Figure 31: Platelet activation on (a) Nexar-THF and (b) Nexar-IPA+Tol

When the membrane interacts with the blood, erythrocytes encounter the membrane and can burst to let hemoglobin out. This is called hemolysis. Hemolysis ratio is the calculation of the breakdown of red blood cells when encountered the foreign material. A material is safe and considered biomaterial is the hemolysis ratio is less than 5% [172]. The hydrophilic nature and the ether group makes the Nexar-THF membrane safer to use as hemodialysis membrane [173]. The ratio is recorded as 3.7 ± 0.02. Figure 32 shows the hemolysis ratio in both membranes.

The blood platelet buildup can promote thrombus development and maintain hemostasis. The thrombus formation was evaluated by using the whole blood [144]. Hydrophobicity and the water contact angle effects the hemostasis. As it is clear from figures 26 Nexar-IPA+Tol membrane is hydrophobic due to this nature of the membrane the thrombus formation is of 2.07 ± 0.012 while that of Nexar-THF is 1.6 ± 0.029. The high thrombus formation leads to high platelet aggregation on the membrane surface. The polar solvent creates hydrophilic membrane that gives better biocompatibility results [174]. The presence of hydrophilic hydroxyl group also benefits the Nexar-THF membrane.

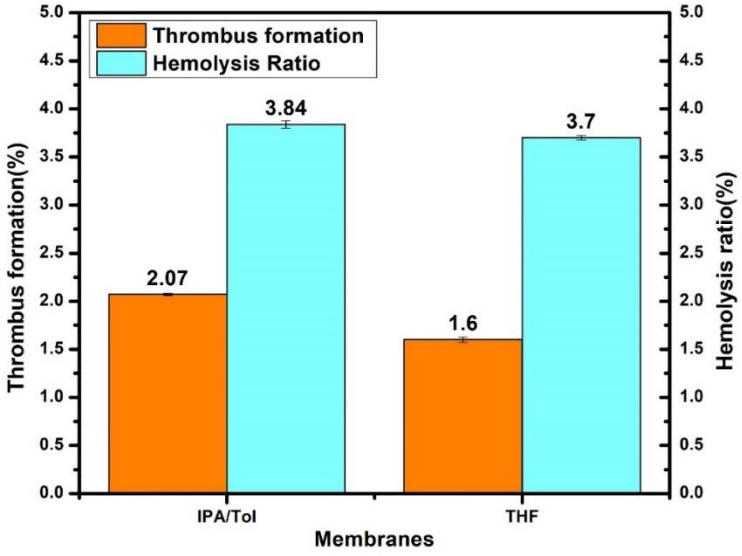


Figure 32: Hemolysis ratio and thrombus formation of the Nexar membrane

To determine the absence or presence of clotting factor and the time plasma recalcification time is measured[146]. Fibrous proteins that are cross-linked together by the presence of Ca^{-2} and activated blood coagulation factor VII in the blood cause thrombus to develop.

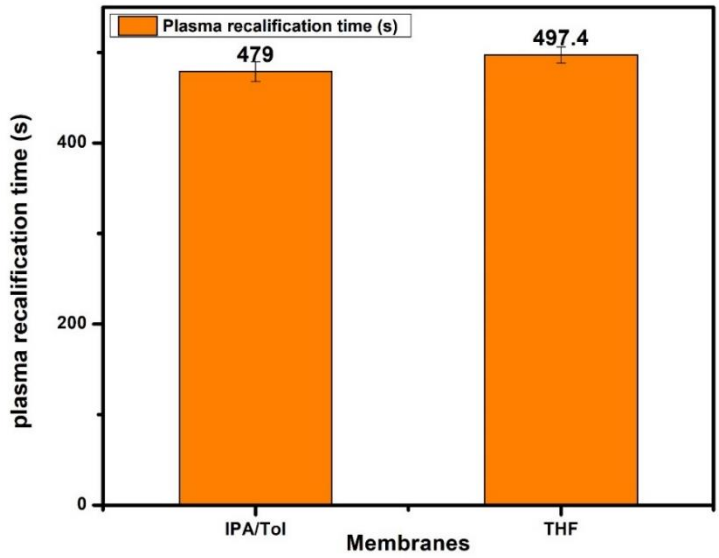


Figure 33: Plasma recalcification time for Nexar membranes

The time at which thrombus forms is influenced by hydrophilicity and the presence of hydroxyl and carboxyl groups [175]. Both the membranes exhibit almost similar behavior when comes to clotting time. This is because the basic polymer is the same and displays

the same characteristics. The hydrophilicity of Nexar-THF membrane is responsible for the slight increase in clothing time (figure 33).

Table 9: Comparison of current work with different polymers

Membrane material	BSA rejection	Urea clearance	Creatinine clearance	Hemolysis ratio (%)	Thrombus formation (%)	Plasma recalcification time (s)	Reference
PVDF / PMWCNTs	91 %	-	-	0.59	-	-	[176]
PSF-b-PEG	93%	69.9%	-	0.48	-	409	[128]
CA-PVA	96%	93%	-	3.2	5	300	[159]
PES/SPES	78%	85%	-	-	-	-	[171]
CA/HA-15	**93 %**	**42 %**	-	-	-	-	[166]
P (VP-VTES-GMA)	**9 ml/min**	**85 ml/min**	**79 ml/min**	-	-	-	[177]
PLA /PLA−PHEMA	**0.31 ml/min**	**0.7 ml/min**	**0.7 ml/min**	-	-	-	[122]
PSF-PEG (zeolite additive)	**93.5 %**	**89 %**	**-**	**0.46**	**5.06**	**392**	[163]
PES/CA/IZC	**79 %**	**-**	**74.9 %**	**-**	**-**	**-**	[170]
Nexar-THF	**79 %**	**89.2 %**	**97 %**	**3.7**	**1.6**	**497.4**	Present work

Conclusion

The main objective of this research was to fabricate a membrane that is biocompatible and exhibits good hemodialysis properties. The hemodialysis performance is majorly investigated by analyzing the membrane's capability to remove uremic toxins and to reject the BSA from the blood. Polymer morphology is dependent on the choice of solvent, so two different solvents were used to study the morphology alteration. First non-polar solvents blends were used to fabricate the membrane (Nexar-IPA+Tol). The membrane was characterized by SEM, AFM and FTIR. The membrane morphology was dense and has disordered morphology. This morphology affects the clearance rate of urea and creatinine, the BSA rejection, and the flux. The membrane also exhibits hydrophobic properties that are not favorable in terms of biocompatibility. The hydrophobic nature of the membrane acts as the site for the platelet activation and causes membrane fouling. Hence the clearance rate is affected. The Flux, urea clearance, creatinine clearance, BSA rejection of the non-polar membrane is 24.79 $\pm$ 2 L/m^{2}h, 87.5 $\pm$ 0.87 %, 67$\pm$ 1.2%, 72.8 $\pm$ 1.73% respectively. On the other hand, the polar solvent alters morphology completely. The membrane Nexar-THF exhibits orderly structured, and self-assembled water channels. These water channels are very effective for the clearance of urea and creatinine as well as the rejection of the BSA. The high flux and water uptake clearly shows the hydrophilic nature of the membrane. This hydrophilicity is responsible for the favorable biocompatibility results. The low thrombus formation and hemolysis ratio makes it fit for hemodialysis. The hydrophilicity makes the membranes less attractive for the platelets and eventually less prone to fouling. The Flux, urea clearance, creatinine clearance, BSA rejection of the polar membrane is 43.08 $\pm$ 1.26 L/m^{2}h, 89.2 $\pm$ 1.1 %, 97 $\pm$ 0.96%, 79$\pm$1.86% respectively. Concludes that, the Nexar-THF membrane is better for hemodialysis because of the highly organized water channels facilitates the clearance process and makes it biocompatible majorly due to hydrophilicity.

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