Fabrication and Characterization of Cellulose Acetate/ Polyethylene Glycol/Polyvinyl Alcohol Blend Membrane for BSA Rejection and Uremic Toxins Clearance

By

Ofaira Azhar

School of Chemical and Materials Engineering

National University of Sciences and Technology

2021

Fabrication and Characterization of Cellulose Acetate/Polyethylene Glycol /Polyvinyl Alcohol Blend Membrane for BSA Rejection and Uremic Toxins Clearance

OFAIRA AZHAR

Registration Number: 00000274597

A thesis submitted in partial fulfillment of the requirements for the degree of

MS Chemical Engineering

Thesis Supervisor: Dr. Zaib Jahan

School of Chemical and Materials Engineering (SCME)

National University of Sciences and Technology (NUST)

H-12 Islamabad, Pakistan

April,2021

THESIS ACCEPTANCE CERTIFICATE

Certified that final copy of MS thesis written by **Ofaira Azhar** Registration No 00000274597), of School of Chemical & Materials Engineering (SCME) has been vetted by undersigned, found complete in all respects as per NUST Statues/Regulations, is free of plagiarism. errors. and mistakes and is accepted as partial fulfillment for award of MS degree. It is further certified that necessary amendments as pointed out GEC members of the scholar have also been Incorporated in the said thesis.

Signature:_____

Name of Supervisor: **Dr. Zaib Jahan**

Date: _____

Signature (HOD):_____

Date:_____

Signature(Dean/Principal): _____

Date: _____

Form TH-1

(Must be type written)

National University of Sciences & Technology (NUST)

MASTER'S THESIS WORK

Formulation of Guidance and Examination Committee (GEC)

Name: OFAIRA AZHAR

NUST Regn No: 274597

Department: Chemical Engineering

Specialization: Chemical Engineering

Credit Hour Completed: (18) 24

CGPA: (3.500) 3.56

Course Work Completed

S/No	Code	Title	Core/Elective	CH	Grade
1	EME 921	Momentum Heat and Mass Transfer	Core	03	B+
2	CHE 843	Separation Processes in ChE	Core	03	B+
3	EME 981	Advance Fuel Technology	Elective	03	A
4	RM 898	Research Methodology	Additional course	02	Q
5	CHE 847	Chemical Kinetics & Reactor Design	Core	03	B
6	CHE 814	Product Technology	Elective	03	B+
7	ESE 911	Carbon Capture & Utilization	Elective	03	B+
8	CHE-848	Gasification Process	Elective	03	A
9	ENE-809	Waste Water Treatment & Design	"		

Date 5/7/2019

Student's Signature Ofaira.

Thesis Committee

1. Name: Dr. Zaib Jahan **(Supervisor)** Signature:
   Department: SCME
2. Name: Dr. Arshad Hussain **(co-supervisor)** Signature:
   Department: SCME
3. Name: Dr. Muhammad Bilal Khan Niazi Signature:
   Department: SCME
4. Name: Dr. Salman Raza Naqvi Signature:
   Department: SCME

Date: 5/7/2019

Signature of Head of Department:

APPROVAL

Date: 5/7/2019

Dean/Principal

Distribution

1x copy to Exam Branch, Main Office NUST

1x copy to PGP Dte, Main Office NUST

1x copy to Exam branch, respective institute

National University of Sciences & Technology (NUST)

FORM TH-4

MASTER'S THESIS WORK

We hereby recommend that the dissertation prepared under our supervision by

Regn No & Name: 00000274597 Ofaira Azhar

Title: **Fabrication & Characterization of Cellulose Acetate/Polyethylene Glycol/Polyvinyl Alcohol Blend Membrane for BSA Rejection and Uremic Toxins Clearance.**

Presented on: **22-04-2021** at: **1400 hrs in SCME Seminar Hall**

Be accepted in partial fulfillment of the requirements for the award of Master of Science degree in **Chemical Engineering**.

Guidance & Examination Committee Members

Name: **Dr M. Bilal Khan Niazi** Signature:

Name: **Dr Salman Raza Naqvi** Signature:

Supervisor's Name: **Dr Zaib Jahan** Signature:

Dated: 27/4/2021

Head of Department
Date 30/4/21

Dean/Principal
Date 3-5-2021

Dedication

Dedicated to my extraordinary parents and adored siblings whose marvelous support and cooperation led me to this wonderful accomplishment.

Acknowledgements

I am thankful to Allah Almighty who guided me entire this work. For every step and new thought which Your frame-up in my mind to ameliorate it. Indeed, without your priceless help and guidance I could have done nothing. Whosoever helped me throughout the course of my thesis, whether my parents or any other individual was Your will, so indeed none be worthy of praise but You.

I am copiously thankful to my exceptional parents who raised me and continued to support me throughout my Masters.

I would also like to express special thanks to my supervisor Dr. Zaib Jahan for her help throughout my thesis. Who guided and encouraged patronage that I will complete the task of writing and arrangement of the project work well in time.

I would also like to pay special thanks to Dr. Bilal Khan Niazi for his support and cooperation. Each time I got stuck in something, he finds out the solution. I appreciate their patience and guidance throughout the whole thesis.

I would also like to thank Dr. Salman Raza Naqvi for being on my thesis guidance and evaluation committee. I am also thankful to Dr. Salik Kakar and Dr. Tahir Baig, for their support and cooperation.

Finally, I would like to express my gratitude to all the individuals who have rendered valuable assistance to my study.

Abstract

For the therapy of end-stage renal disease (ESRD), hemodialysis is a widely used extracorporeal technique. Hemodialysis considered as superior technique for the separation of protein and uremic toxins based on their molecular weights using semi-permeable membranes. It is hard to modernize anticoagulant dialyzers for anticoagulant exempt hemodialysis. So, we fabricate an eco-friendly high-performance biocompatible membrane. Cellulose Acetate (CA) hemodialysis membrane with enhanced filtration capability and hemocompatibility was developed by using Polyvinyl Alcohol (PVA) and Polyethylene Glycol (PEG) as the blending additives. By blending different ratios of PVA in the CA-PEG, the phase inversion technique was used to cast the membranes, and separation was done by dead-end filtration cell. The synthesized membranes were described in terms of chemical structure using Fourier Transform Infrared Spectroscopy (FTIR) and morphology by Scanning Electron Microscopy (SEM), Atomic Force Microscopy (AFM), pure water flux, solute permeation, and protein retention. Biocompatibility of the membranes was tested by the platelet adherence, hemolysis ratio, thrombus formation, and plasma recalcification time. SEM images exposed that the CA-PVA membrane has a uniform porous structure. 42.484 Lm-2 h-1 is the maximum pure water flux obtained. The CA-PVA rejected up to 95% of bovine serum albumin (BSA). A similar membrane separated 93% of urea and 89% of creatinine. Platelet adhesion and hemolysis ratio of casted membranes were less than the pure CA membrane. Increased clotting time and less thrombus formation on the membrane's surface showed that the fabricated membrane is biocompatible. Depending on such results, it can be concluded that the CA-PVA membrane is well biocompatible can be used for hemodialysis membranes.

Key Words: *Hemodialysis membrane, Cellulose Acetate, Polyvinyl Alcohol, Polyethylene glycol, Urea and Creatinine clearance, BSA rejection, Biocompatibility.*

Table of Contents

List of Figures

List of Tables

List of Abbreviations

CRF	Chronic Renal Failure
AKI	Acute Kidney Injury
HFD	High Flux Dialysis
CA	Cellulose Acetate
PEG	Polyethylene Glycol
PVA	Polyvinyl Alcohol
SEM	Scanning Electron Microscopy
FTIR	Fourier Transform Infrared Spectroscopy
PWP	Pure Water Permeation
AFM	Atomic Force Microscopy
MWCNT	Multi Wall Carbon Nano Tubes
CBT	Coagulation Bath Temperature
PRP	Platelet Rich Plasma
PBS	Phosphate buffer solution
PPP	Plasma poor plasma
GFR	Glomerulus filtration rate

CHAPTER 1

Introduction

1.1 kidney

Kidney is an important organ of the body that control waste disposal and keeps the balance of water and salt through osmoregulation. Kidney failure occurs when glomerular filtration rate is lower than 16 $mL.min^{-1}$ or its not screening toxins properly [1]. It is important to take balance diet and drink the right portion of water to reduce the uremic toxins and keep the kidney healthy. Hypertension, diabetes, infections, and abundant usage of medications are the main causes for the renal failure [2].

Dialysis is the treatment for chronic kidney failure requires artificial kidney. For renal patient it is a life support therapy. To separate excess fluid, salt, and uremic toxins from the patient's blood a dialysis machine is used [3]. It is the only successful therapy, which is use as substitution of the organ with the help of the modern dialysis techniques.

1.2 Kidney structure and function

Humans have two bean shaped kidneys with approximately weight 125-170 g in male and 115-155 g in women. Tough fibrous surrounds each renal capsule. Nephron is the main functional unit of kidney and each kidney consist of nearly one million of them. Glomerulus is the main part of the nephron, surrounded by network of capillaries called Bowman's capsule. The capillaries walls consist of tiny micro voids that filter toxic wastes from the blood to capsule by pressure difference [3].

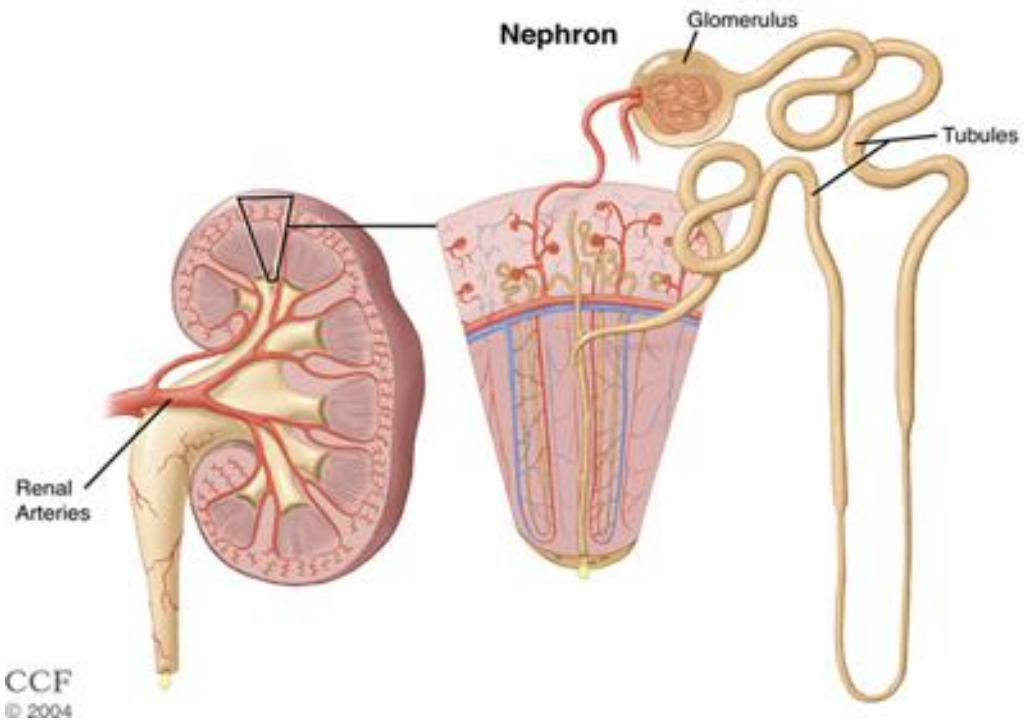


Figure 1.1 Structure of human kidney [4].

Kidney performs necessary functions in the body, which are as follows [5]:

- Maintains acid-base level of the body.
- Produces hormones erythropoietin, the production of bone marrow blood cells controlled by it, which ultimately regulates the blood pressure.
- Accumulation of urine and removal of it through urinary pathway.
- Maintains production of vitamin D level, which helps to provide bone stability and the amount of calcium in the blood.

Table 1.1 Urine composition toxicity level [13].

Components	**Concentration (g/day)**
Water	1500
Urea	30
Creatinine	0.6
Uric acid	0.9
Sodium	5
Chlorine	10
Potassium	2.2
phosphate	3.7
Calcium	0.2
HSO_4^-	8.2
Phenols	Traces

1.3 Uremic toxins

Uremic toxins are the main reason for the chronic renal failure (CRF). They have different molecular weights attached to the proteins, primarily Albumin. These toxins have three types: water-soluble toxins, protein-bound toxins and large toxins [6].

Molecular weight less than 500 Da like urea and creatinine are considered as water-soluble toxins. They are easily soluble in water and are not attached to protein; therefore, they can be easy to separate.

Protein-bound toxins are the toxins, which are attached with Albumin. Indoxyl sulfate and p-cresol and indoxyl sulfate fall in this category. They are routinely ignored in hemodialysis, but they also cause chronic kidney disease (CKD) and can generate cardiovascular diseases. Their increasing amount in blood causes decrease in kidney functions [7].

Molecular weight greater than 500 Da are classified as large toxins. Collection of these molecules in blood directly increase the death rate [8].

Table 1.2 Types and sizes of uremic toxins in blood [11].

Toxins	**Molecular weight ($gmol^{-1}$)**	**Toxin type**
Urea Urea acid creatinine	60 168 113	Water-soluble toxins
p-cresol Indoxyl sulfate	108 251	Protein-bound toxins
β2-microglobulin	< 500 Da	Large toxins

1.4 Kidney failure

Partly or total loss of healthy kidney functions is considered as kidney failure. Separation of large amount of water and toxins from the blood improperly is the initiation of failure. It has direct effect on the blood pressure, volume, and content.

Chronic renal failure (CRF) and acute kidney injury (AKI) are the two types of renal failure depending on the causes [9].

CRF is considered when the renal capsule filtration rate for minimum three months goes below 60mL/min/1.73m^2 of body's surface area [1].

Creatinine level increases more than or equal to 0.3mg/dL (≥ 26.4 μmol/L) or a reduction in urine output less than 0.5mL/kg per hour for more than six hours [10].

Table 1.3 Classification levels of CKD [17].

stage	Description	Glomerulus Filtration Rate (GFR) (mL/min/1.73m^2)
1	Kidney loss with normal or increase GFR	≥90
2	Kidney damage with mild decrease GFR	60-89m
3	Mild decrease GFR	30-59
4	critical decrease GFR	15-29
5	Kidney failure	<20 or Dialysis

1.5 Solution of Kidney Failure

1.5.1 Kidney Transplant

A kidney transplant is a treatment in which a healthy kidney is placed inside the body to replace a kidney that cannot work properly. Through this treatment health and energy can be maintained, and the patient can spend the life like before the kidney disease. Kidney transplant has major drawbacks, the risks of the surgery. The patient will also need anti-rejection medicines for as long as the new kidney working causing serious side effects. The patient is also at high risk of cancer after the treatment [11]. It also requires a donor either alive or dead. The treatment is very expensive in terms of the cost of surgery and medication even after the surgery [12].

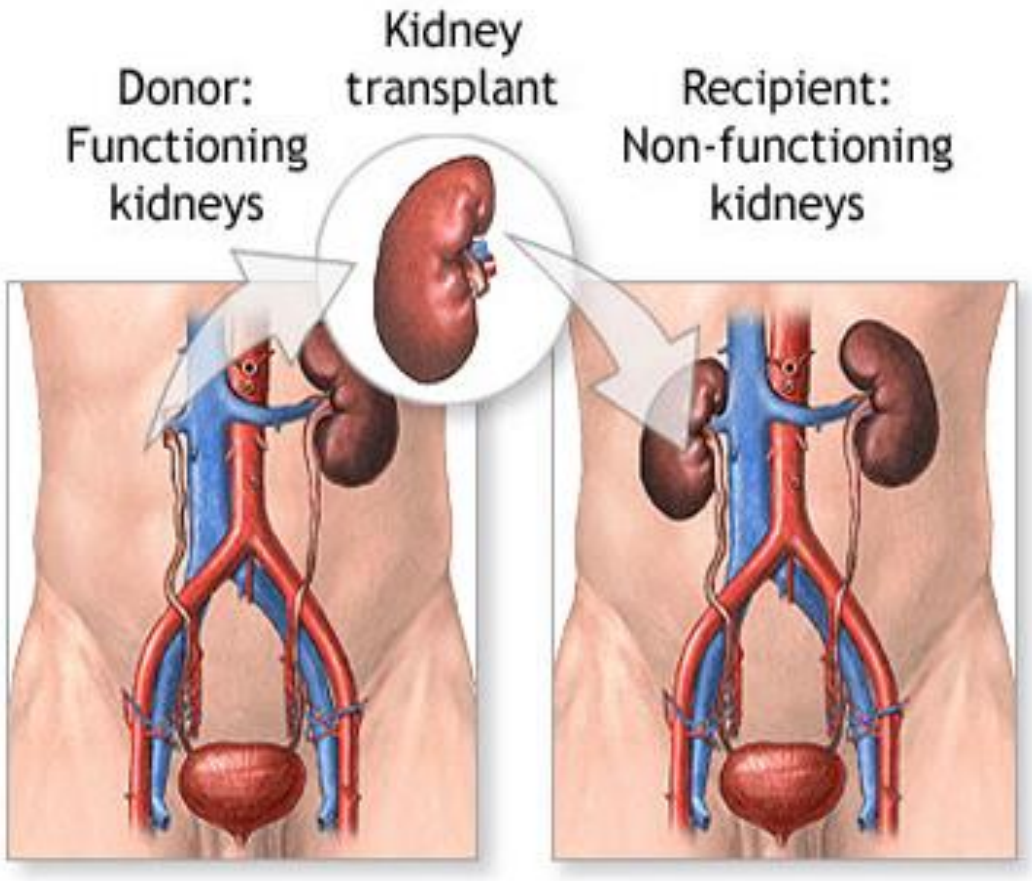


Figure 1.2 Kidney Transplant [12].

1.5.2 Peritoneal Dialysis

Renal replacement therapy modified form is also peritoneal dialysis. Many patients prefer to take this treatment as survival of the patients is now equal to that with hemodialysis [13]. In this process, exchange of fluid takes place by diffusion through peritoneal membrane. Permanent thin tube is left in abdomen known as catheter, inserted into the incision and the opening is left to heal for few weeks. The catheter is permanently attached to patient's abdomen, which is painful and difficult. The other drawback of this treatment is that it causes peritonitis and nearly 21-42g/1.73m^2 bovine serum albumin loss on weekly basis [14]. As compared to this treatment hemodialysis is more preferable because it causes infection in the body [15].

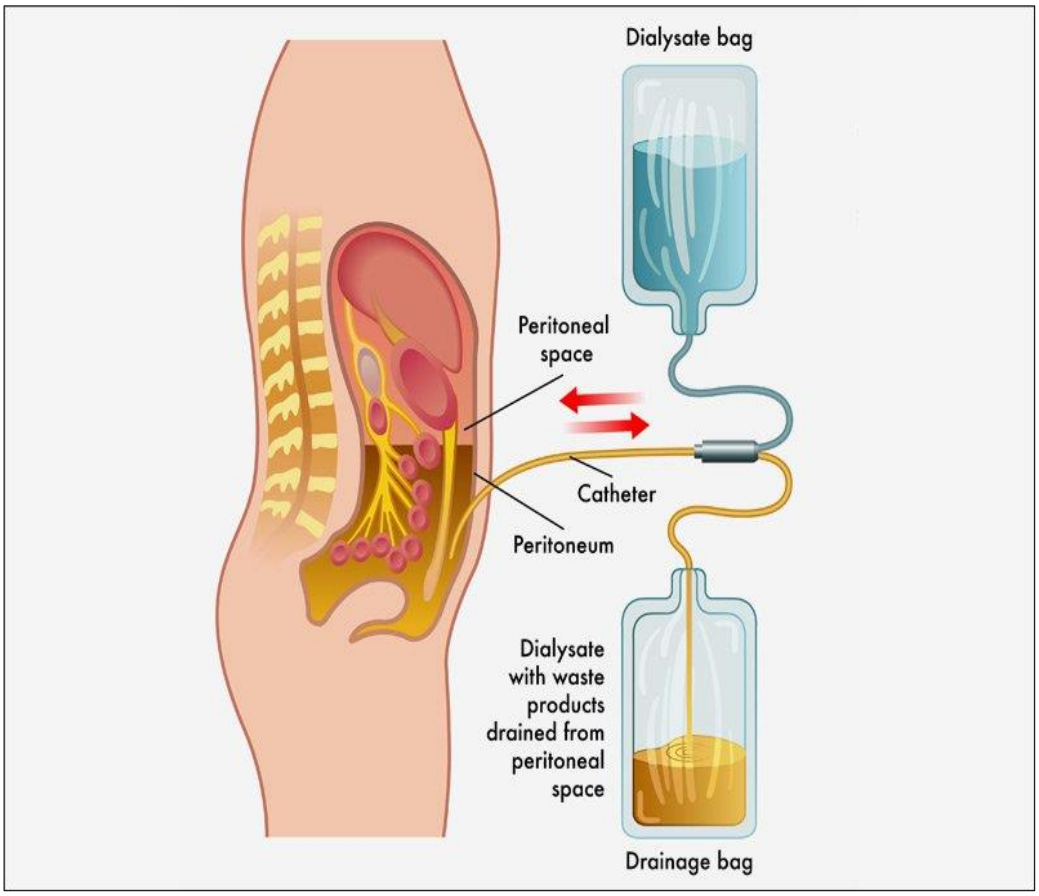


Figure1.3 Peritoneal Dialysis [13].

1.5.3 Hemodialysis

Most common type of dialysis is hemodialysis. It is an artificial kidney process. Impure blood goes to dialyzer in blood tank by maintaining the body pressure. Heparin is infused in the blood stream going in dialyzer to avoid coagulation. The dialyzer consists of the membrane, when blood comes in contact of its excess waste from the body goes to the dialysate by mechanisms of convection, diffusion, or ultrafiltration. The dialysis fluid is continuously changed to maintain the level of minerals. After the separation, the patient's body received purified blood [16]. In the whole process membrane is the essential portion whose pore size decide selectivity of molecules. Dialysate is the fluid, which extract the toxins. It usually, consists of sodium chloride, magnesium chloride, calcium chloride, potassium chloride, and sodium bicarbonate. Treatment last about 4 hours and is done three times per week normally but recent research reveals that dialysis six times a week shows better results [17].

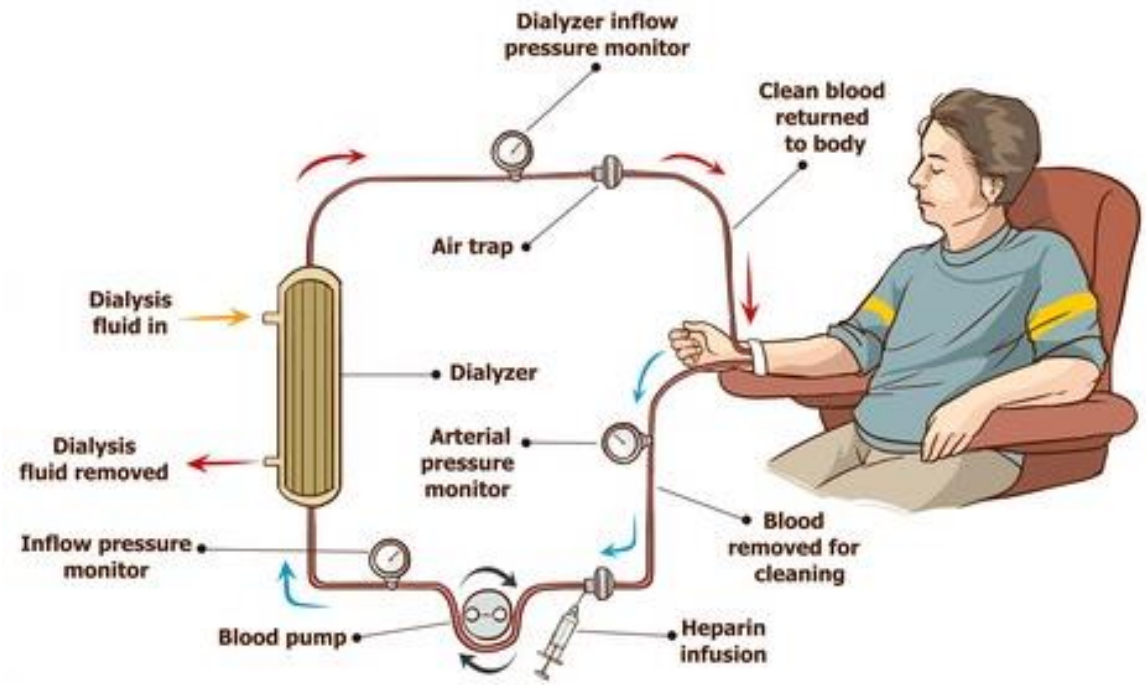


Figure 1.4 Hemodialysis Treatment [18].

1.6 Justification of the topic/need for hemodialysis

600 million patients have kidney problems worldwide and the worst part is number of patients are still increasing 6-7% yearly [19]. This reveals that there is stillroom of improvement in the current ongoing kidney replacement treatment for the betterment of the patient's life. As the number of patients are increasing in the world the demand for the hemodialysis treatment increases. It is preferable treatment as compared to kidney transplant and peritoneal dialysis

The option of kidney transplant is not affordable by every patient and is a risky procedure [20]. Hemodialysis is an excellent alternative, but Pakistan has very less advancement in this technology. Certain clinical upgradation is required, and some uremic solute molecules are still unresolved [21]. Work should be done on hemodialysis process to separate the small, middle and large toxins efficiently and make it cost effective.

1.7 Objectives of the study

Removal of toxic molecules based on their molecular weights across a semi-permeable film, hemodialysis is considered the best example. Traditional CA hemodialysis membranes have less solute clearance ability and compatibility with blood. The objective is to fabricate CA-PVA blend hemodialysis membrane to achieve high flux and permeance.is The aim is to achieve more than 90% of BSA rejection and almost more than 60% for toxin clearance which is optimum results for hemodialysis process. The other objective of this study is to make the membrane biocompatible with blood. For that, the PEG and PVA as additives are selected which have a biocompatible property and can improve the pore size for better separation of solutes.

1.8 Scope of the study

The scope of this research is to develop more efficient and effective hemodialysis membrane. CA polymeric membranes as compared to synthetic membranes are considered as less selective to small and middle size molecules and less biocompatible [22]. Improvements can take place in patient health by the selection of the biocompatible polymer and reduction in medication. Recommended urea and creatinine clearance should be more than 60% and BSA rejection must be above 80% which considered suitable for hemodialysis process [23]. Recent research shows that dialyzer have been improved to remove uremic toxins upon molecular weight up to 50,000 Da [24].

Originally, hemodialysis techniques still have a high risk of death, diabetes, and cardiac diseases. The process designed to remove urea and creatinine while rejecting Albumin [9]. The focus of this study is to retain the maximum amount of albumin in the blood and collect toxic wastes as permeate by making the membrane biocompatible. This can be achieved by modification in polymer blending, pore size variation, structure and distribution, morphological and characterization techniques.

1.9 Outcome of research work

As glomerular membrane is more selective than synthetic membranes. Current hemodialysis membranes still do not have the ability to remove all the uremic toxins over a wide range of molecular weight. After the treatment, the patients have higher level of middle and large molecule toxins in the plasma [25]. Therefore, the membrane should be closer to natural glomerular membrane in the kidney.

In this work, CA-PVA blend hemodialysis membranes will prepare which mimics the glomerular membrane. It should have lager pore sizes that removes large toxins and have biocompatibility with blood. Maximum bovine serum albumin must retain by CA-PVA blend hemodialysis membrane to make it effective and efficient for the patient's health.

CHAPTER 2

Hemodialysis Membrane

2.1 Hemodialysis history

Prof. Abel performed first dialysis by using celloidin tube, hundred years ago in Philadelphia [22]. He investigated mass separation between two fluid phases using these tubes. Prof. Alwall in Lund performed an experiment on the blood cleaning on his first artificial kidney, thirty years ago. This experimentation provided the paths to develop the artificial hemodialysis treatment [26]. In 1942, Willem Kolff developed practical artificial kidney containing rotating drums [27]. That was the first example of the ESRD in USA and UK. It was not commercialized until 1960, until Belding Scribner developed arteriovenous Teflon shunt in Seattle. After the establishment of this treatment James Haviland and Scribner established the artificial kidney center. It was the first nonprofit kidney center in 1962. T their next challenge was to cure the patients of ESRD and further establish the technique [28].

By the time, efficiency of the process increased by reducing dialysis time from 12 to 4 hours. Blood flow level maintained at 400-500 mL/min and cleared the urea efficiently [29]. After few years, home hemodialysis treatment was established which was less expensive and reduces the risk of hepatitis [22].

Hemodialysis treatment efficiency depends on the permeation of uremic toxins from blood. Urea and creatinine is considered as the most toxic solutes but despite its toxicity, of the treatment is depended on it [30]. Dialyzers did not work efficiently because of the accumulation of the middle and large size toxins and not able to measure the amount of urea separated from the blood. Various problems remain in the end of this treatment causing diabetes, carpel tunnel syndrome, anemia, hypertension and skeleton abnormalities [31].

The progress of this separation process is depending on the membrane, which is the heart of this process. When pressure is applied on the membrane it passes the specific molecules while retaining the passage of others. Feed stream is the effluent of the

membrane module. Permeate is the liquid that passes through the semipermeable membrane and retained phase is the liquid containing the retained constituents [32].

Ease of operation, compactness, energy sustainability, good efficiency and versatility in separation process are the main properties of membrane that enhances its popularity [33]. This technology has various end use applications such as dialysis process, pharmaceuticals, water treatment, gas separation, chemicals, food, and beverages [34]. Since the start of World War II, the membranes importance increased for purification of drinking water and in biomedical field [35]. Now the membranes are used as biomaterials in which it is in contact with biological fluids, cells, organs, and tissues. Membranes also proved their importance as part of medical gadgets and implants, diagnostic assay, bio separations, bioreactor systems, artificial organs and tissue engineering etc. [36].

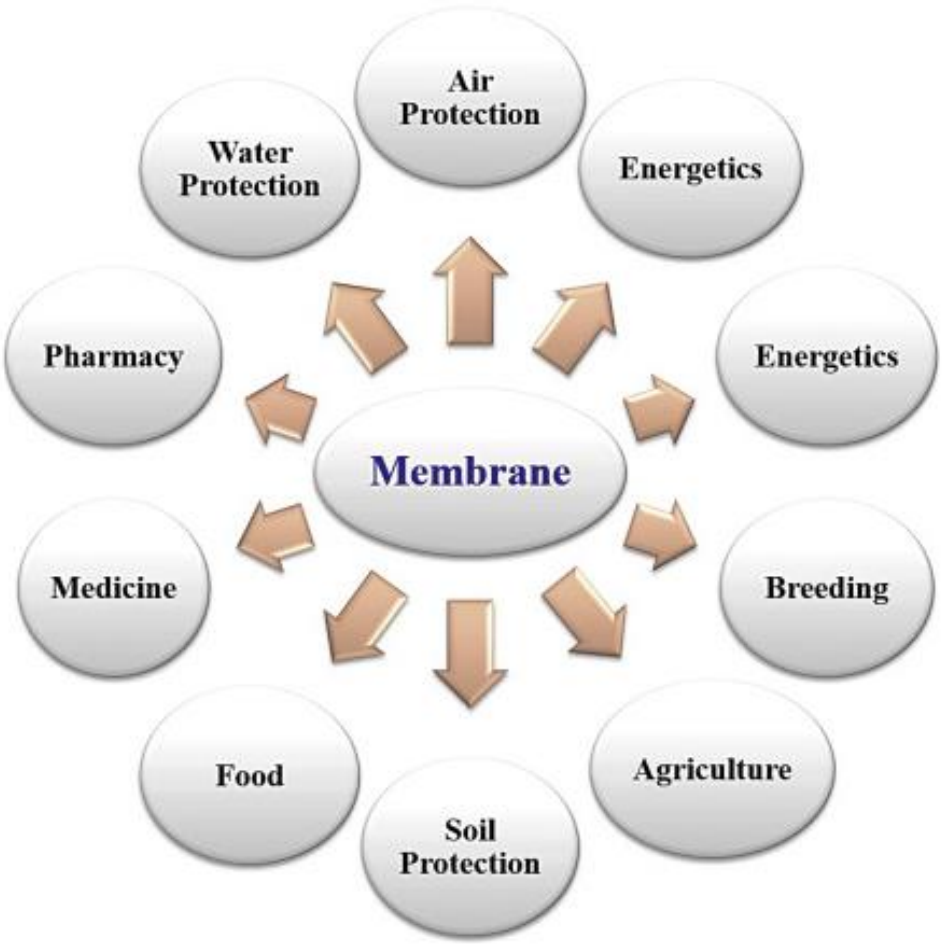


Figure 2.1 Applications of the membrane processes [34].

For the cleanup of the endogenous and external toxins from blood, membrane technology is highly recommended in hemodialysis, hemofiltration, hemodiafiltration, plasmapheresis and blood oxygenation [37].

Kedem-Katchalsky suggested frictional model that define the membrane transport phenomena through the capillary system. Due to the presence of concentration gradient passive transport is formed in the membrane system. It is also defined that the blood flux and the dialysate flux are the main components obtained as permeate and retentate, respectively. The flux of the membrane is depended on the osmotic pressure gradient and hydrostatic pressure difference[38]. The derived KK equation could be used for the analysis of process in which the boundary layers had a key role [39].

The social impact of hemodialysis treatment is estimated by the number of patients willing for this treatment. In 2008, more than 90 % of the patients had this treatment as compared to only 8.5% patients who undergone peritoneal dialysis [40]. From 2009 it was observed that dialysis centers and machines are continuously increasing. As the treatment increases psychological problems arises in hemodialysis patients. Depression, malnutrition, inflammation, quality of life and suicide are the major issues. These problems are managed by the pharmacological and non-pharmacological ways [41].

In 1994, hemodialysis membranes costs were reported up to US$ 1400 million worldwide. By the time hemodialysis profit margin around increases about US$ 20,000 per year [42]. This shows that in the future demand for the hemodialysis membrane is expected to increase. Indigenous manufacturing of the dialyzers and tubing can help to bring down the cost of hemodialysis. In Pakistan funding, non-governmental charity organizations can have a larger role to play to establish centers for hemodialysis patients by collecting funds [43]. Membrane manufacturing industries are working on formation of membranes bring down the cost of the treatment.

As a summary, hemodialysis is preferable because of it is less painful and mortality rate increases than other therapies. However, true patient centered innovations have also slowed down in establishment of this treatment. Still many patients cannot undergo this treatment and millions of deaths are recorded every year [44].

2.2 Hemodialysis technical aspects

2.2.1 Dialysis Machine

Dialysis machine is use for the controlling of the system during hemodialysis treatment of the patient. It controls the blood and body temperature for the improvement of the hemodynamic stability. It controls the amount of the blood in the circulation with the help of the volume control indications. On-line urea clearance can be detected at the moment to better treatment.

2.2.2 Dialyzer

Since the early 1960's, dialyzer has been practiced in United States [28]. The motivation to use dialyzers was economic benefit, ability to use high flux dialyzer and reduction in biomedical waste. It is also known as artificial kidney which removes the excess waste and fluid from the human blood. Dialyzers consist of the semi-permeable membrane through which small solutes and liquid pass. Fresh dialysate enters the dialyzer on one side and human blood enters from other. By diffusion gradient wastes are percolated from the blood into the dialysate. Dialysate having waste products leaves the dialyzer and are washed out. Then clean blood goes back into the human body. They are classified based on permeability, surface area, membrane composition, geometry design and biocompatibility [45].

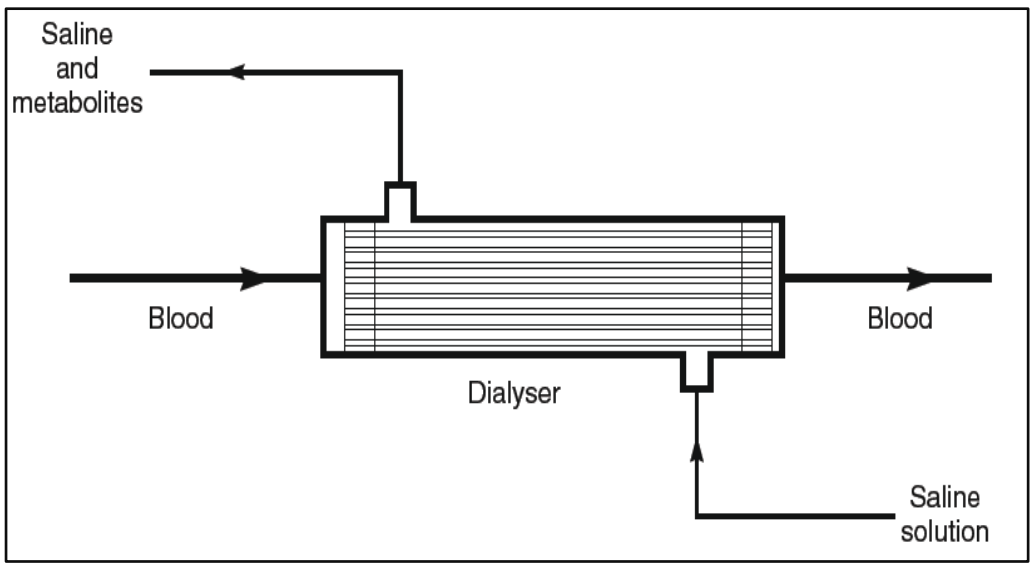


Figure 2.2 Schematic Diagram of Dialyzer [34].

2.2.3 Dialysate

The solution of pure water, electrolytes, salts e.g., sodium and bicarbonates is called as dialysis fluid, solution, or bath. The function of the dialysate is to extract the toxin wastes from the blood through the diffusion process. Uremic waste diffuses from blood to fluid due to concentration gradient. The electrolytes in the fluid also used to balance the patient's body electrolytes. The dialysate solution is then flushed off to drain containing toxins from the renal patient's body. Over 300 liters water used to treat the hemodialysis patient [46].

2.2.4 Extracorporeal Circuit

In blood circuit, with the help of arterial needle the blood is separated. Using peristaltic pumps blood is passed through the dialyzer and reentered to the body through needle venous. For the prevention of the coagulation of the blood, heparin anticoagulant is added into the system. Fistula is protected by arterial pressure monitor by investigating large negative pressure. Venous pressure monitor is used to detect the blood loss from the circuit due to mislocation of the fistula. Air can also enter the circulatory system from the environment through arterial needles. It can be detected by air bubble trap and switch off the pump if air is detected. Dialysate and blood flow rate, fluid removal rate, and duration of dialysis treatment are some variables which should be adjusted according to the need of the patient at the time of process [47].

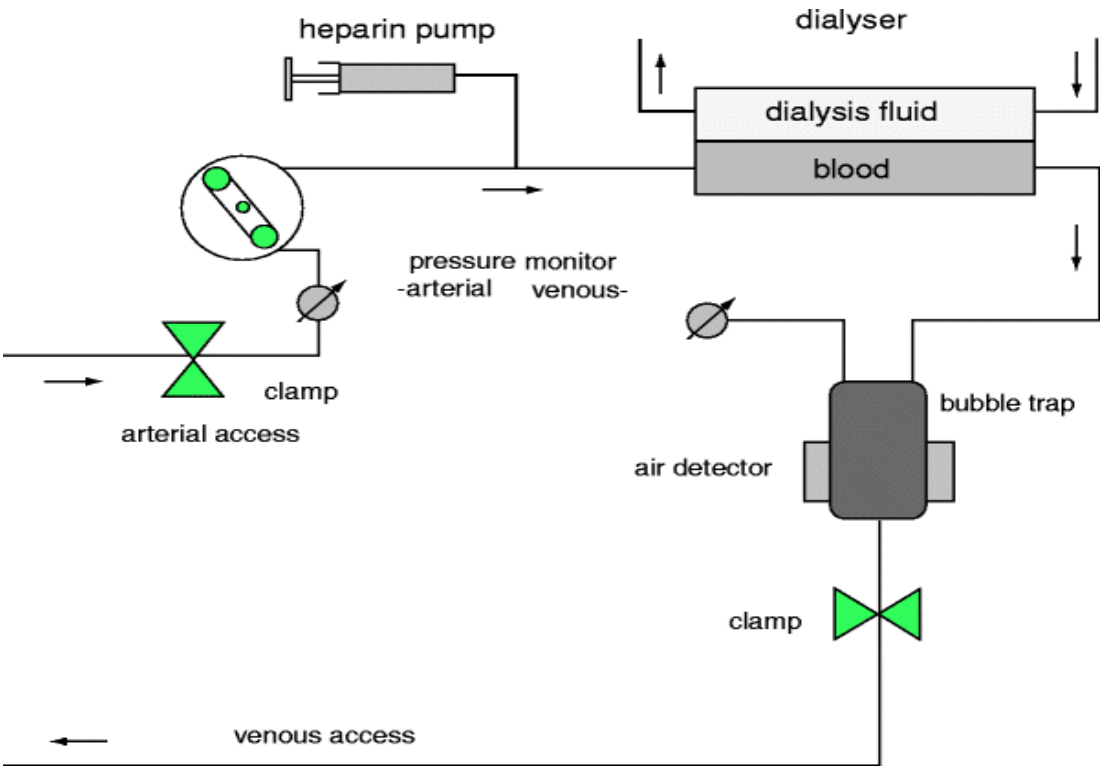


Figure 2.3 Extracorporeal Blood Circuit [48].

2.3.Techniques for hemodialysis

2.3.1 Conventional hemodialysis

In the 1980's, dialyzers with acetate dialysate were considered as the conventional hemodialysis. Low flux ultrafiltration coefficient membranes were used in the dialysis machines without volume control. It removes middle size uremic toxins while the rate is low for separation. The major drawback of this technique was that it removes large amount of water and equal amount of blood from patient's body using dialysis pump. Principle of diffusion was used across the membrane for the separation. In 1990's, bicarbonate dialysate and synthetic high flux dialyzers overcome the conventional hemodialysis technique [49].

2.3.2 Hemofiltration

In 1977, hemofiltration was described as a useful technique for the removal of the extracellular fluid from the patient's body. Principle of convective treatment was used as it removes middle molecules better than small molecules. Highly permeable membranes were used in this technique which removed large amount of toxins from the body [50]. In this technique, clearance rates dependent on the filtrate flow and is

free of the molecular weight of the sample substance. Continuous hemofiltration is known as renal replacement therapy. Hemofiltration process mechanism had many similarities with hemodialysis. However, this process is not suitable for ESRD as it only focuses on the removal of middle molecules. Furthermore, minimum number of small molecules are separated. However, it provides better results for the acute renal failure patients [51].

2.3.3 High flux dialysis (HFD)

In the HFD, compound fluid balance is formed within the system. Net filtration rate is controlled volumetrically however true filtration rate in the dialyzer are equalized by back filtration. It is considered far better than the conventional hemodialysis by removing the middle size molecules with mechanism of convective transport. However, it is less effective than hemodiafiltration. Middle size toxins are separated by convective mechanism usually done by internal filtration [52].

In this technique internal filtration depends on the oncotic forces. The hydraulic permeability is performed on the membrane along the dialyzer length [53]. Filtration and back filtration of blood flow is regulated by the filter resistance. This generates the pressure drop. The pressure gradient develops in both the compartments of the dialyzer usually known as transmembrane pressure (TMP). When the TMP is positive the water molecules separated from blood and move towards the dialysate. Back filtration takes place when its value is negative. The relationship between TMP and filtration rate is as follow:

$$Kuf = \frac{Uf}{TMP} \tag{2.1}$$

Where Kuf is the membrane ultrafiltration coefficient, mL/h/mmHg. Uf is the ultrafiltration in ML and TMP is the trans membrane pressure in mmHg.

High flux membranes are effective for the separation of the small molecules and some middle solute currently. The drawback of this technique is that it retain the other molecules in the current renal therapy [33].

2.3.4 Hemodiafiltration (HDF)

Hemodiafiltration is a new technique which improves the removing potential of the high flux dialyzer by establishing the convective transport in it. Introducing the convection phenomenon greatly enhances the separation of toxins of middle and large size molecules restricted they remove by diffusion mechanism. More than 70 mL/min ultrafiltration rate is used for conventional transport of solutes in conventional HDF [54]. The desired weight loss in the patients is exceeded by the ultrafiltration so that the sterile fluid is inserted into the patient body. This process demands complex machinery with a large amount of exchange fluid. The difference between the overall ultrafiltration rates and the reinfusion rate in the patient's body is consider as the net ultrafiltration rate in the system. Internal filtration in the adjacent side of the dialyzer is always kept high and the net ultrafiltration rate is kept low by the machine [55]. Back filtration in the lateral part of the dialyzer kept the balance of the final fluid. The dialysis system controlled the amount of net filtration rate [56]. In contrast, morphology, hydraulic permeability, oncotic or hydrostatic forces and structural geometry of the dialyzer determined the true and back filtration properly [57].

Middle size molecules such as insulin, β2-microgobulin and leptin are considered as the important part in the formation of amyloidosis in long term scenarios. So, the current issue for the hemodialysis treatment is the removal of these middle size solutes. This technique showed the best results for the clearance of the middle size molecules [58].

Increase in quantity of substitution fluid from the conventional ones enhances the cost of the process. So, this complexity is the disadvantage of the system that made it costly [59]. Sterile dialysate is recommended in this system as kidney health issues caused by the back filtration. Hence, the high ultrafiltration rates used with cautions provided by theses dialyzers [60]. Hydrophobic membranes are used in hemodiafiltration whereas dense hydrophilic membranes are used in hemodialysis [61].

2.4 Hemodialysis membranes classifications

2.4.1 Symmetric membranes

The polymeric membranes consist of two types of fiber structure symmetric and Asymmetric. Symmetric membranes are homogeneous, non-porous/dense having single layer of polymer. In comparison with the Asymmetric membranes, these membranes significantly thicker and gives low fluxes [62]. They can fabricate by the cellulose or any synthetic polymer containing similar size pores in the inner and outer layers of the wall [63].

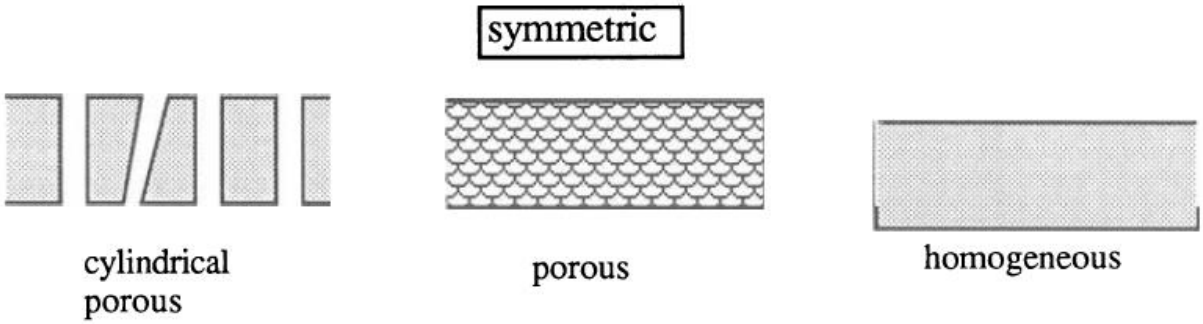


Figure 2.4 Extracorporeal Blood Circuit [48].

2.4.2 Asymmetric membranes

Asymmetric membranes comprising two main layer one is relatively dense and other is extremely thin top layer. These two layered membranes have diverse properties, such as morphology, permeability, selectivity and high-pressure mechanical strength [62].These types of membranes usually used in reverse osmosis, ultrafiltration, and gas separation. Small water bound toxins face diffusive resistance due to thickening of the wall, but the porosity of the membrane helps toxins to pass through the membrane. Three layers Asymmetric membranes are fabricated in these days to increase the flux in which the outer layer is for the support [63].

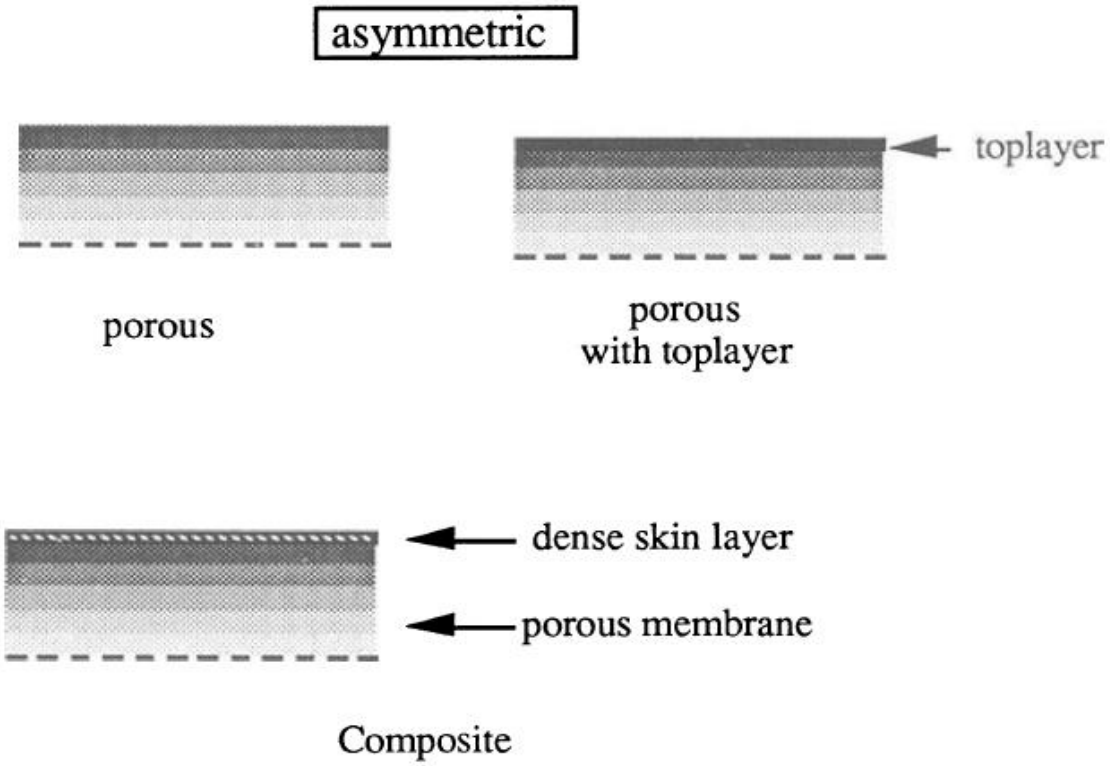


Figure 2.5 Extracorporeal Blood Circuit [48].

2.4.3 High flux membrane

High flux membranes are the porous membranes contain fixed pores in the range of 2-100nm for ultrafiltration and 0.1-10µm for microfiltration. The selectivity is depended on the dimensions of the pores. Medium and high molecular size toxins such as β2-microglubulin and phosphoric moleucles that conglomerate during the chronic kidney disease separated higher in high flux membranes. It also slows down the long-term side effects of hemodialysis. High flux membranes remove more amount of toxins which causes uremia and decreases the risk of cytokines. It also reduces the inflammation reactions in the body in comparison to low flux membranes. High flux membranes improves the control on anemia, reduces the cardiovascular diseases and reduce the need of erythropoietin [64]. However, high flux membranes have ultrafiltration is greater than 20ml/mmHg and sieving coefficient of β2-microglubulin is almost 33.90±2.94mg/dL [65]. High flux membranes fit in the hemodialysis, hemofiltration and hemodiafiltration mechanisms and gives the required result of permeation. Using the high flux membranes if the patient containing serum albumin less than 40g/l, it decreases the risk of mortality. Serum albumin quantity is inversely

proportional to the mortality risk rate of the patient. Concluded that mortality of the patient does not depended on membrane material [66]. It has drawback that high performance membranes consist of large pore size that removes albumin also with the toxins. The loss of albumin in large amount is may led to harmful results for the renal patients. It is considered not useful for all types of patients but to a subgroup. The patient which cannot bear the loss of the protein must be shift to the conventional dialysis membranes or low flux membranes [67]. Cellulose membrane usually used in high flux membranes whose permeability is higher than the low flux membranes.

2.4.4 Low flux membranes

Low flux membranes are the non-porous membranes mainly use for the liquid and gas separation. The performance of the membrane depends on the intrinsic properties of the materials. Low flux membranes can be used for the hemodialysis patients for the removal of small size molecules due to low average pore size and low porosity. For the large size toxins low flux membranes have sieving coefficient for β2-microglubulin is equal to zero and ultrafiltration is less than 20 ml/mmHg. These membranes have low adsorption capacity on the surface, so the rate of protein loss is higher than other membranes.

The major drawback of low flux dialyzers that it could not remove the toxins efficiently, which causes side effects on different parts of the body after some years [64].

2.5 Multidimensional classification of the hemodialysis membrane

Hemodialysis membrane is classified into multidimensional parameters. Important parameters are shown in figure 2.4.

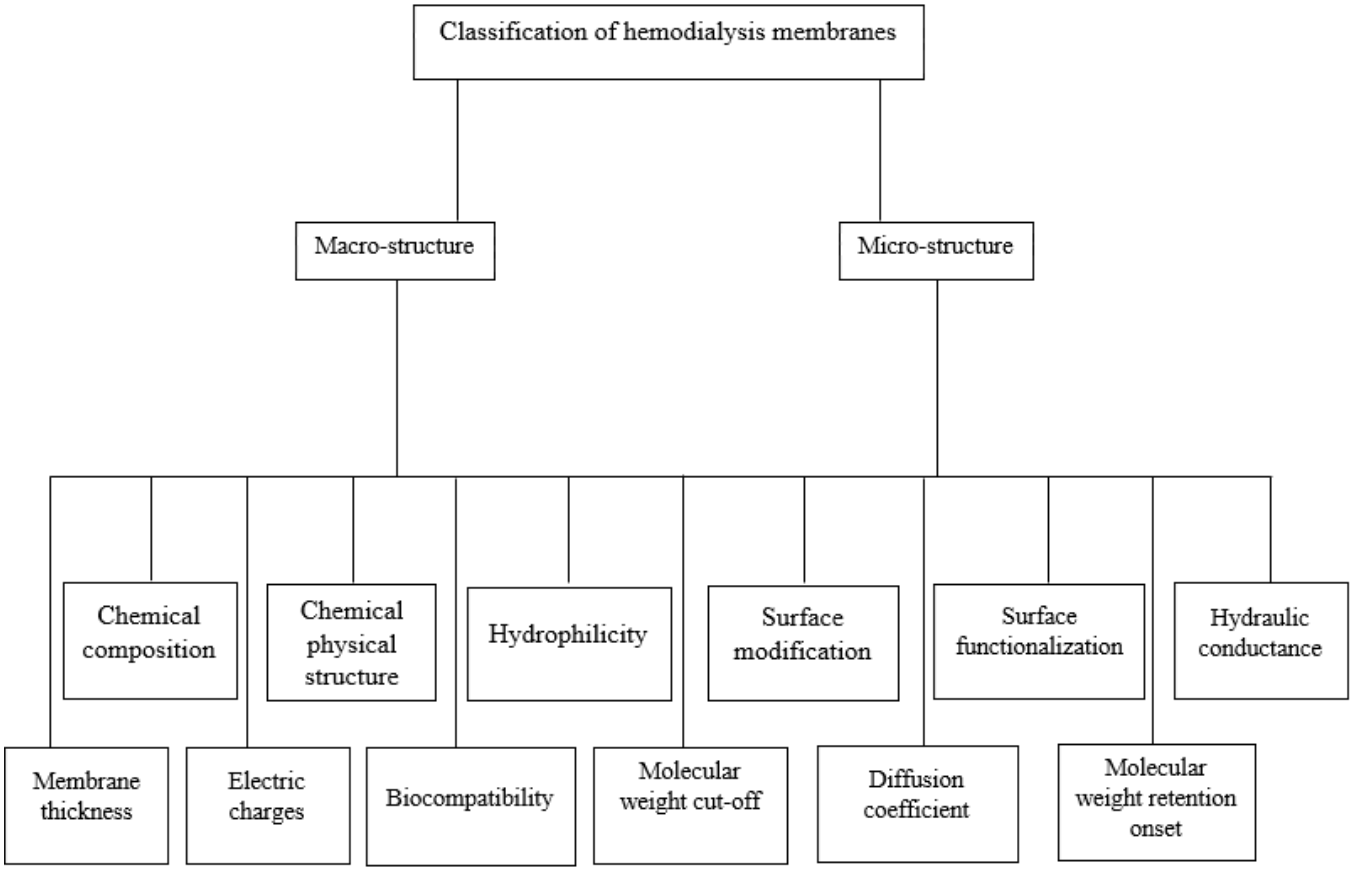


Figure 2.6 Classification of hemodialysis membrane [68].

2.6 Chemical composition of hemodialysis membranes

2.6.1 Unmodified Cellulose membranes

Since 1960's the most used membranes for the reduction of the small molecules from blood were the cellulose membranes. Unmodified cellulose membranes known as cuprophan membranes. Cuprophan membranes are considered as the start of the artificial kidney that separate urea and creatinine type toxins efficiently. This material is popular for the minimal thickness, high mechanical strength, low cost, and uniform porosity [69]. Cellulose is prepared from natural occurring plants or cotton. Cellulose membranes are considered hydrophilic as it consists of large quantity of hydroxyl

groups on the cellulose monomer [70]. Flow of small size impurities and retention of middle molecules is the major drawback of this material. It does not adsorb the unwanted impurities. These are considered as low flux unmodified cellulose membrane that causes bio incompatibility by activating the leukocytes and complement activation system [71].

2.6.2 Substituted cellulose

Substituted cellulose membranes are like cellulose membranes but later chemical modification was done to remove the hydroxyl group from the cellulose monomer. The modified material is known as substituted cellulose and it is more biocompatible than the unmodified ones. The free space of hydroxyl group is occupied by the acetyl residues of the acetate, diacetate, or triacetate [72]. Hemophan and vitamin E coated membrane was modified to increases the biocompatibility. It was estimated that substituted membranes provide more flux than the previous membranes and considered more biocompatible[73]. The drawback of these membranes is the low permeability of larger molecules of toxins and still have a gap to improve the properties of membranes.

2.6.3 Synthetic polymeric membranes

For the biocompatibility improvement in membranes and separating the middle size toxins, many synthetic membranes are developed. Poly sulfone, polyether sulfone, polyacrylonitrile, polymethyl methacrylate, polylactic acid, polyvinyl alcohol, polyamide and chitosan are the synthetic materials used to fabricate hemodialysis membranes.

2.7 Hemodialysis and Membrane Transport Mechanism

Hemodialysis is the process in which large amount of uremic toxins separated. Interchanging of the patient's blood and dialysate balanced the blood electrolytic components, through a semi-permeable membrane. Diffusion and convection are the transport mechanism in the latest hemodialysis. Osmosis, ultrafiltration, and adsorption are also important mechanism in hemodialysis treatment.

2.7.1 Diffusion

Diffusion largely removes the small molecules by the Brownian movement [74]. In which the solutes move from higher to lower concentration. The basic process is

explained in figure 2.5. Due to concentration gradient urea diffuses from blood to dialysate and the dialysate moves in opposite direction to maximize the toxins removal [75]. Diffusion depends upon the blood-dialysate concentration, blood- dialysate flow rates, thickness, temperature, conductivity and surface area or morphology of the membrane. It highly depended on the concentration gradient between the fluids keeping all the other factor constant during the process [74]. Fick's law elaborates the diffusion mechanism [76].

$$J = -cD\left(\frac{\partial C}{\partial X}\right) \quad (2.2)$$

Where J is the rate of diffusion flux$m^{-2}s^{-1}$, D is the diffusion coefficient in ms^{-1} and c is the molar density in kmol. ∂X_A and ∂Y is the concentration gradient in g m^{-3} and distance in m^{-2}, respectively.

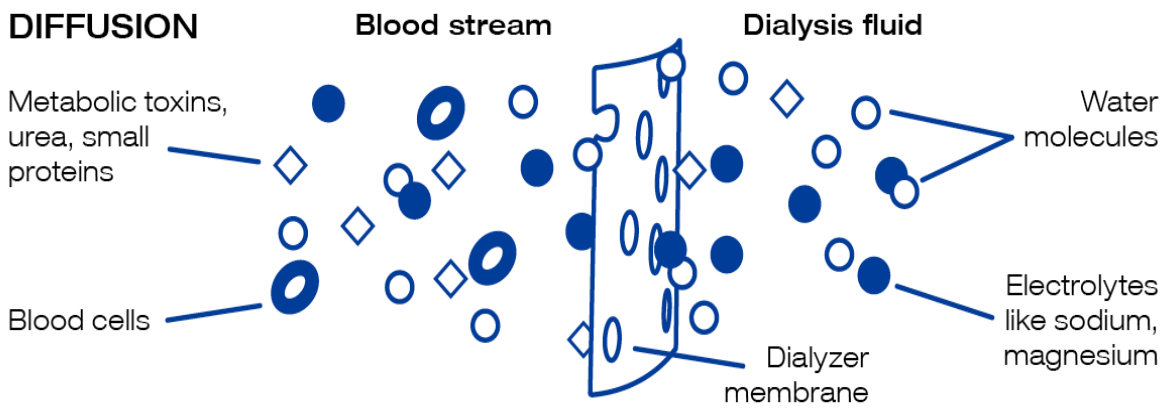


Figure 2.7 Diffusion mechanism [75].

2.7.2 Convection

Process of transport of wastewater and toxins from the blood to dialysate through the membrane due to pressure gradient co currently is convection. The focus was on the separation of middle-sized molecules from all the other toxins transported through semi-permeable membrane during the high flux dialysis. Sieving coefficient, hydraulic permeability, concentration of the toxins, surface area of membrane and the pressure gradient through the membrane are important factors on which convection depends [33].

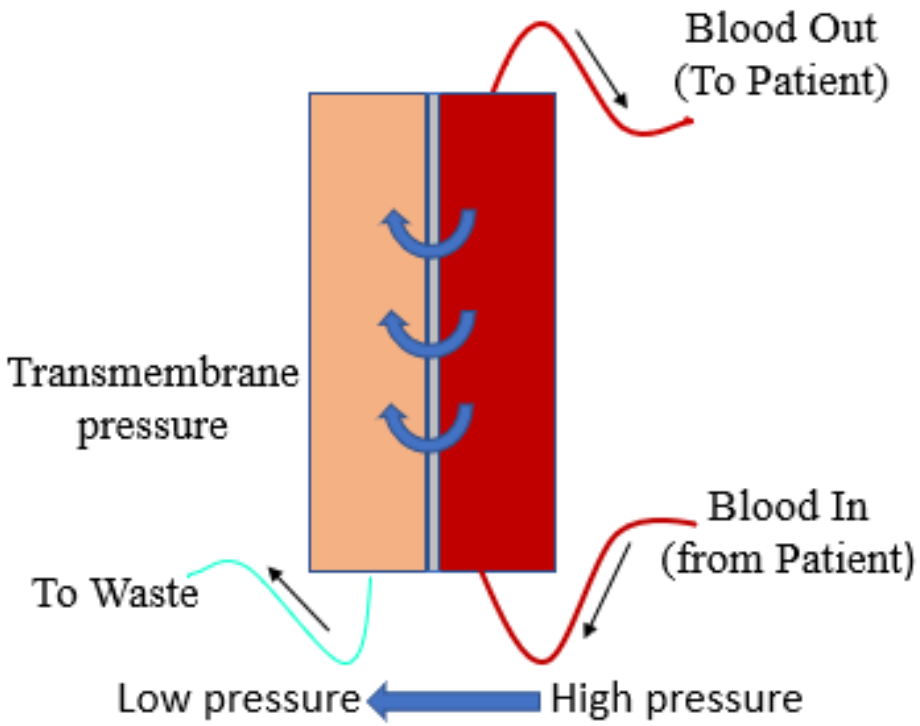


Figure 2.8 Convection mechanism

2.7.3 Osmosis

Osmosis depends upon the concentration gradient. In this process, the net movement of molecules of solvent into the area of high solute concentration occurs through semi-permeable membrane to balance the concentration. In hemodialysis, osmosis is the transfer of water through hemodialysis membrane into blood plasma or fluid [77]. Figure 2.7 illustrates the process in detail.

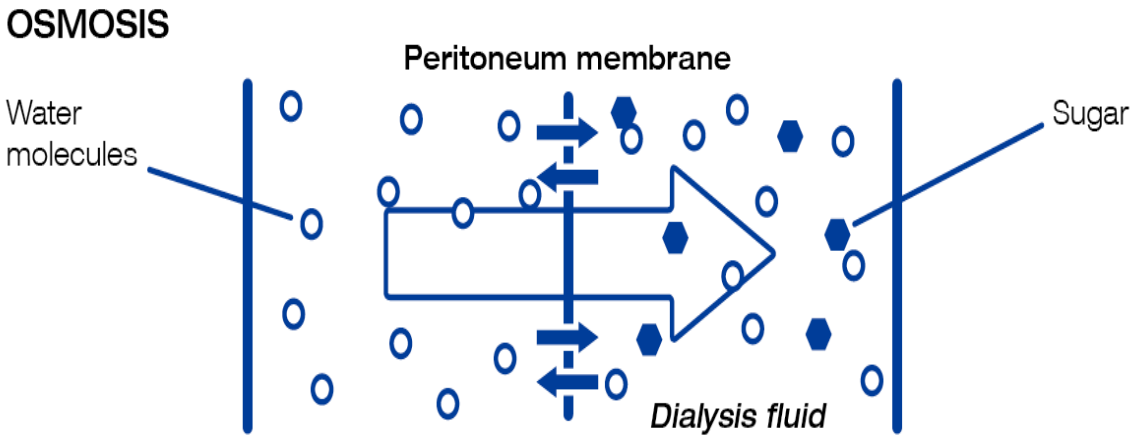


Figure 2.9 Mechanism of Osmosis [78].

2.7.4 Ultrafiltration

Ultrafiltration is basically a process of removal of excess water from the body as described in fig 2.8. The water moves from the blood plasma to the dialysate due to the difference in pressure [79]. The blood side is higher in pressure, so the water moves towards the lower pressure side i.e., dialysate. Ultrafiltration depends on the hydrostatic blood pressure and porosity of the membrane. The patients are pre- and post-weighted during the treatment. The difference in the weight of patient determines the efficiency of the membrane to calculate the efficiency of the membrane [38]. This treatment focused to remove the middle size toxins. However, it causes uremia.

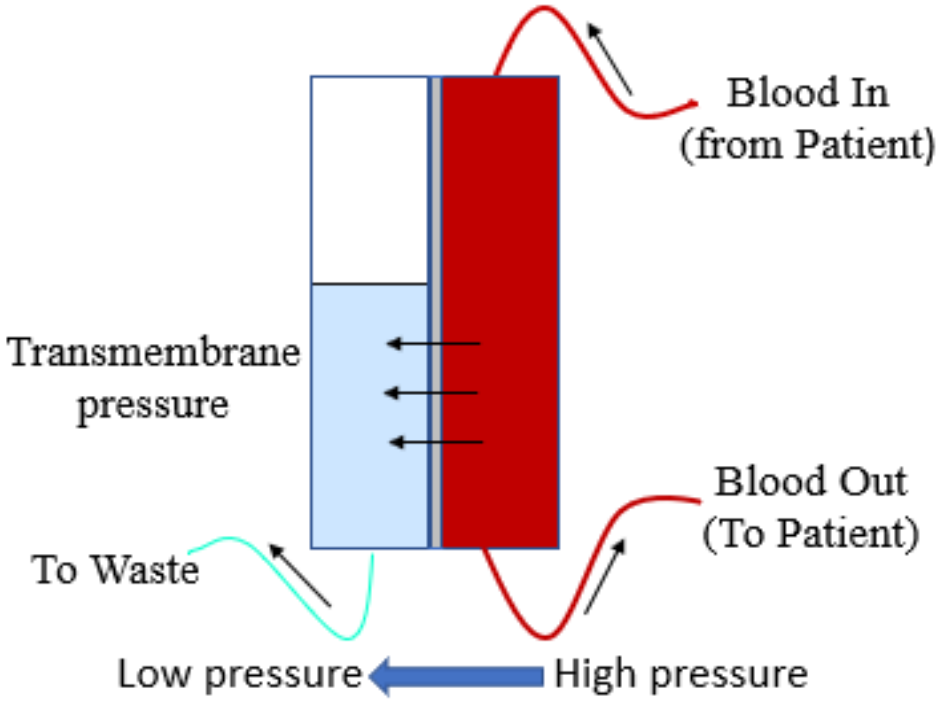


Figure 2.10 Principle of Ultrafiltration

2.7.5 Adsorption

The solutes form the bonds with the surface of the membrane is known as adsorption. The toxin solutes are adhesive with the surface of the membrane or the adsorbent in the membrane obey the principle of adsorption in hemodialysis as shown in figure 2.9. P-cresol, Indoxyl-sulphate, peptides are the toxins whose separation is quite difficult [80]. They are preferably removed by adsorbing on the surface of the membrane or adhesive to the adsorbent in the membrane. Protein bound toxins are also absorbed on the surface of the membrane which are essential for the body. They can be retained by using back flushing.

Membrane pores could be saturated by the toxins easily and efficiency decreases. It can be improved by increasing the capacity of adsorption of the membrane because the removal of toxins is depended on the surface area [81].

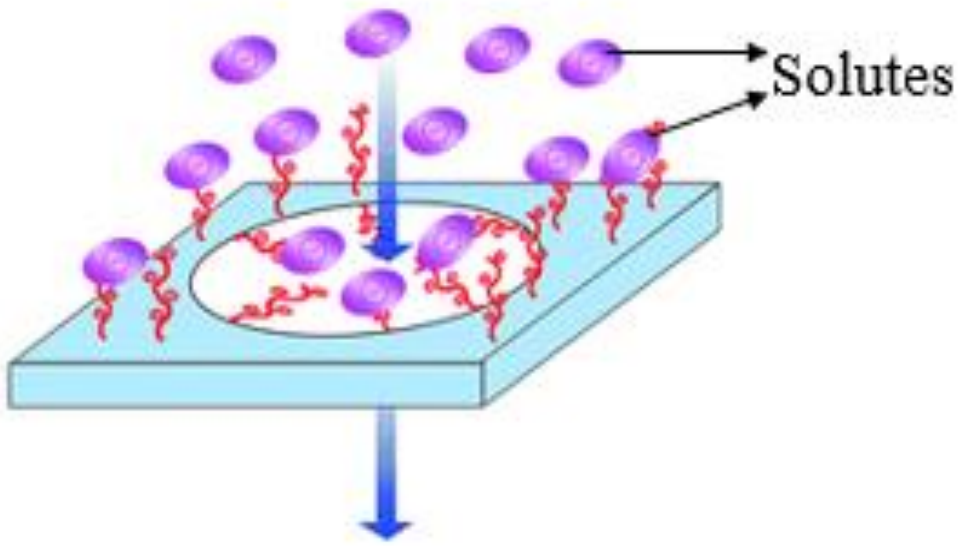


Figure 2.11 Extracorporeal Blood Circuit [48].

2.8 Challenges for hemodialysis membranes

In spite of all the progress in blood purification biocompatible membranes, death rates are still recorded to be high [82]. It even reflects that conventional hemodialysis cannot attain the healthy life it can only enhance the life span of the patient. Several modified techniques have been introduced for surface modifications. Moreover, not all the membranes studied considered hemocompatibility assessment [83]. In other words, few research articles reporting hemocompatibility aspects. While research wok reported hemocompatibility assessments with few factors. Technology improves Porosity, flux and solute clearance and rejection aspects of hemodialysis. Material improved along with pore size adjustments and surface modifications done regarding purification of blood which increase the demand of hemodialysis in hospitals and home dialysis. Still the quality of life is major challenge for the hemodialysis patients. Accordingly, efforts must be put to enhance the surface morphology to increases the flux, protein rejection and solute clearance and the membrane should be biocompatible with blood. [84].

CHAPTER 3

Literature Review

3.1. Hemodialysis membrane development

Membrane technology become increasingly important in world. In the middle of the eighteen century membrane technology phenomena was studied for the first time [34]. In 1960s the important establishment of synthetic membranes industrial applications started. Capabilities to restructure process, environment protection, public health and enhances revolutionary technologies for constant growth [85]. Membrane technology like other applications such as gas separation, water cleaning, medicine etc. developed a lot in the hemodialysis field.

In hemodialysis technology product modification starts from the semi-permeable membranes which was the simplest type of membrane made of biological and synthetic material to separate unwanted components from blood by concentration difference. But it causes certain problems during the dialyzing process like less efficiency, more cost investment, and less biocompatibility. The replacement of the semi-permeable membranes take place by the collodion tube membranes in which the crossflow mechanism occurs between the dialysate and blood [86]. The major problem of the collodion tube membrane is long time requirement for the cleaning process causing phycological and mental problems to the renal patients. Membranes were used in the rotating drum dialyzer in which blood and dialysate rotate in the drum like arrangement [87]. It was effective than collodion tube but due to complex manufacturing the financial expenses increases which was unaffordable for the dialysis centers. In 1980s, phase separation method was used to fabricate flat sheet membranes, solution and dip coating method [88]. It was the breakthrough in the hemodialysis industry. To increase the efficiency of the flat membranes, modifications such as adding additives, incorporation of nanoparticles and zeolites etc. was done on the surface of the membranes. To decrease the surface area of the membrane coil or tube membranes were fabricated. The blood and dialysate flow in parallel pattern in the dialyzer which enhance the ability of the membrane, which ultimately take the form of modified hollow fiber membrane which is efficient towards solute removal and protein rejection [89].

3.2. Review of CA, PVA and PEG hemodialysis membranes

Chuang et al. [90] in 2000 investigated the Polyvinyl Alcohol (PVA) membranes. Acetic acid used as an additive that effects the filtration and structural properties of the membrane. Influx rate of coagulant medium improves with increasing the amount of acetic by acid base equilibrium. Results offer better understanding of relationships between the fabricated membrane and the skin structure.

Ye et al. [91] in 2005, fabricated CA hollow fiber membranes with water soluble amphiphilic 2-methacryloyloxyethyl phosphorylcholine (MPC) copolymer. This study demonstrated the enhancement the biocompatibility of membrane. Less fouling, protein adsorption and excellent permeability was observed.

In 2006, Ani Idris et al. reported a study that was done on the various molecular weight Polyethylene glycol (PEG); 200, 400 and 600 blends with cellulose acetate (CA). The performance and morphologies were investigated based on different weight percent. Low amount of PEG 200,400 and 600 increase the urea removal as compared to high amount. The low molecular weight PEG 200 showed the best results for the urea removal through dialysis membranes. Human blood test showed that up to 24.62%, creatinine 5.75% and Uric acid 15.95% could be removed through CA membranes [92]. It concluded that changing the additive PEG changed the uniformity and membrane pore size which effect the permeation. This research lacked in the separation of the middle and large size toxins.

In 2006 Li et al. [93], synthesized CA membranes using liquid-liquid demixing of solvents such as N-methyl pyrrolidone and γ- butyrolactone (GBL). Clearance properties of the membrane improved by controlling the amount of GBL. It turned the macro voids into sponge like structure which enhanced the permeability and flux of the membranes..

Chou et al. [94] in 2007, investigated CA asymmetric hollow fiber membrane was fabricated to determine the pure water flux (PWF) and protein retention. PEG was added as an additive. By increasing the amount of PEG dextran rejection and PWF increased. It also reduced the macro voids and changings in coagulation temperature enhanced the permeability performance.

In 2008, Saljoughi et al. [95], CA membranes were casted with various composition of Polyvinyl pyrrolidone (PVP) as additive. Two parameters PVP and coagulation bath temperature (CBT)concentrations were changed during the study. By varying, the additive macro voids occurs, enhancing the pure water flux (PWF). In the case of CBT, it decreases the formation of macro voids thus reducing the PWF and hydrophilicity of the membrane.

In 2009, Ani Idris et al. [96] ,published another study on CA dialysis membranes. D-glucose monohydrate was added as additive in CA membrane fabricated by phase inversion method. Main purpose of this research was to investigate the toxins removal from the blood in terms of D-glucose monohydrate. Macro voids formation promoted by this additive which increased the removal of creatinine and urea up to 19.54% and 49.77% respectively. 96.78% of the BSA retained revealed by the results. D-glucose monohydrate considered as the appropriate for the dialysis membranes.

In 2009 Mahlicli et al. [97] published a research on the cellulose acetate hemodialysis membranes modified by urease enzyme immobilization. Research was focused on the protein adsorption capability and toxins transportation through the membrane. CA membrane was chosen for the modification with urease enzyme immobilization. Through CA modified membranes the permeation results for the urea and creatinine enhanced due to the spongy structural change in the membrane. The rates of the uric acid also enhanced in comparison to pure CA membranes. It was revealed that the protein adsorbed on the surface of the membrane and decreased the loss of the protein from the plasma.

Kee et al. in 2010 [5], carried a research on the CA solution contained various concentration of monosodium glutamate (MSG) and formic acid. Results revealed that by increasing the amount of MSG up to 6 wt% removal of toxins also enhanced. After this weight percent the permeability did not improved. The membrane surface roughness increases with the amount of MSG which provided the high ultrafiltration rates converting the CA high flux membrane. The negative effect of MSG was also explained in this study that membrane has very low tensile strength value due to the formation of the macro voids. It can overcome using high molecular weight CA. Results showed that the BSA rejection was up to 94.72%, 156.67±12.55×10−4 cm/min

and 84.15±5.67×10−4 cm/min was the permeation for the urea and creatinine, respectively.

Asymmetric Cellulose acetate (CA) membranes were synthesized by E. Saljoughi et al. in 2010 [98]. The membranes were fabricated by phase inversion method using Polyethylene glycol (PEG) and 1-methyl-2-pyrrolidone (NMP) as an additive and solvent, respectively. The study was done to investigate the morphology, thermal and chemical stability of the membranes, pure water permeability (PWP) and human serum albumin (HSA). Results revealed that by increasing the CA/PEG concentrations and reducing coagulation bath temperature (CBT) the thermal and chemical stability increased. By increasing CBT and decreasing CA/PEG resulted in increased PWP and HSA.

Saljoughi et al. [99] in 2010, fabricated symmetric CA membranes with additive PEG/NMP by phase inversion process. It investigated the PEG and CBT behavior on the membrane morphology. Increasing PEG concentration with higher CBT enhances the macro voids, PWF and membrane thickness. On the other side, increasing PEG concentration along with lowering CBT improves the thermal stability of the membrane. Varying the molecular weight of the PEG also increases the porosity and permeability of the membrane.

Hollow fiber membrane of CA base polymer was fabricated by S. Yu et al. [100] in 2013. Then modification of cellulose triacetate semi-permeable membrane was done by hydrolysis and carboxymethylation. Effects of modification was examined by SEM and FTIR. Surface hydrophilicity and membrane pore size improved by hydrolysis. Carboxymethylation had increased the negative charge and effected porosity of the membrane. This study concluded that CA modified membrane showed better results than the pure CA membranes.

In 2013, Han et al. [101] reported the carboxyethyl cellulose acetate CMCA/ CA blended membrane with PEG as additive to generate the pores. It decreased the contact angle to enhance the hydrophilic nature of the membrane and increaseof the PWP. The carboxymethyl effected the anti-fouling and permeability properties. Up to 86.3% of the BSA retained on the surface of the membrane.

M.S.L. Tijink et al. in 2014 [89],reported the study on the mixed matrix membranes (MMM) polyether sulfone or cellulose acetate /polyvinylpyrrolidone mixed matrix flat

sheet and hollow fiber membranes fabricated by phase inversion method. Activated carbon was used as the adsorptive particles in both cases. The MMM was examined mainly for the removal of creatinine and protein bound toxins by applying diffusion and adsorption method. Albumin was retained more by the membrane in diffusion method as compared to adsorptive method. Osmolarity and pH of the plasma changes significantly due to toxins removal in both cases. The amount of activated carbon in the membranes improved the removal of the protein bound toxins and it enhanced the permeation results. The work can be done one this composition by increasing the amount of activated carbon which ultimately affect the pore size and low or high flux of the MMM for hemodialysis.

Hizba et al.[102] in 2014 synthesized CA/PEI mixed matrix membranes which was investigated for the hemodialysis process. To investigate the importance and homogeneity of the PEI into CA various characterization techniques such as SEM, FTIR and AFM were done. The results for the water flux, urea, and creatinine clearance and BSA rejection are enhanced by adding formic acid as solvent than acetic acid , Dimethyl acetamide and 1-methyl-2 pyrolidone

chan et al. [103] in 2014, Polyvinylidene fluoride membranes with addition of functionalized multiwall carbon nano tubes (FMWCNT) and PEG additives were investigated. Results showed that hydrophilicity, urea, creatinine clearance and PWP improved by the interaction of the FMWCNT with PEG in PVDF membranes. Various characterization techniques were used to determine the results.

Ahn et al. [104] in 2014, CA flat sheet membrane with PVA coating was fabricated. PVA was used as surface modifying agent which effects the permeability, hydrophilicity and water flux. It improved the permeation by decreasing the average pore size of the membrane.

In 2016, Bernal-Ballén et al. [105] reported the fabrication of the bioartificial polymeric material membranes. Bilayer of cellulose acetate (CA) and polyvinyl alcohol (PVA) was successfully provided by the casting method. In this study, water vapor transmission and permeability determined based on PVA.

In 2016, Hizba Waheed [23] investigated CA flat sheet membranes using additives Polyethylene glycol (PEG) 400 and glycerol. The CA/PEG400/glycerol membrane was fabricated by the phase inversion method. First CA/PEG membrane was fabricated

and then modified by adding glycerol keeping the constant quantity of PEG 400. By this modification enhancement in the urea clearance was observed. After 10.1 wt% of the glycerol the rate of removal decreased. PEG and Glycerol combined hemodialysis membranes also showed better results for the separation of glucose

Xufeng Yu et al. [106] in 2017 investigated PVA hemodialysis membranes. Thin film nano fibrous composite membrane (TFNC) was fabricated for the high performance. PVA/PAN membrane showed excellent results for hemocompatibility, mechanical property and hydrophilicity. By this work,82.6% of urea was cleared and 98.8% of bovine serum Albumin rejected.

In 2017, Hizba Waheed et al. [107] reported CA membranes blend with additive Polyethylene imine (PEI).The purpose was to study the performance and morphology of CA/PEI blend membranes using solvents acetic acid, formic acid, 1-Methyl-2-pyrolidone (NMP) and N, N-Dimethylacetamide (DMAC). The best performing membrane was selected and was modified using various solvents to choose the best solvent that could enhance the membrane performance efficiently**.** For the dialysis application homogeneous and macro void formation is better. These membranes were tested for Bovine Serum Albumin (BSA) rejection and removal of urea. It focused on the separation of the small size toxins. Results showed that from all the solvents the formic acid solvent was easy to make a homogenous blending and gives the best results for the BSA rejection and urea clearance. Microporous hydrophilic membrane was able to be retained 95% of BSA and 63% of urea clearance.

In 2017, Hizba Waheed et al. [108] published the study on the comparison on the cellulose acetate membranes (CA) with cellulose acetate blend with hydroxyapatite (CA/HA) membranes. To increases the porosity of the membranes PEG was added the membranes were fabricated by phase inversion method. The results showed that by adding the HA in CA membranes, it modified the pore size. Glucose, urea, and water flux obtained was seven times higher than the pure CA membranes. The rejection of BSA was measured to be twelve times higher than the CA/HA composite membranes. Water absorption capacity was increased due to hydrophilic nature of the HA in the CA matrix.

For the hemodialysis membranes research published by Hizba Waheed et al. [109] in 2017, involving cellulose acetate (CA) blend with sericin. The purpose was to

investigate the performance of the CA membranes by changing the amount of sericin in the blend. The impact was examined on the urea clearance and BSA rejection by varying CA/sericin blend membranes. It was concluded that sericin due to its protein nature was responsible for the 96% rejection of the BSA through the membrane and urea clearance up to 60%.

Cellulose acetate hemodialysis membranes could be fabricated in hollow fibers to obtain more permeate and toxin removal. In 2017, Raharjo et al. [110] researched on the cellulose acetate hollow fibers for hemodialysis application. The flux and rejection of the proteins were tested by the membranes. Acetone and formamide was added in CA in 51% and 27% ratio, respectively. The samples were fabricated on different temperatures 5°C to 25°C with the 5°C intervals. The air gap distance was also varied from 15 cm to 30 cm with 5 cm distance interval. Results showed that urea flux of 49.4 L/m^2h and the rejection of urea up to 19.65%. Modifications can be done in this work for the BSA rejection.

Ani Idris et al. in 2018 [111], investigated the removal of urea through CA hemodialysis membranes based on water content and acetic acid/PEG ratio. ANOVA analysis was done to investigate the urea clearance by acetic acid/PEG ratio and water content. It revealed that significant improvement was obtained based on the ratio of acetic acid/PEG. Finger like macro voids formed on higher ratio of acetic acid/PEG which ultimately enhanced the urea clearance. Results showed that also with lower ratio urea removal decreases because of the formation of dense spongy macro voids. It concluded that urea clearance and morphology of the dialysis membrane does not change with the amount of water.

Seddik et al. [112] in 2019, focused on the management of ketoacidosis in CKD patients treated by hemodialysis. Insulin secretion decreases in CKD patients because of acidosis, lack of calcium and second hyperthyroidism. In patient's diabetes and many other abnormalities occurred during hemodialysis.

Juan Martin- Navarro [113] in 2019 found that dialyzers in dialysis process face problems with the biocompatibility of the membranes. Reactions occurred between them and remained stable for years. With polyvinylpyrrolidone and poly sulfone results had been reported but cellulose triacetate is considered as appropriate for the treatment.

Lusiana et al. [114] in 2019, fabricated blended membranes of citric acid cross-linked with chitosan/PEG-PVA. Heparin graft with an active sulfate group on blended membrane. Citric acid and grafted heparin increase the mechanical strength and membrane swelling. This membrane also improved urea and creatinine permeation.

In 2019, Hizba Waheed et al. [115] reported the study on the CA membranes using the additive polyvinylpyrrolidone (PVP). Flat sheets were fabricated using the phase inversion method. With the addition of the PVP in the CA matrix hydrophilicity was enhanced. Testing showed that pure water flux, BSA rejection and urea clearance percent increased with the amount of PVP in CA matrix. In comparison with CA membranes, it concluded that 62% urea reduction and 99% BSA rejection was obtained.

Cellulose acetate (CA) mixed matrix membrane (MMM) having polyaziridine as additive was introduced by Hizba waheed et al. in 2019 [102].The MMM was fabricated by the diffusion-induced phase separation (DIPS) method. The morphology and performance of the CA membranes was examined by variation in the amount of polyaziridine. The results revealed that hydrophilic MMM membranes rejected more than 90% BSA in comparison to pure CA membranes. 67.6% of the urea separated by polyaziridine/CA MMM relative to pure CA membranes.

Raharjo et al. published an article on the modification of Polyethersulfone (PES) with cellulose acetate, in 2019 [116]. PES can be widely used in hemodialysis application using diffusion, adsorption, and mixed matric membranes but it has less permeability for the uremic toxins. In this study, the PES/CA mixed matrix by dry-wet spinning technique was used to fabricate the hollow fiber modules using imprinted zeolite to enhance the permeation. The results showed that PES/CA/IZC membranes improves the creatinine removal up to 74.99% relative to PES/CA membranes. BSA rejection increased up to 79.05% which was 2.5% more than the PES/CA membranes. It concluded that PES/CA/IZC can be considered as hemodialysis membranes and work can be done on the removal of small size and middle size toxins.

CHAPTER 4

Research Methodology

4.1.Selection of material

4.1.1 Cellulose acetate

CA can be prepared from different unprocessed raw materials like cotton plant, rice husk, sugarcane straw and bagasse [117]. It can be synthesized in two steps. Extraction of cellulose from raw material is done in first step, and second step is cellulose acetylation. Cellulose has both crystalline and amorphous structure. Ether bond joined the anhydrous glucose molecules structure of CA and forms β-1, 4 glycoside linkages. The hydroxyl group of the anhydrous glucose can be replaced by acetyl groups in 2, 3 and 6 positions [118]. The thermo plasticity of the CA could be enhanced by the ether bonding and esterification done on the free hydroxyl groups.

CA is considered as cheap, nontoxic, and commercially available which make it useful for the hemodialysis membranes. Hemodialysis membranes fabricated by CA are porous and gives the required amount of flux which is attractive for the hemodialysis process. CA asymmetric membranes are highly performing membranes for the blood purifications and complement system activation could be reduced [119]. CA is considered as bioincompatible polymer as compared to other polymers. Its biocompatibility can be enhanced by increasing the hydroxyl group in the composition by interaction with the biocompatible additives [120].

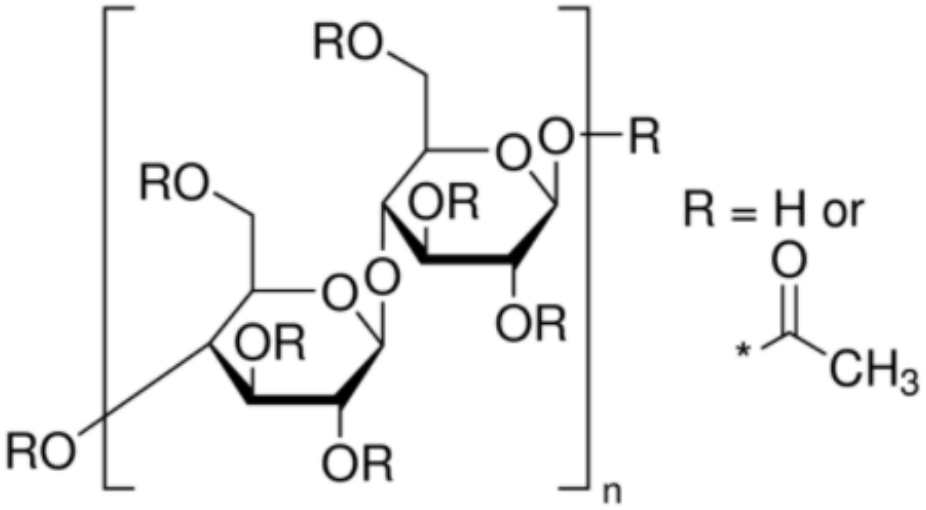


Figure 4.1 Structure of Cellulose acetate (CA) [121].

4.1.2 Polyvinyl alcohol

PVA is usually synthesized by the alkaline hydrolysis of polyvinyl acetate. It consists of 1, 3-glycol structure by chemical perspective. Its solubility depends on many factors such as lower to higher molecular weight, free OH groups in the molecule, aldehyde radicals [122]. The acetate group quantity changes the solubility of the PVA. If PVA contains 5% of acetate group, it easily soluble at 60-70°C. Presence of 12% of acetate groups make the PVA very water soluble. If the acetate groups reaches to 20-30%, PVA dissolves at 30-35°C. PVA becomes insoluble in water when acetate groups exceeds than 50% [123].

PVA also has importance in biological field [122]. It has been widely used in medicines because human body is able to tolerate it without any difficulty. Pharmaceutical technologies prefer it because of hydrophilic nature and has biocompatibility property. It prevents the cell attachment, protein adsorption and proliferation. It is the promising biomaterial used in tissue engineering [124].

Large number of applications of PVA have been reported in hemodialysis membrane technology. because of the dehydration of organics and good flux PVA hemodialysis membranes are widely used. It has poor selectivity due to membrane swelling, so PVA blends with various polymers are reported to enhance the performance [125]. Recent research has been done to enhance the performance of the membrane by various optimization techniques such as crosslinking, mixing and grafting of reacting agents.

It has good film forming properties with physical and chemical stability, so efficiently used for the ultrafiltration, microfiltration and hemodialysis membrane [126]. In this research work, PVA is used due to its hydrophilic nature which enhances the hydroxyl functional group in the CA membranes and increase the biocompatibility. The porosity of the membranes and adsorption of the protein bound toxins increases on the membranes surface due to hydrogen bonds and carboxyl groups [90].

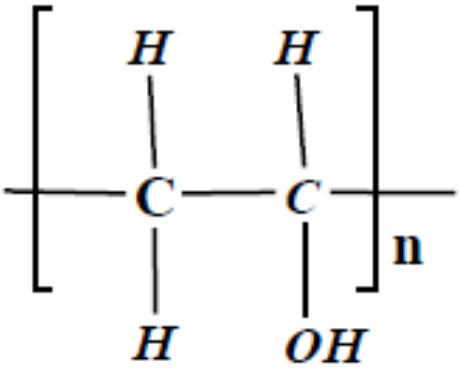


Figure 4.2 Structure of Polyvinyl Alcohol (PVA) [127].

4.1.3 Polyethylene glycol

PEG is the synthetic polymer with important properties consisting of low cost, biocompatibility, pore generation and water-soluble. It is the widely used polymer in pharmaceuticals and medical dew. Good solubility, low toxicity, enhances the smoothness of the material are properties of the PEG. It also prevent immune responses, complement activation, attachment of platelets and protein adsorption [128]. Latest researched showed that PEG increases the hydrophilicity and porosity of the membranes. Hemodialysis membranes having PEG in composition are highly porous and properties in terms of flux, permeability, size of pore and protein retention [129]. These properties are attractive and useful for the hemodialysis membranes.

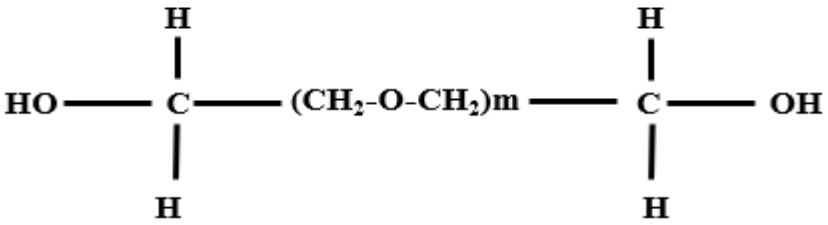


Figure 4.3 Structure of Polyethylene Glycol(PEG) [130].

4.2.Materials and methods

4.2.1 Materials

CA (average molecular weight of 30,000 Da, Sigma Aldrich was utilized as base polymer. Acetic acid was used as solvent analytical purity of 99%. Polyethylene glycol (PEG) 400 (Aladdin) was used as an additive. Polyvinyl Alcohol (PVA) with 31,000 Da average molecular weight (Sigma Aldrich) was used as modifying agent to blend with CA. Non-solvent agent is distilled water. Experiments were performed using urea 60.02 Da and creatinine 113.54 Da and Bovine Serum Albumin (pure) was obtained from Sigma Aldrich. The 500 mL whole anticoagulant blood of sheep was purchased.

4.2.2 Methods

4.2.2.1 Solution Preparation

PVA of 25 wt% concentrated solution was prepared in distilled water. 25 g PVA was dissolved in 75 g of distilled water at 90°C with 12 hours continuous stirring to make homogenous solution. Casting solutions with different compositions of CA/PVA/PEG blend were prepared with different PVA weight percentage in acetic acid having constant CA wt% of 11 and PEG wt% of 2. Table 4.1 shows the composition of casting solutions prepared during this work. For the homogeneous mixing the solution was stirred for 24 hours at 70°C. After polymer was totally dissolved, as shown by the transparent appearance, it was sonicated for 2 hours and slow down its ageing process placed away from light.

Table 4.1 Composition of membranes

Membrane	CA wt%	Acetic Acid wt%	PVA wt%	PEG wt %
CA	11	87	-	2
CA-PVA 1%	11	86	1	2
CA-PVA 1.5%	11	85.5	1.5	2
CA-PVA 2%	11	85	2	2
CA-PVA 2.5%	11	84.5	2.5	2

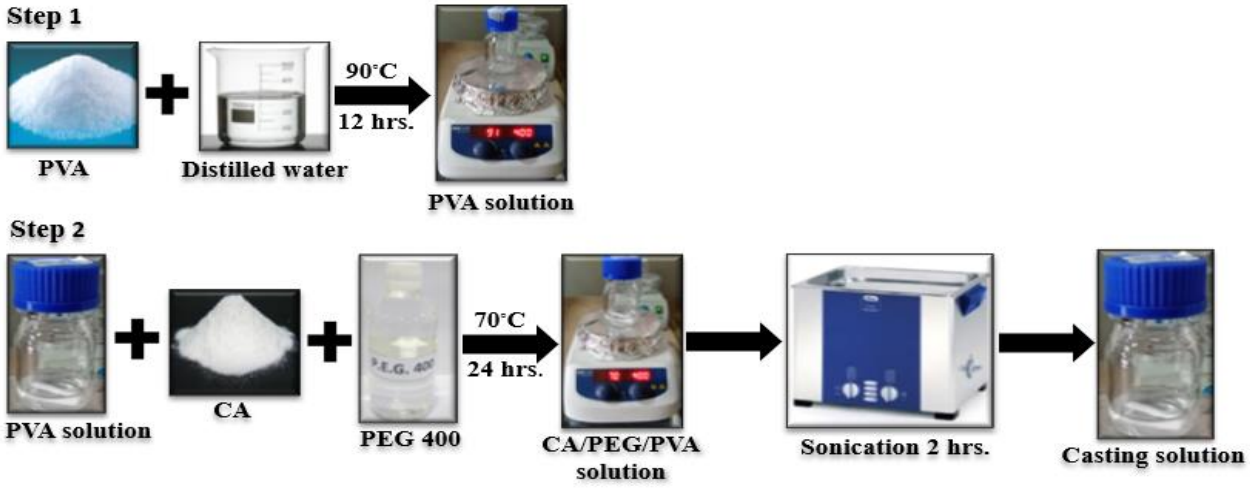


Figure 4.4 Solution preparation process

4.2.2.2 Membrane casting

The casting solution was casted on a glass plate at room temperature with a thickness of 200 µm utilizing casting knife. After evaporating the solvent for 30 seconds, film was then soaked in a coagulation bath for the completion of the phase inversion, where interchange between the non-solvent (distilled water) and solvent (acetic acid) occurred. At 25°C film was immersed in bath for 30 minutes. Then the membrane was placed to glycerol container 30 minutes as post treatment for the removal of excess solvent, increases the smoothness and strength of the membrane. After that, the membrane was transferred to another distilled water container at 25°C to remove glycerol so that the pores must be clearer. After removing the membrane from coagulation bath, it was post treated by air drying.

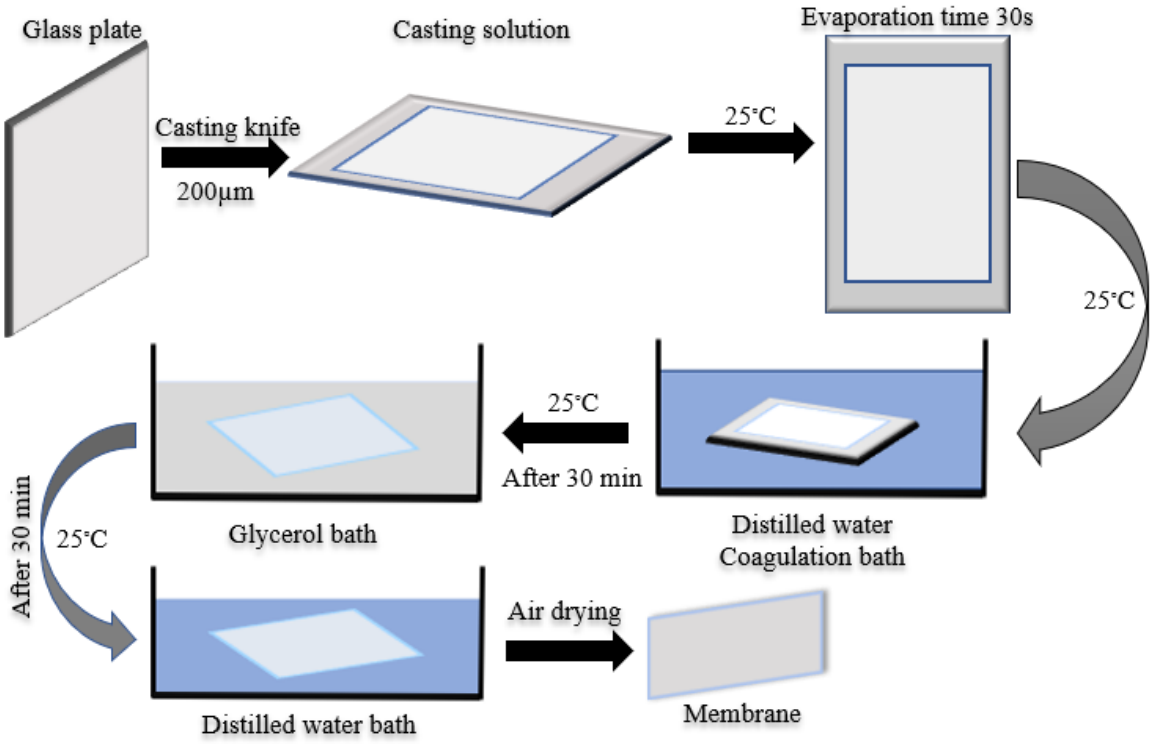


Figure 4.5 Membrane casting process

4.3. Membrane characterization

4.3.1 Scanning Electron Microscopy (SEM)

It is the most important technique, which helps in characterizing the membrane surface, morphology, size of pore and membrane thickness [131].

In SEM analysis, using the resisting heat a beam of electron is produced through thermionic process. The electron beam reacts with sample is converted into secondary electrons, backscattered electrons an X-rays. It produced images of membrane's surface and cross-section [132]. An image is displayed on the monitor after detection. 10 kV voltage was used to record the magnifications of X250, X500, X1000, X2000, X5000, X10,000, X15,000.The membrane sample was cracked in liquid nitrogen using dual sided bondable tapes in a lateral position and mounted onto brass plates. For the detection of the morphology of surface and cross-section of pure and blend membranes SEM model JSM 6409A, JOEL, Japan was utilized. In most of all the experiments, three samples of each composition were tested to ensure results.

Figure 4.6 Scanning electron microscopy (SEM)

4.3.2 Fourier transform infrared spectroscopy (FTIR)

FTIR is the characterization technique, which shows the changes happened in functional groups and elemental chains of polymer and can give detailed information on the covalent bonding. It has a function of high spectral resolution and to measure over a wide range in short period of time [133]. 100 PerkinElmer, MID-IR FTIR Spectrum instrument was used for the FTIR measurements of the membrane samples. The pure and blend membranes pieces were cut and kept in sample holder. The holding was then set-in above-mentioned instrument. 500-4000 cm^{-1} wave number range was used with 1 cm^{-1} in transmission mode at 25°C. Three samples for each composition of the membrane were tested to ensure results.

Figure 4.7 Fourier transform infrared spectroscopy (FTIR)

4.3.3 Atomic Force Microscopy (AFM)

AFM used to examine the roughness of the surface of pure and blend membranes. It was a replacement of the scanning tunneling microscopy. It is consider a best tool designed to use the level of sensitivity [134].

JSPM-5200, Japan with 3D micrographs instrument was used for AFM. It was used in tapping mode. Approximately 10μm×10μm membrane area was used for the scanning. AFM software program determined the roughness parameters of the sample membranes from AFM images. In roughness data 'Ra' is the average roughness and 'RMS' represent root mean square roughness of membrane surface.

Figure 4.8 Atomic force microscopy (AFM)

4.4.Membrane testing

4.4.1 Porosity of membrane

Porosity determines the diffusive transport of the membrane. Ratio between the void volumes present in the membrane to overall volume of the membrane [135]. For flat sheet, gravimetric method was used. 1×1 cm^2 area of the membrane was cut and oven dried. After that, weighed and then for 24 hours immersed in distilled water and weighed again. The membrane porosity was obtained using Eq. (4.1)

$$\text{porosity } \epsilon = \frac{\frac{W_{wet} - W_{dry}}{\rho_w}}{\frac{W_{wet} - W_{dry}}{\rho_W} + \frac{W_{dry}}{\rho_p}} \tag{4.1}$$

Where W_{dry} and W_{wet} are the of dry and wet membranes weights (g) whereas $\boldsymbol{\rho}_w$ is the pure water density (g/cm^3) and $\boldsymbol{\rho}_p$ is the polymer density (g/cm^3), respectively [109].

4.4.2 Water uptake

Slow swelling phenomenon appears by the diffusion of solvents in the polymeric chains that leads to swelling of the membranes [108]. .Swelling is recommended because it avoid membrane dissolution by displacing polymer-polymer interactions to polymer-solvent [136]. Cross-linking, inter-molecular interactions, and crystallinity are the ways to achieve the degree of swelling. It can be seen that at macroscopic level polymer or solvent can also change its properties [137].

1 cm ×1 cm area of the membrane samples was taken to perform test. Samples were oven dried for 12 hours at 60°C and weighted. After that, the samples were immersed in distilled water for 24 hours and weighed again [109]. The degree of swelling can be calculated by Eq. (4.2)

$$\text{water uptake} = \frac{W_{wet} - W_{dry}}{W_{dry}} \times 100 \qquad (4.2)$$

whereas,

W_{wet} = the weight of the wet membranes (gm)

W_{dry} = weight of dry membranes (gm)

4.4.3 Contact angle measurement

Water contact angle is termed as the angle formed between the active top layer surface of membrane and a liquid droplet. When solid, liquid and gas molecules come in interaction with each other, then liquid molecule forms angle at the three-phase boundary. It is the wetting ability of the polymer and helps to determine whether the surface is hydrophilic or hydrophobic [138]. If the theta angle is less than 90 it considered as hydrophilic but if it greater than angle 90 it considered as hydrophobic. Contact angle system OCA (Data physics, USA) was used to perform the test. The sample membranes were cut into stripes and the static contact angle was used to measure by the sessile contact angle. With the help of the micro syringe, distilled water dosing rate was adjusted to 0.1µL/s, with a constant dosing rate of 0.2 µL. The water drop was recorded on the membrane surface. On average three times the angle was measured on the membrane surface [107].

4.4.4 Mechanical properties

Tensile strength is a mechanical test, which determines the stress and strain of the membrane samples [105]. SHIMADZU, AGS-X used to test ultimate tensile strength of 50 kN. Strain rate of 0.5mm/min maintained for all samples by using ASTM-standard D 8802-02. It was done until the membrane was broken. This behavior was studied for all the samples individually.

Figure 4.9 Mechanical testing machine

4.4.5 Pure water flux

The most common test done in membrane prior to use is flux of pure water through the membrane. In this study, hydraulic permeability experiment was done on the dead-end filtration cell HP4750-Sterlitech. Experimental setup is presented in Figure 4.10 [139]. The main components of the experimental setup were (1) a nitrogen cylinder to supply the required pressure; (2) feed container where the feed was inserted (3) membrane filtration cell, (4) membrane piece, and (5) collected permeate container after membrane filtration.

To perform this experiment, distilled water was used as feed stream. To fill the volume of the module and stabilize the flow and pressure of the module the whole system was run for almost 10 minutes. The 0.00146 m^2 area of the sample membrane was used 2 bar pressure was maintained by nitrogen gas. The experiment was run for 1 hour and

50 minutes at room temperature to achieve the constant flux. For every 10 minutes permeate was collected in a beaker. The pure water flux was calculated by using eq. (4.3) [109].

$$J = \frac{V}{A \times T} \tag{4.3}$$

Where J is the flux, L/m^2h. T is the time in hours. The total area A of the membrane in m^2. V is the volume of the permeated water in Liters.

The permeability ($L/m^2h^1bar^1$) was calculated by the following eq. (4.4)

$$\text{permeability} = \frac{\text{Flux}}{\text{pressure}} \tag{4.4}$$

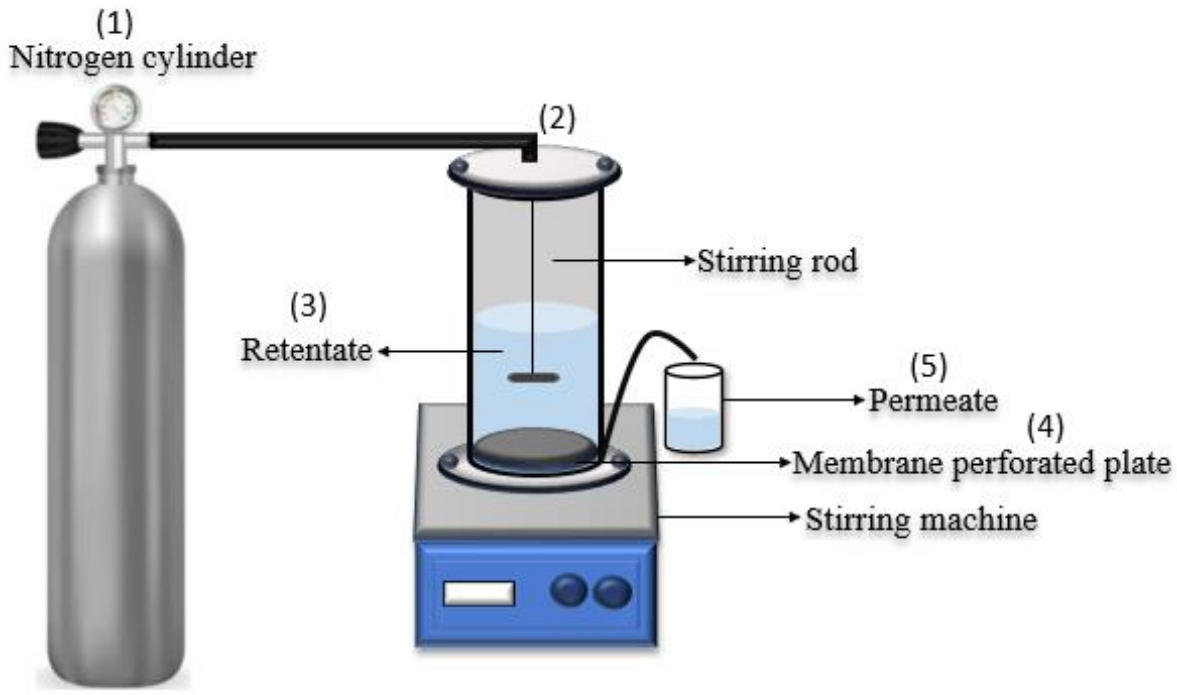


Figure 4.10 Dead end filtration cell setup

4.4.6 Dialysis experiment

Membrane dialysis experiments were done using the dead end stirred batch cell to examine the effect of the PEG and PVA additives on the BSA rejection, urea and creatinine clearance.

4.4.6.1 BSA rejection experiment

BSA rejection was calculated by a unit HP4750- Sterlitech with an operative membrane area of 0.00146 m^2 .1 mg/ml of BSA solution was prepared in distilled water at room temperature. Experiment was performed at room temperature at 2 bar pressure. BSA solution was used as feed stream and permeate was collected. During the whole process, stirring was maintained at 600 rpm to maintain the homogeneous solution [140]. The experiment was performed for 210 minutes. BSA was detected by using spectrophotometer (Shidmazu UV 1240) at a 278nm wavelength. The BSA rejection by the membrane samples was calculated by Eq. (4.5) [139].

$$\text{BSA \% rejection} = 1 - \frac{C_p}{C_r} \times 100 \qquad (4.5)$$

where C_p and C_r represented solution concentrations (gL^{-1}) in the permeate and retentate, respectively.

4.4.6.2 Urea and Creatinine Clearance

Hemodialysis membrane performance was estimated by toxins clearance. For the performance 1 mg/ml urea and creatinine solutions were prepared in distilled water at 25°C, which approximates the toxin concentration level of kidney failure patients [141]. Experiment was performed at room temperature at 2 bar pressure. During the whole process, stirring was maintained at 600 rpm to avoid concentration polarization [140]. The experiment for toxin removal was performed for 210 minutes and readings were taken after every 1 hour. The variation in concentration on the permeate and retentate side was measured by UV spectrophotometer (Shidmazu UV 1240) at wavelength 190 nm for both urea and creatinine. The clearance was determined by the Eq. (4.6) [92].

$$\text{Clearance \%} = \frac{C_i - C_f}{C_i} \times 100 \qquad (4.6)$$

where C_i and C_f are the initial and final concentrations in $g.L^{-1}$, respectively.

4.4.7 Biocompatible testing of the membranes

In hemodialysis various biological changes occur during the treatment and the blood interactions with the membrane surface is of primary importance [2]. For this reason, following test performed to evaluate the membrane performance.

4.4.7.1 Thrombus formation test

The formation of thrombus occurs whenever the fistula is attached to the vein or artery of the human body. If the blood vessels are damaged platelets helps in formation of thrombus and fibrin; coagulation of blood [142]. During hemodialysis, the process of hemostasis occurred to control the vascular damage and became a seal on the vein or artery of the human body.

For this experiment, 1×1 cm^2 membrane samples were immersed in the 1.5mL blood and incubated in 5% CO_2 for 2 hours at 37°C.Then the samples were washed by using the phosphate buffer solution. The samples were then dehydrated with graded ethanol [143]. Then, calculated the degree thrombus formation by Eq. (4.7)

$$DT = \frac{W_t - W_d}{W_d} \tag{4.7}$$

Where DT is degree of thrombus, W_t and W_d (g) represent the weight of blood coagulated membrane and weight of dry membrane, respectively.

4.4.7.2 Platelet adhesion

Platelets are the small blood cell fragments that causes clot formation in our body to stop bleeding. When arteriovenous fistula enters the body, platelets receive the signals and rush to the place of damage and forms clot to repair the damage. In the same manner biological reactions occurs when the membrane is exposed to the blood. The platelets start forming clot on the solid surface. The main purpose of this research is to minimize the amount of platelets attached on the membrane surface [144].

Centrifuge tube was taken in which 10 ml of blood was added, followed by centrifuging at 1000 rpm for 10 minutes. Platelet Rich Plasma (PRP) was obtained by taking out supernatant tubulars [141]. After washing with phosphate buffer solution (PBS) 1×1cm^2 membrane samples were added into the 24-well plate. Using the pipette 100 µL PRP was added by dropping on each sample and maintained at 37°C for 1 hour.

After that, PBS was used to rinse twice the membrane samples to remove unstable platelets. Glutaraldehyde 2.5 wt.% was added into the solution for 24 hours to attach the adsorbed platelets. In 50, 75, 85, 95, and 100% ethanol/water solution samples were dehydrated systematically for 10 minutes in sequence. Platelets adhesion was observed by SEM on blend membranes [145].

4.4.7.3 Hemolysis ratio

When hemoglobin is released in blood due to red blood cell lysis during collection and handling of blood samples is known as hemolysis [146]. Plasma is the major portion of the blood. Biological process occurs when blood in a vessel is exposed to the artificial solid surface. When the erythrocyte destruction is increased, causes release of hemoglobin hemolysis. By certain biocompatibility problems during hemodialysis, the plasma changes its color from transparent golden to reddish brown in color and reduce itself [147].

To perform this test, 1×1 cm^2 membrane samples were washed with deionized water thrice and then with aqueous solution of NaCl 0.9 wt% for 10 minutes in a sequence. After washing, the samples were immersed in the 0.9 wt% of NaCl solution at 37°C for 30 minutes in water bath. Whole 200 µL of blood was added in the NaCl solution and kept for 1 hour at 37°C. At 1500 rpm the blood was centrifuged for 10 minutes. UV spectrophotometer at 545 nm determined the top layer absorbance. Aqueous solution 0.9 wt.% NaCl was taken as a negative reference and pure water taken as a positive reference. The ratio was calculated by using the following Eq. (4.8) [36]

$$\mathrm{HR} = \frac{\mathrm{HS} - \mathrm{HN}}{\mathrm{HP} - \mathrm{HN}} \qquad (4.8)$$

Where HS represent the absorption value of membrane samples, HP and HN represent absorption value as negative reference and positive reference, respectively.

4.4.7.4 Plasma Recalcification Time

When the blood is exposed to the environment, it starts to coagulate. 20 to 45 minutes is consider as normal blood clotting time but if the anticoagulant is added in the blood this time increases [148]. During hemodialysis when blood touch the surface of membrane, it starts to coagulate and effect the biocompatibility. For this behavior, test was done by adding anticoagulant agent in sample to enhance the clotting time and biocompatibility of the membrane.

To perform this test, 10 mL anticoagulated blood was poured in the centrifuge tube and then centrifuged at 3000 rpm for 15 minutes. Plasma Poor Plasma (PPP) was taken as supernatant. 0.2×0.2 cm^2 sample area was taken in 48-well plate and added 200 µL drop of PPP into it. After that, incubate the culture plate at 37°C in water bath for 10 minutes. 0.025 mol/L $CaCl_2$ aqueous solution was prepared and 100 µL of solution was added in the sample. The time was calculated on the formation of fibrin thread. Experiment was repeated thrice for each sample and the average value was figured out [149].

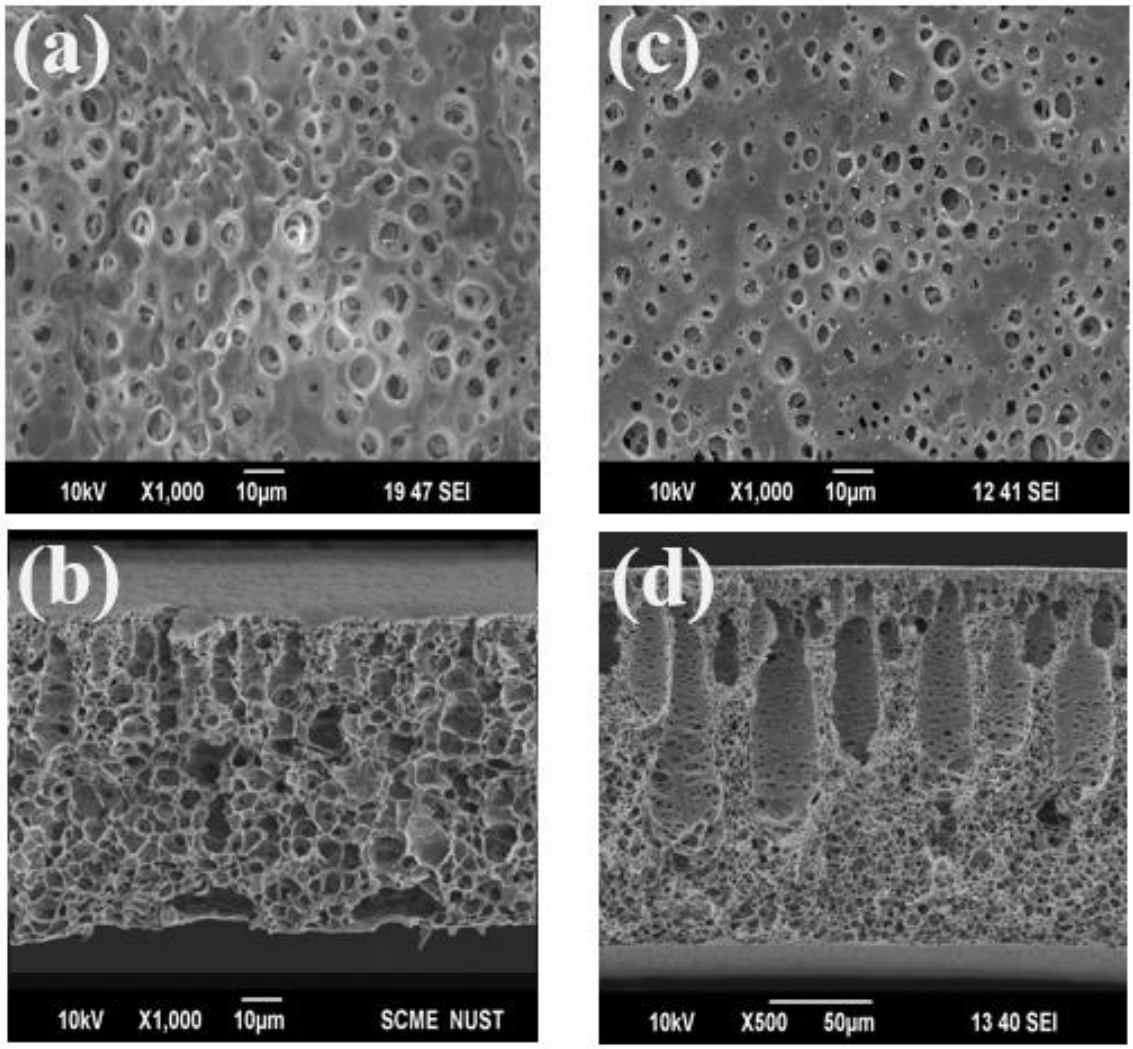
CHAPTER 5

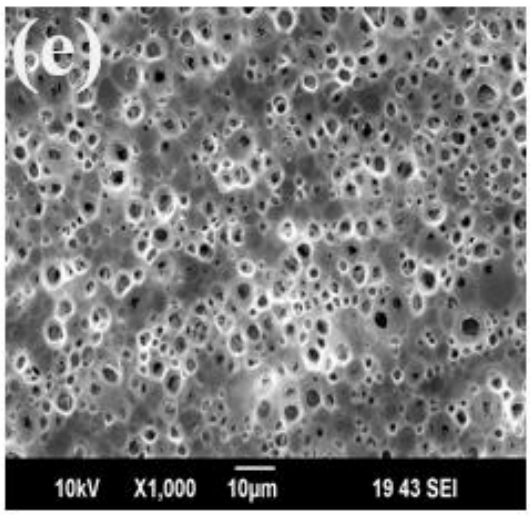
Results and Discussion

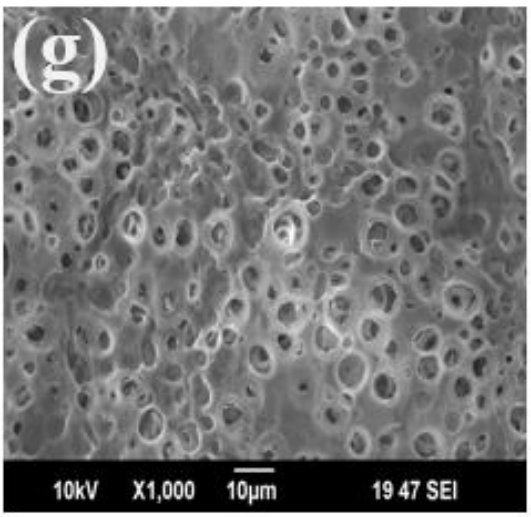
5.1. Scanning Electron Microscopy (SEM)

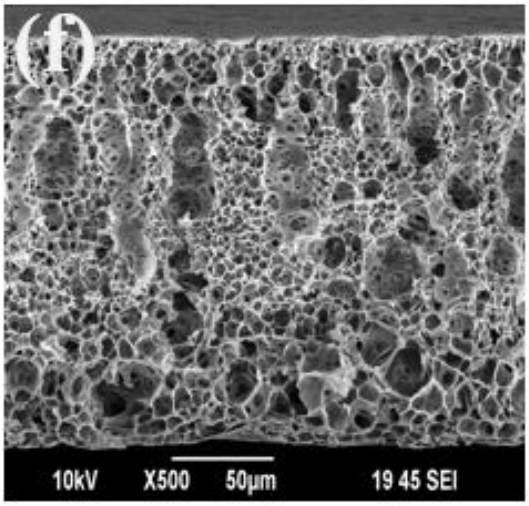
To study the morphology of the membrane SEM is basic analytical technique. CA and CA-PVA membranes cross sectional and surface morphologies were characterized by SEM. According to Figure 5.1 (a) CA membrane has less number of pores on the surface with average pore size 0.492 µm but in Figure 5.1 (b) cross section shows finger like structure featured as finger like cavities formed as same observed by A. Idris [92]. The addition of the PVA in CA/PEG blend showed the changes occurred on the surface as well as in the cross section. Figure 5.1 (c) CA-PVA 1% shows uniform pores formation of 4.04 µm of average pore size which is more than the CA membrane. The surface becomes more porous and the uniformity increases. The cross section in Figure 5.1 (d) indicated the structure change with the addition of PVA in the membranes. The macro voids structure changes forming pores in layers. Figure 5.1(e) CA-PVA 1.5% justified it by showing the more sub-pores and uniform structure with average pore size 6.93 µm. The porosity of this composition increases which provides the high solute removal results and protein rejection[150]. Figure 5.1(f) showed layers of pores and the change in structure forming pores and sub pores. As the PVA concentration increased from 1.5wt% the pore size started decreasing more than the required size. Finger-like structure also completely suppressed forming spongy structure. Figure 5.1(g) CA-PVA 2% membrane has the average pore size of 1.98µm, as a result, low flux and permeability visibly observed. The cross section in Figure 5.1(h) indicated the spongy and dense structure than the previous samples. The thick layer with average pore size 1.25 µm is formed on the membrane CA-PVA 2.5% surface showed the polymer concentration increases Figure (i). Figure 5.1(j) cross section indicated the dense and irregular structure. It determined that adding the PVA in CA-PEG blend membrane enhances the results. CA-PVA 1% provide the better results for the solutes removal than CA membrane. CA-PVA 1.5% showed maximum efficiency for the flux and solute removal, as the PVA acts as pore forming agent and forms regular structure which enhances the performance of the membranes [151].

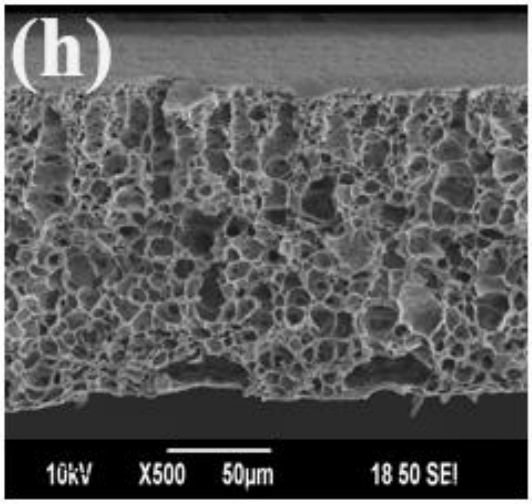
After that polymer quantity increased in the composition CA-PEG-PVA forming the membranes structure dense and spongy ultimately performance efficiency decreased [150].




(e)
10kV X1,000 10µm 19 43 SEI


(g)
10kV X1,000 10µm 19 47 SEI


(f)
10kV X500 50µm 19 45 SEI


(h)
10kV X500 50µm 18 50 SEI

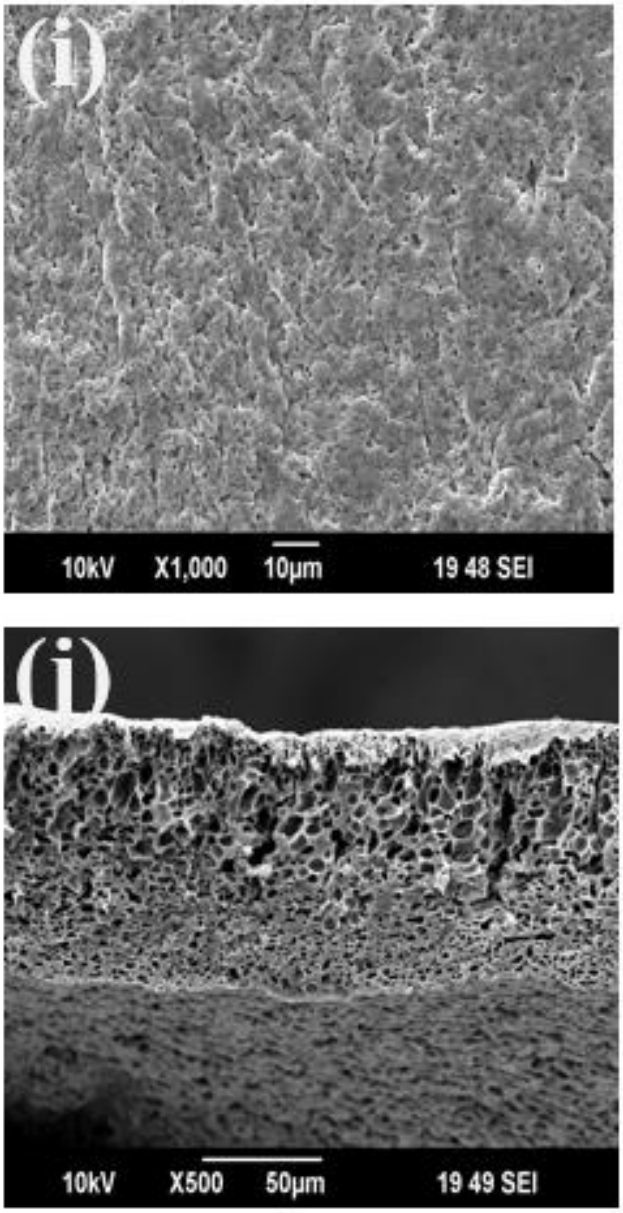


Figure 5.1 (a), (c), (e), (g) and (i) are the SEM images of surface of original and blend membranes; (b), (d), (f), (h) and (j) cross sectional morphology of membranes CA-PVA 0-2.5 wt.% respectively.

5.2. Fourier Transform Infrared Spectroscopy (FTIR)

For qualitative analysis of polymeric membranes FTIR is the important technique. Figure 5.2 shows the FTIR spectrum of different composition membranes. The FTIR spectra composite membranes with varying proportion of PVA are depicted.

In all spectra's, a band around 3486.53 cm^{-1} is seen and has been designated as the O-H stretching vibration. This band shows the hydrogen bonds intramolecular within the CA and by the addition of PVA intermolecular interaction hydroxyl groups of CA-PVA membranes. Strong band of O-H (3622.17-3210.92cm^{-1}), C-H (2940-2878.21cm^{-1}) and C=O (1733cm^{-1}) has shown the existence of CA-PVA blend in membranes.. In all the spectra's, the existence of C-O at (1246.61-1229.04) cm^{-1} and C-O-C at 1158 cm^{-1} shows the presence of PEG in all the CA-PVA blend membranes.

However, the amount of PVA increases the O-H peak stretches due to intramolecular hydrogen bonds and intermolecular hydrogen bonding of PVA and CA hydroxyl group [152]. C-H peak is attributed to the aliphatic chains from alkyl groups broadened in all formulations. These peaks become broad as PVA concentration increases because of the addition of the alkyl groups. The peak due to C=O are more stretched clearly from the carbonyl group [153]. C-O stretching of the acetate groups in the PVA is observed. The stretching of this peak is increasing due to interaction of CA-PEG-PVA. 1158 cm^{-1} represents the C-O-C ether group due to asymmetric stretching [23]. C-O-C is mainly showing the presence of PEG. The interaction of the bonds of the CA-PEG-PVA blend broadened the curve. Increasing the wt% of the PVA shorten the broadening of the curve. This phenomenon shows the possible interaction between PVA and CA-PEG.

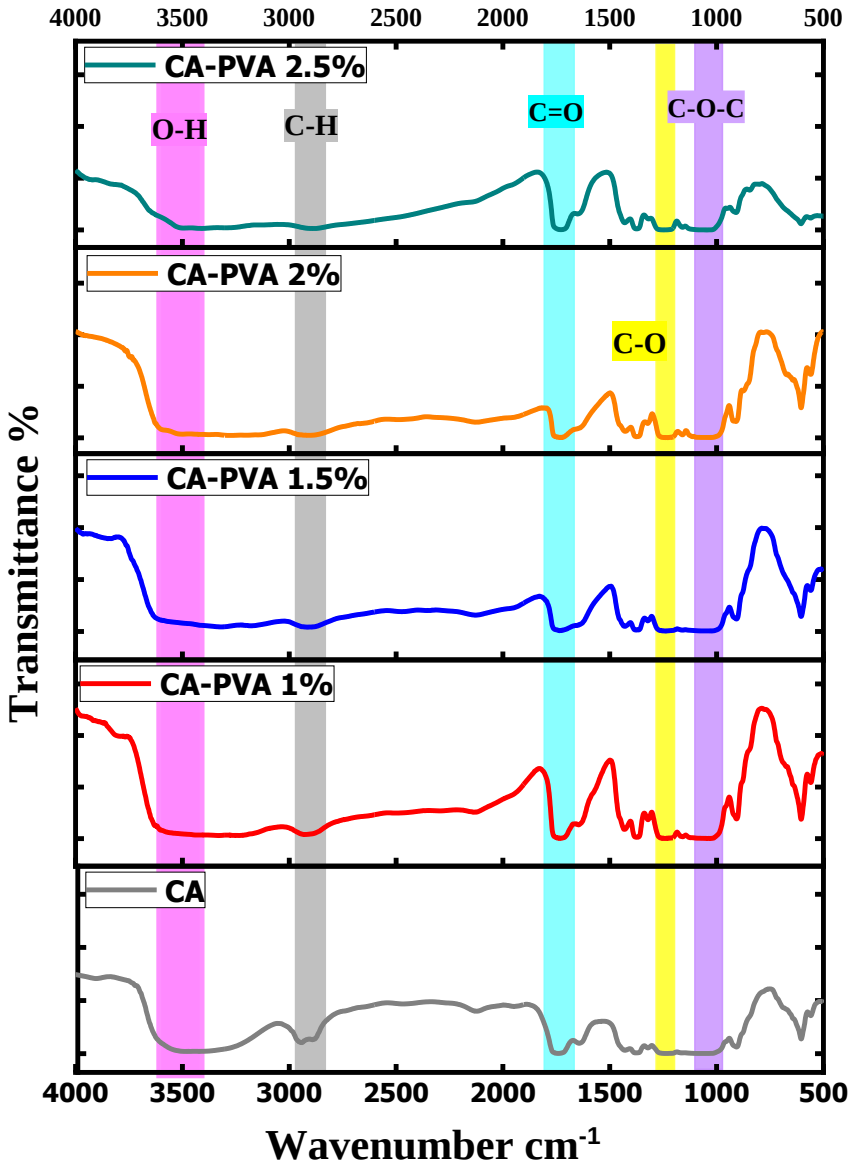


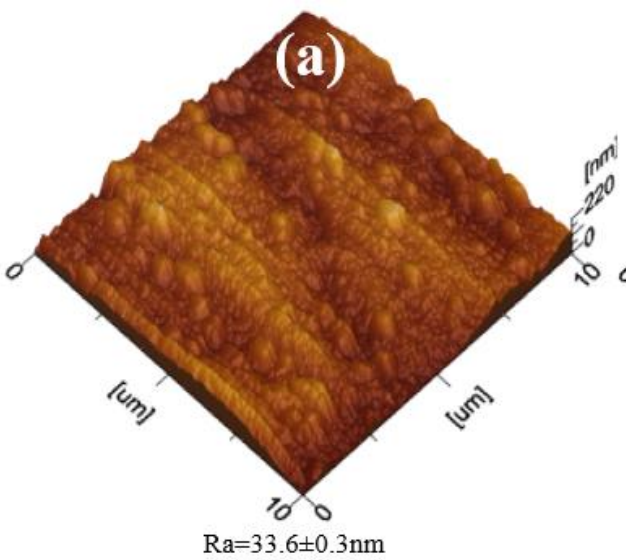
Figure 5.2 FTIR of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes

5.3. Atomic Force Microscopy (AFM)

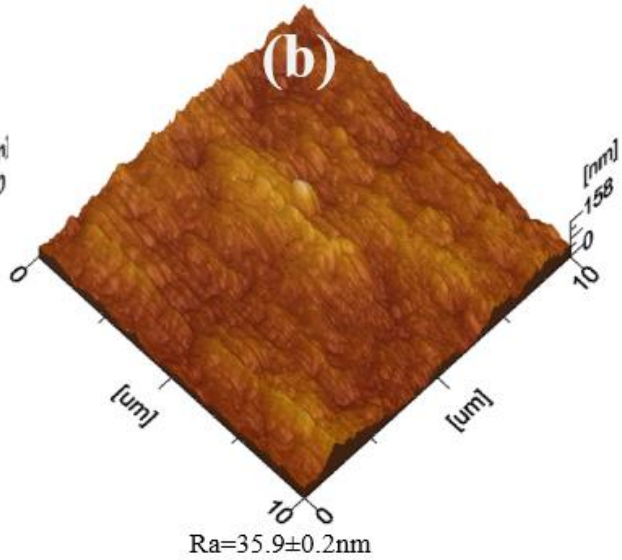
Surface topography of the membranes surface is shown in Figure 5.3. All the samples were determined under AFM in tapping mode. 3D AFM images of the top surface of all the membranes with scanning area of (10×10 μm) are taken. The dark regions showed depressions and the light regions defined the heights on the surface topography [154].

From the literature, it can be referred that CA membranes has smooth surface [92]. As the PEG added in the CA membrane's surface roughness of the membranes increases because of the pores and macro voids formation [23]. In CA-PVA 1% the increases in roughness of the membrane due to the formation of the pores more than the CA membrane and the structure of the macro voids deformed. CA-PVA 1.5% has the lowest roughness as compared to other samples. The lowest roughness trail to good biocompatibility results because of the low amount of protein adsorbed on its surface. It also assures high fluxes and low fouling rate [155]. CA-PVA 2% and CA-PVA 2.5% the increment in roughness of the membranes. The increment in depressions on the membranes showed the polymer quantity increases forming the membrane dense. It concluded that homogenous blends are formed. The addition of PVA in various composition increases the roughness of the surface due to formation of micro and nanopores in the membranes.

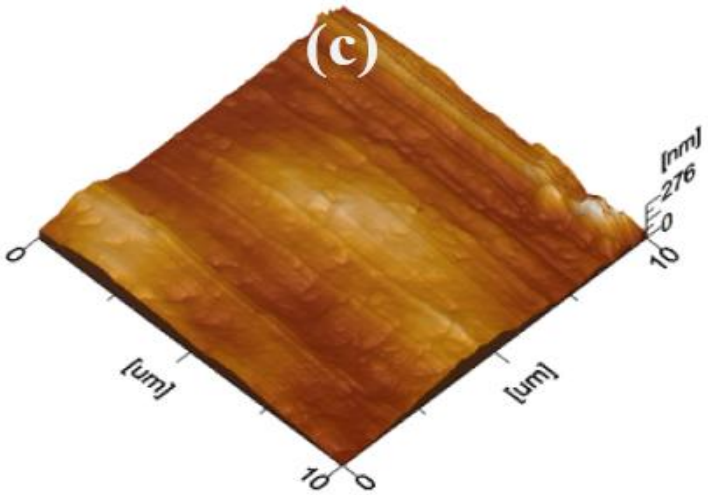
CA-PVA 1% roughness is more than CA sample due to large pores formation. Then the decreasing trend is shown for the 1.5 wt% sample exhibited smooth surface could be understood by the control small size pores and tightly packed polymer in the top surface [156]. After that the membranes CA-PVA 2% and CA-PVA 2.5% surface becomes rough because of the pore size is decreasing with an increment in composition of PVA in the casting solution.



Ra=33.6±0.3nm



Ra=35.9±0.2nm



Ra=21±0.3nm

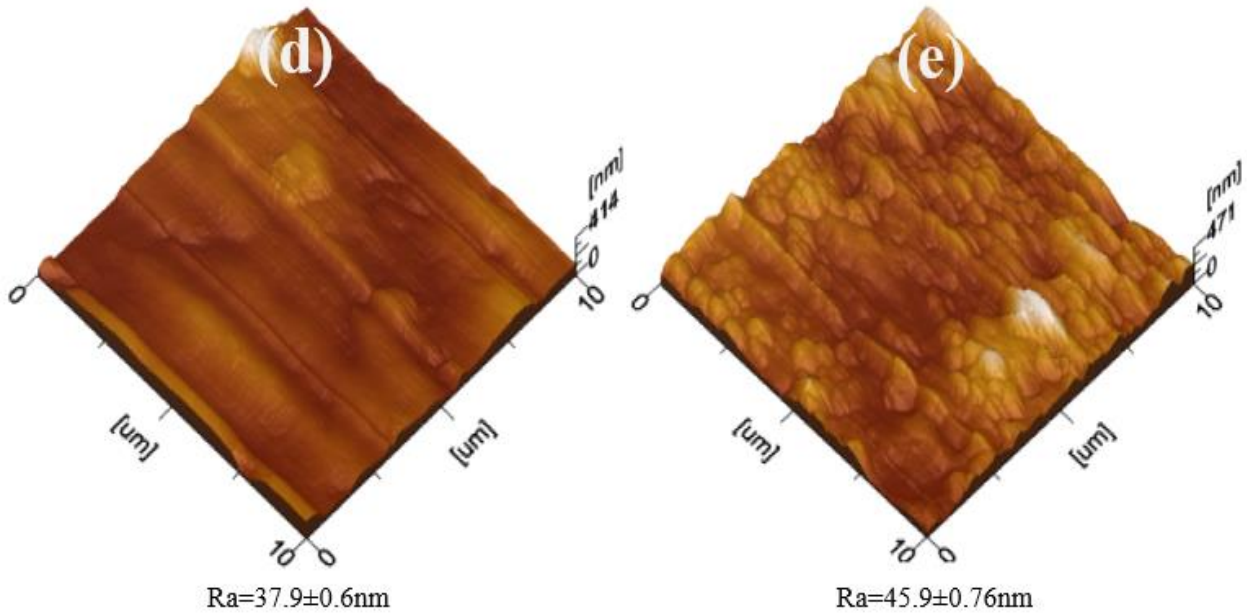


Figure 5.3 Surface roughness comparison from AFM images of membranes of CA-PVA 0-2.5wt.%.

5.4.Porosity of membranes

The permeability and flux are highly depending upon the porosity that allows the solute from the solution to pass across the membrane. The variation in pore size distribution and porosity has major influence on the permeability of the protein rejection and uremic toxins clearance [157].

Figure 5.4 elaborates that membrane porosity is enhanced from 80.6%±0.59 to above 92.5±0.56%. Porosity of pure CA membranes is less than the membranes in which PVA has been added. However, it has been observed that by increasing the amount of PVA the porosity has also been increased. CA-PVA 1% and CA-PVA 1.5% has the porosity of 87.1±1% and 92.5%±0.56 respectively. CA-PVA 1.5% is the highly porous membrane and finger like pore size increasingly expands. PEG and PVA in the composition acts as porogen resulted increase in the porosity. The flux and rejection of protein enhances with the increment in porosity. But the amount of PVA beyond 1.5 wt.% resulted in dense membrane formation and small pores on the surface. CA-PVA 2% and CA-PVA 2.5% compact membranes formed with low porosity in comparison to previous compositions due to the increase in the quantity of the polymers. The porous structure changes into layered and more spongy structure which decreases the performance results [158]. The trend shows that addition of the PVA formed the membrane more porous than CA membrane. As the PVA composition increases the membranes become highly porous which enhances the performance [159]. After composition 1.5 wt.% the trend decreases due to the formation of compact and dense membranes with low porosity.

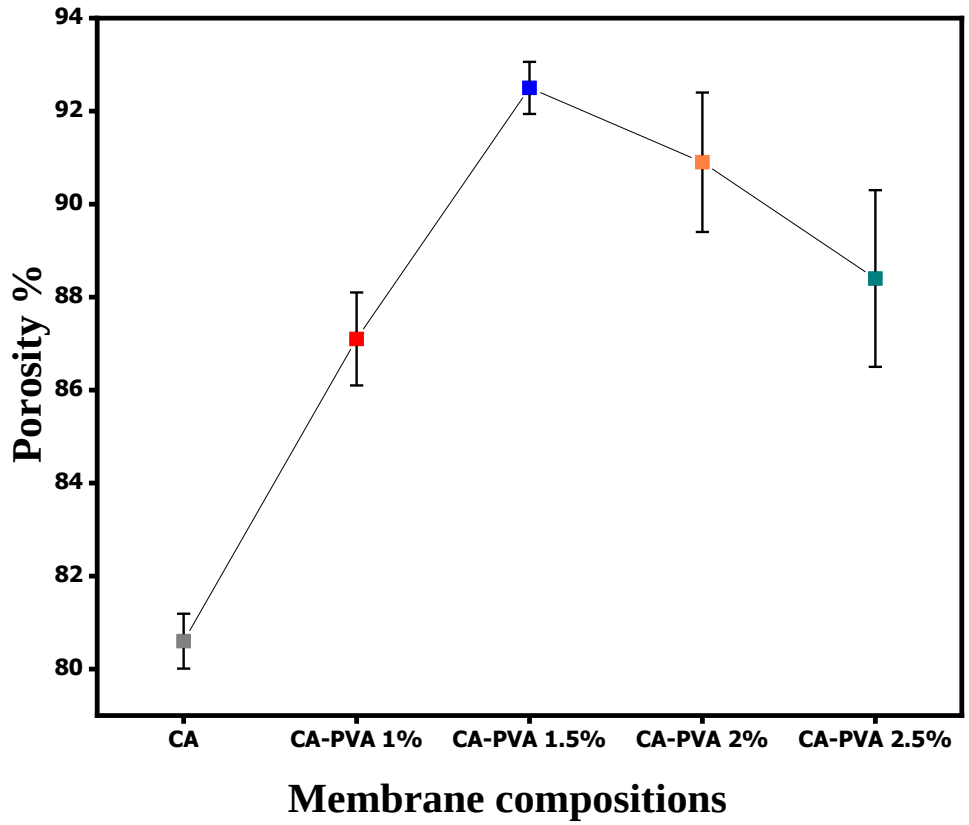


Figure 5.4 porosity% of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes.

5.5. Water uptake

This test basically determines the hydrophilicity and hydrophobicity of the membrane. High water absorption means low hydrophobicity [96].

Figure 5.5 indicated that CA sample has low value of water absorption up to 320%±37 due to less pores and macro voids in structure. CA-PVA 1% showed water uptake 620 %±34 which is more than CA membranes [160]. It shows that hydrophilicity enhances by the addition of PVA. The maximum absorption value 880%±27 was achieved at composition CA-PVA 1.5 wt.% due to the addition of more hydroxyl group than previous compositions. The membranes hydrophilicity increases which enhances the water absorption by the membranes. CA-PVA 2wt.% and CA-PVA 2.5wt.% shows the decrease in the water uptake 780%±31 and 725%±30, respectively. The water uptake of these two composition is higher than CA-PVA 1wt.% due to more hydrophilicity [104]. However, less than CA-PVA 1.5wt.% due to small pores and non-uniformity in the pore size of the membranes. The trend shows that water content increases due to decrease in finger like structure and enhancement in spongy structure. After CA-PVA 1.5wt.% the casting solution becomes dense and compactness of membrane increases. Due to which the water uptake of the membranes reduced.

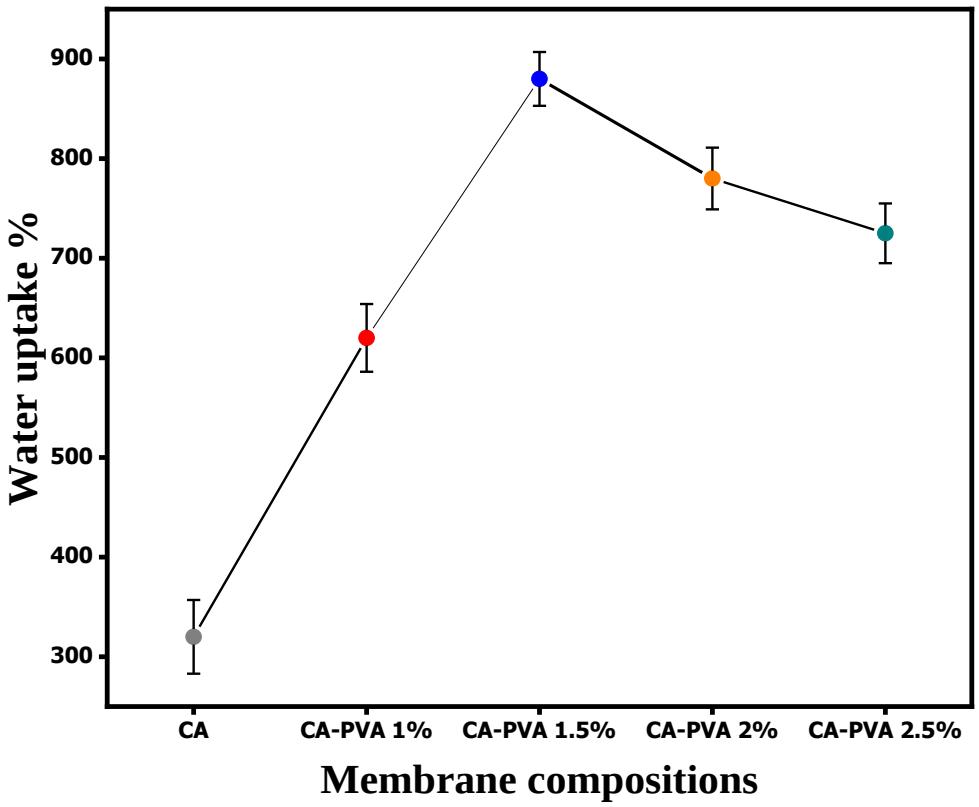


Figure 5.5 Water uptake of pure CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes.

5.6. Contact angle measurement

Water contact angle of the membrane is measured usually to determine the hydrophilicity or hydrophobicity. Contact angle less than 90° is considered as hydrophilic and the more than 90° as hydrophobic [161].

The addition of PVA in various composition the angle starts to decrease as shown in the comparison graph of CA and CA-PVA membranes in Figure 5.6. The angle of CA membrane has 52.3° which is more than the other samples due to absence of PVA in membrane indicated in Figure 5.7(a). The measured angle of Figure 5.7(b) CA-PVA 1% is 37.36°. The angle reduces due to the increment in hydrophilicity of the membrane. Figure 5.7(c) The CA-PVA 1.5% sample has the minimum contact angle 36.5° due to increases in the hydroxyl group. After 1.5wt% the angle start to increase but remain less than the CA membranes due to presence of more hydroxyl group. Figure 5.7(d)and(e) CA-PVA 2% and CA-PVA 2.5% increment in the contact angle 44.1° and 50.1° respectively, due to higher densities and compaction of the synthesized membranes.

It is concluded that PVA is an uncharged polymer that mostly increase the hydrophilicity of the membrane due to hydroxyl groups [126]. For optimum hemodialysis results the membranes should be hydrophilic [162]. In this work, membranes modified by PVA are hydrophilic justified by the contact angle measurement. The trend shows the reduction in the angle as PVA added in comparison to CA membranes. After CA-PVA 1.5% the trend shows the increment is due to compact structure of the membranes.

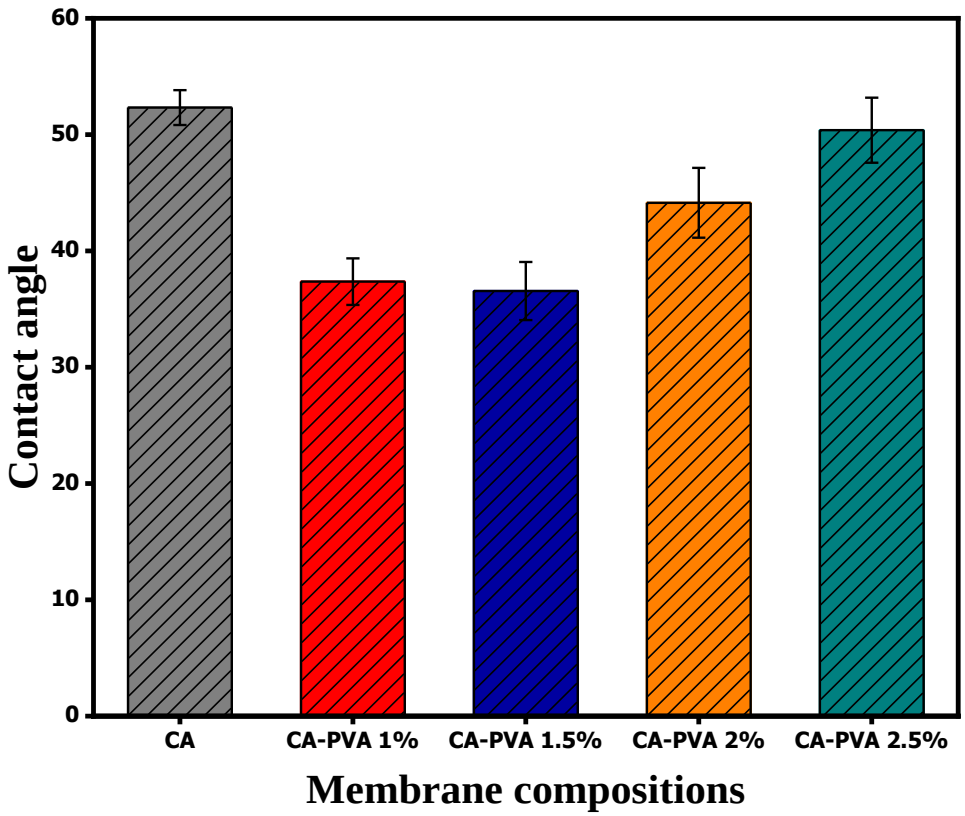


Figure 5.6 water contact angle measurement of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes.

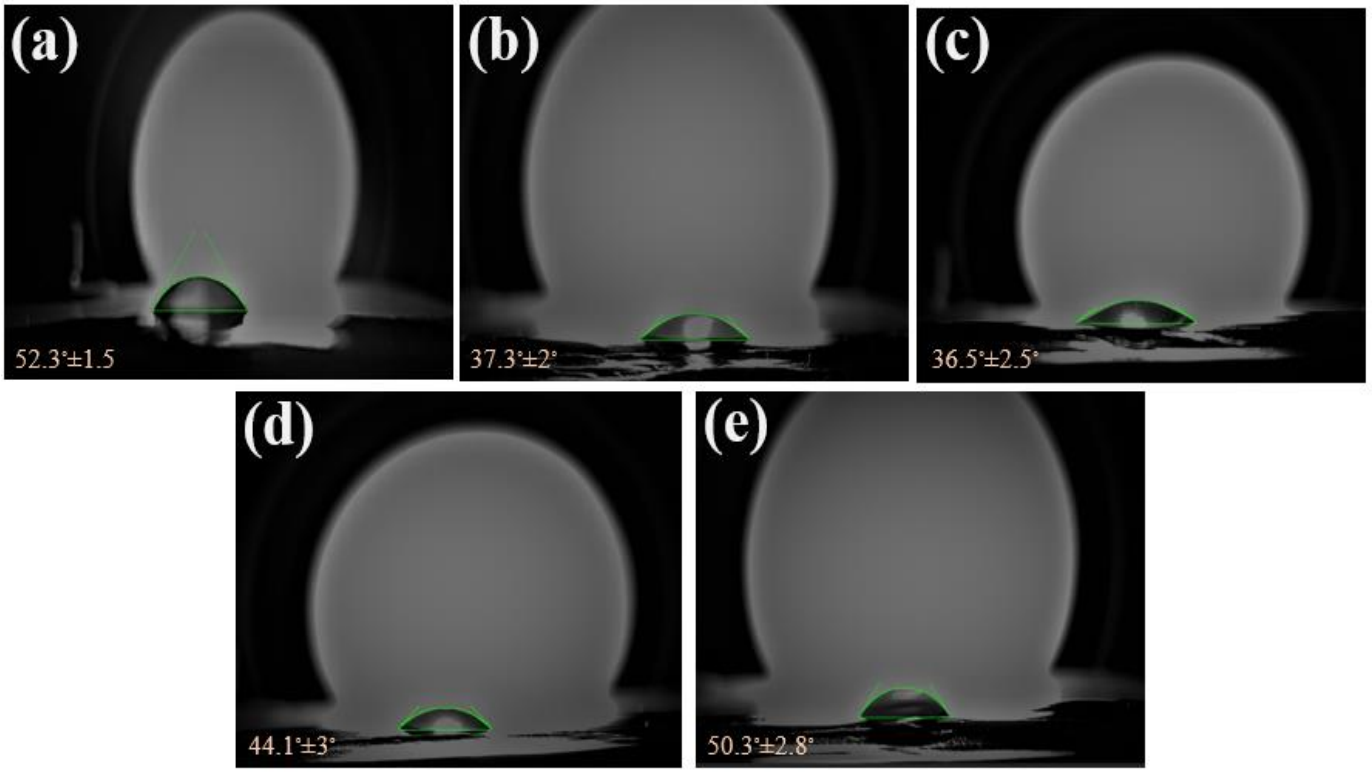
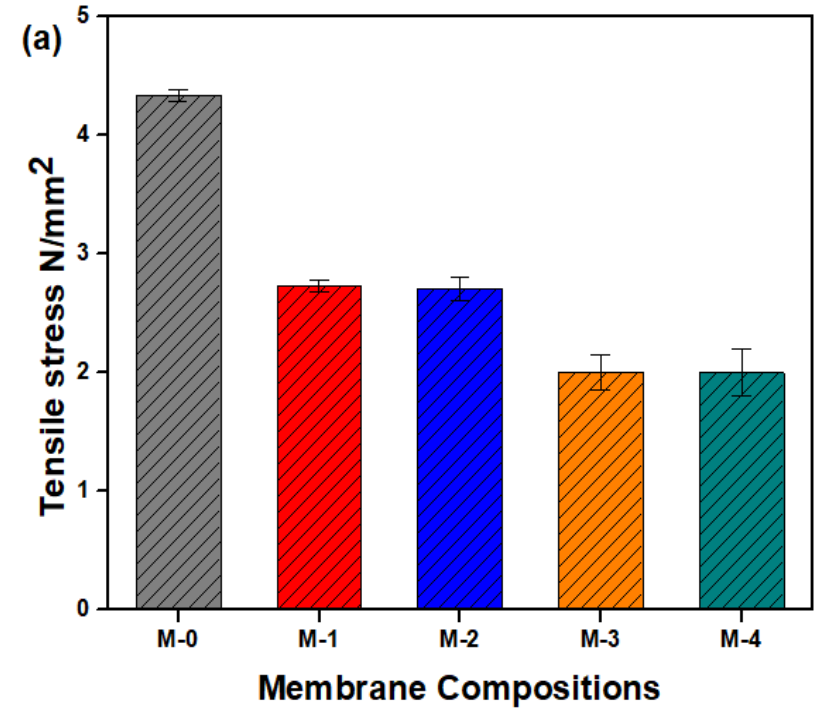


Figure 5.7 (a) CA membrane contact angle measurement image; (b) CA-PVA 1%; (c) CA-PVA 1.5%; (d) CA-PVA 2%; (e) CA-PVA 2.5% Contact angle measurement of blend membranes.

5.7. Mechanical properties

All the casted membranes were tested for their mechanical properties such as tensile stress (N/mm^2) and % strain and results are shown in Figure 5.8(a) and (b) respectively. The CA membrane has shown the highest value for the tensile stress bearing rate due to lack of interfacial adhesion between CA and PVA. Figure 5.8(a) tensile stress graph shows that CA-PVA 1% and CA-PVA 1.5% stress is less as compared to the CA membrane. As the PVA added in the membrane the elongation rate increases as compared to stress. In the trend of the Figure 5.8(b)strain % it is clearly seen that CA membrane has low strain rate than CA-PVA 1% due to presence of macro voids. Cross-section morphology has influence on mechanical properties. CA-PVA 1.5wt% strain rate reduces due to more formation of pores on the surface due to which by applying force membrane break at less rate compared to previous compositions. As the structure changes to more porosity the strain rate starts decreasing. CA-PVA 2% has the lowest strain rate, after that the strain % for CA-PVA 2.5wt% strain increment is due to compaction in the structure.



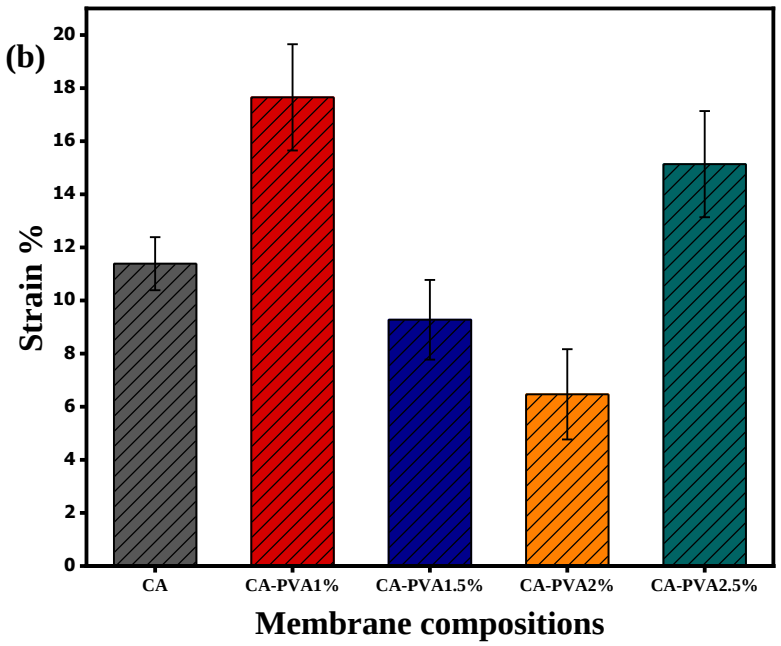


Figure 5.8 (a) Tensile stress N/mm^2 of the CA; CA-PVA1%; CA-PVA 1.5%; CA PVA 2%; CA-PVA 2.5% blend membranes; (b) strain% of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% membranes blend membranes.

5.8. Pure water flux and permeability

To find the optimize additve concentration in the CA membranes, pure water flux experiment was done. To find the effect in the effectivity of the membrane the graphs for flux comparison permeability is plotted shown in the Figure 5.9(b). In reference to flux and permeability distilled water is used as primary solvent to observe the membrane behaviour.

The flux was measured for every 10 minutes and after almost 110 minutes the fluxes becomes constant for all the samples due to decreaes in membrane efficiency as shown in Figure 5.9(a). CA sample gives pure water flux maximum up to 16.4±0.005 L/m^2h which is less than other samples due to less hydrogen bonds interaction . CA-PVA 1% flux 25.9±1.2 L/m^2h is more than CA membrane due to large pores and increses in average pore sie.The PVA acts as the pore forming agent due to which the porosity enhances and ultrafiltration through membranes trends start to increase. The interaction of the hydrogen bonds, hydroxyl bonds, carbonyl and alkyl groups can be observed by the presence of PVA in CA membrane. CA-PVA 1.5% has the maximum flux 42.4±2 L/m^2h due to more porosity,uniform structure and ultrafiltration mechnaism. The bonding of the CA and PVA in this blend pass the water in controlled amount. For hemodialysis, to avoid more loss of water from patients body moderate flux is required. The trend can be clearly seen that flux as well as permeability with respect to PVA composition membranes increases and after 1.5 wt% CA-PVA 2% and CA-PVA 2.5wt% starts reducing. It is due to the agglomeration of PVA in polymer chains and forms less voids and synthesize denser structure which create less pore sizes in the membranes [163].

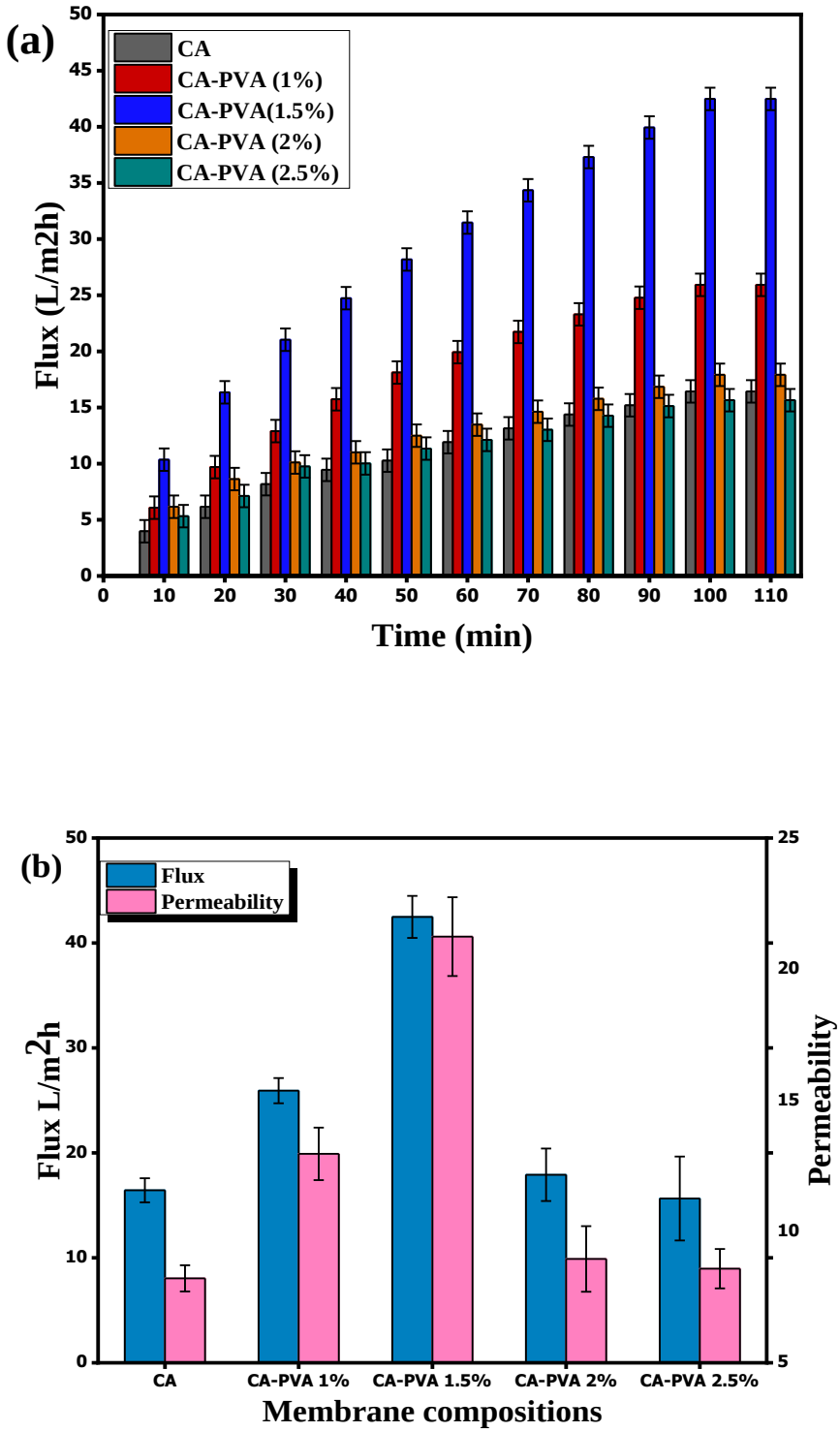


Figure 5.9 (a) pure water flux with respect to time comparison of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes; (b) pure water flux and permeability CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes comparison.

5.9. BSA rejection % from CA-PVA membrane

BSA molecular weight of 67 KDa was used to determine the solute rejection percentages. When the renal patient goes through the dialysis treatment loss of Albumin occurs. Albumin loss should be avoided for good results of dialysis operation. BSA rejection depends upon the membrane morphology and composition [138]. Some membranes can have poor water flux but BSA retention should be higher than 75% for dialysis treatment.

Figure 5.10 shows the % rejection of all CA and CA-PVA 1-2.5 wt% blend membranes. CA-PVA 1% has the protein rejection of 88.3% which is more than the CA membrane. The membranes CA-PVA 1.5% and CA-PVA 2% have retention of 95±1.023% and 90±1.085% respectively which is very attractive for commercial hemodialysis membranes. CA-PVA 2.5% has BSA retention less than the previous membrane fabricated having PVA in the composition. As PVA added in the composition uniform pores forms and surface morphology changes as compared to CA membrane. The size of the pores is less than the protein molecular size due to which high rejection obtained. Due to ultrafiltration transport mechanism when 2 bar pressure is applied the solute separated through membranes. It concluded that 1.5wt% sample is considered optimum in properties contact angle, water content, pure water flux regarding hemodialysis. As the concentration of PVA increases BSA retention decreases which shows that the max pores size starts to increase than 66 KDa.

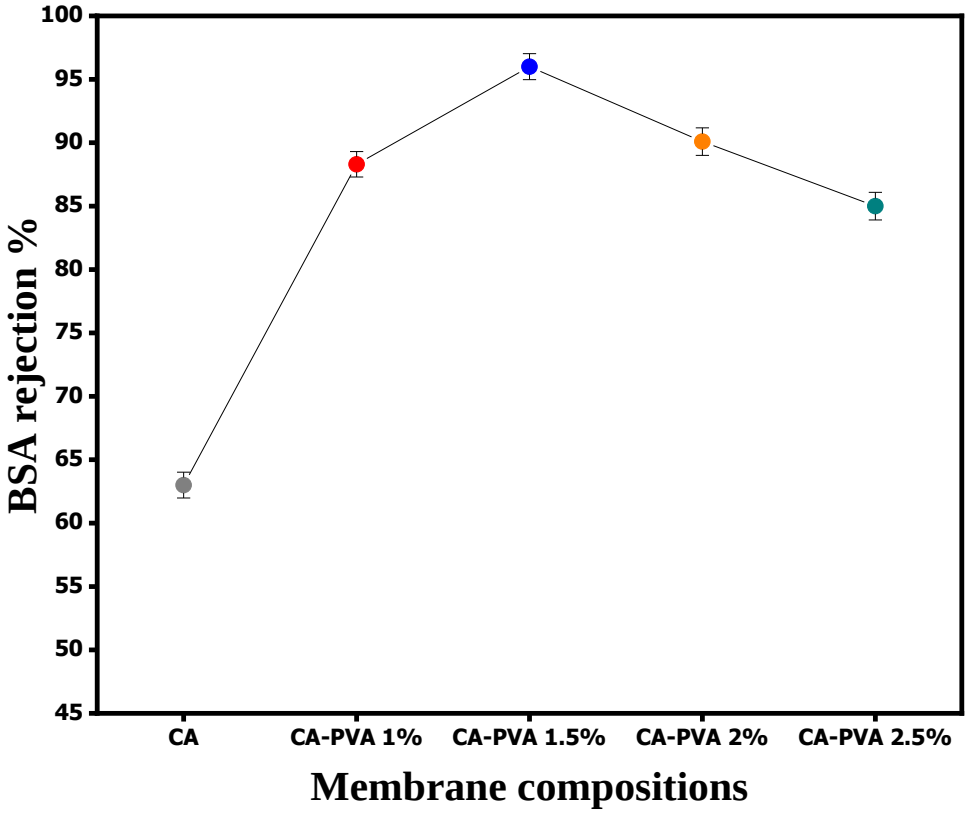


Figure 5.10 BSA rejection % of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes.

5.10. Urea and creatinine clearance

Waste including urea, excess water, and creatinine etc. reduction is important to maintain the balance of patient's blood. Prepared membranes were passed through the experimentation following the ultrafiltration transport mechanism shown in the Figure 4.10. According to the literature at least 60% of urea clearance value separated from the blood through hemodialysis membrane [115]. Figure 5.11 CA-PVA 1% shows the clearance of 85±1.004% which is more than the CA membrane with the water flux increment. Maximum removal obtained by CA-PVA 1.5% as the more suitable pore size formation and distribution of uniform pores on the membrane surface enough to pass the urea molecules up to 93±1.023%.CA-PVA 2% and CA-PVA 2.5% showed the clearance of urea 88±1.085% and 84±1.09% which is less than the previous CA-PVA 1.5% membrane. The trend decreases after that due to denser membranes and blockage of the pores with urea molecules coming from different directions.

As the Figure 5.11 elaborates the percentage clearance of the creatinine. It observed that removal is less than urea molecules. creatinine adsorption takes place in two ways. i) creatinine molecules bulk diffusion into the pores the membrane. ii) creatinine molecules sorption on the surface of the membrane [164]. Trend increases with the concentration of the PVA due to increase in hydrogen bonding which adsorbed creatinine on the membrane surface due to adsorption transport mechanism.CA-PVA 1.5% achieve the maximum result 89±1.023% for creatinine separation from solution than CA and CA-PVA 1% 59±1.02%and 75±1.004% respectively. The creatinine clearance result shows reduction in removal in CA-PVA 2% 85±1.085% and CA-PVA 2.5% 80±1.09% because the average pore size decreases. It is due to adsorption on the surface increase, but the diffusion decreases due to clogging of the creatinine molecules.

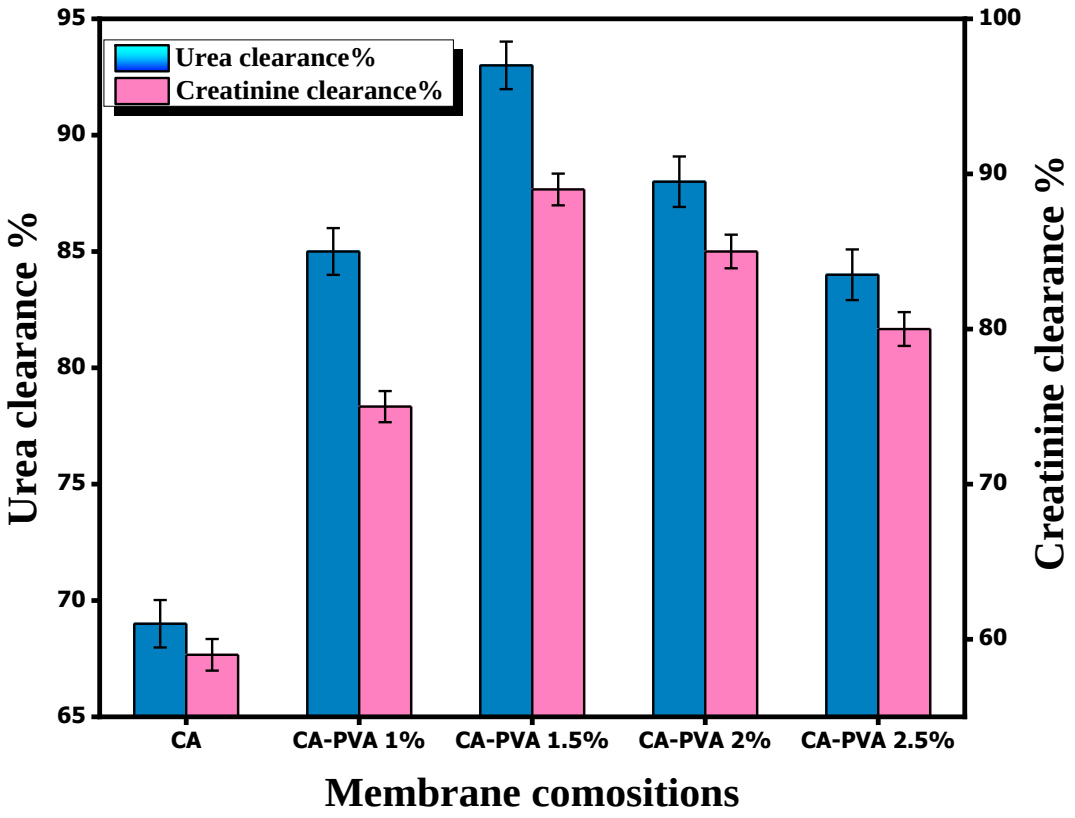


Figure 5.11 Urea and Creatinine clearance comparison of CA and CA-PVA Membranes

5.11. Platelet adhesion

Platelet adhesion is the important parameter for the evaluation of biocompatibility. Platelet activation leading to adhesion causes when the fibrinogen adsorbed on the membrane surface with integrins.

In this study SEM was used to study the attach platelet on the CA membrane and CA-PVA blend membranes. Comparing the images in Figure 5.12, it is determined that number of platelets are adhere, aggregated, and observed on the surface of the CA membrane. The platelets attached on the CA membrane are more than PVA added membranes and not well structured observed in fig5.12 (a). The additives play an important role in the membrane biocompatibility by limiting the hydrophobic interactions of CA with the plasma. Figure 5.12(b) elaborated that as

the PVA added with CA/PEG less platelet adhere on the surface of CA-PVA 1% as compare to CA sample. Fig5.12(c) indicated that platelets attached on the surface and in pores CA-PVA 1.5% are smooth edged with little deformation. Increasing the amount of PVA beyond 1.5wt% the hydrophilicity enhances for a certain extent and the layers of platelet adhere on the surface with irregular shapes. Plasma proteins are preferentially adsorbed on the surface of the membrane when the blood contacts with artificial surface[165]. The plasma protein forms the layer on the membrane surface due to which platelet attached on the membranes [141]. It concluded from the SEM images that CA-PVA 1-1.5 wt.% are suitable for hemodialysis.

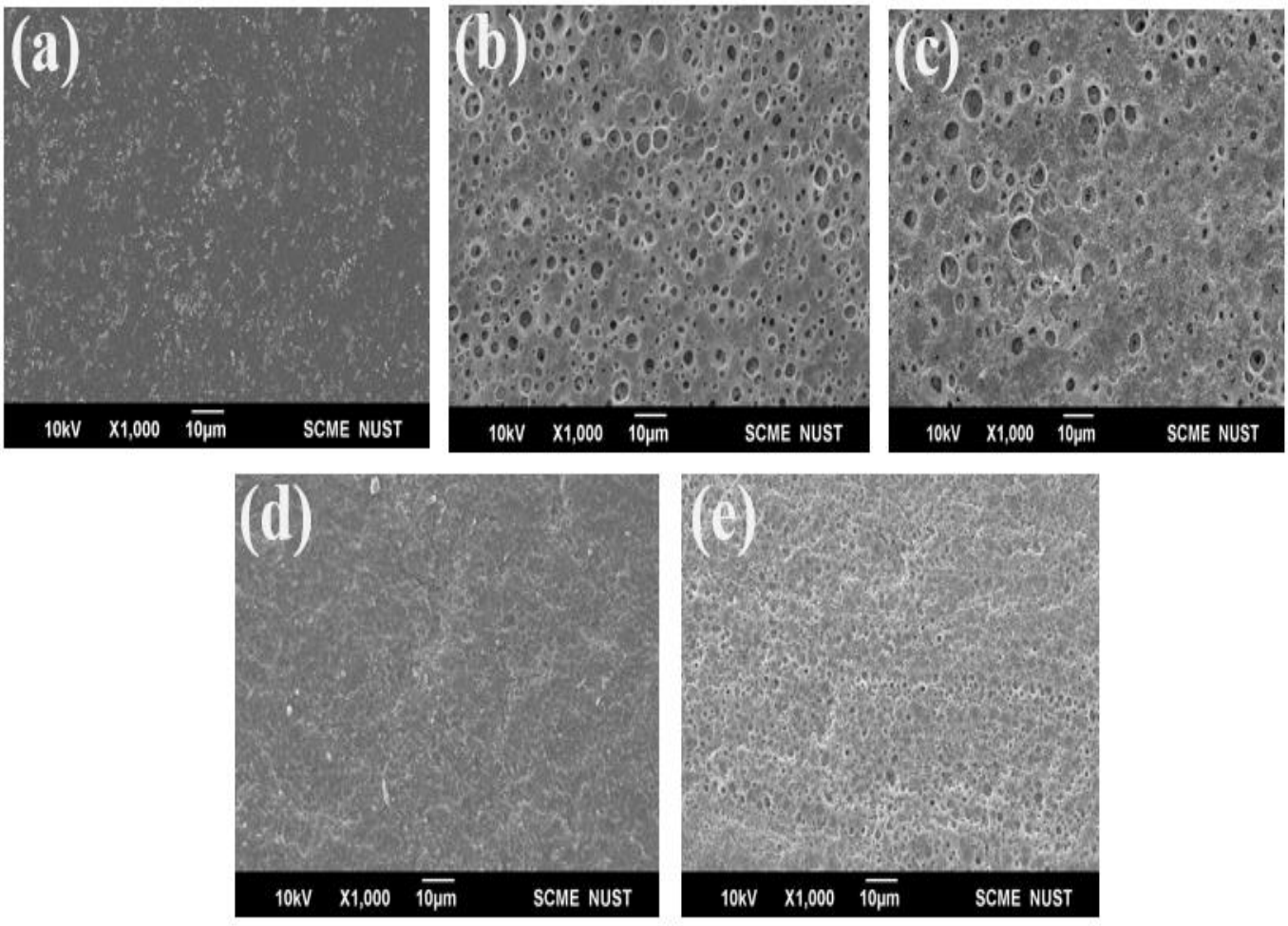


Figure 5.12 Platelet adhesion SEM micrographs of original and modified membranes

5.12. Thrombus formation

When the blood meets the outside substances, initially adsorption of blood protein takes place, which lead to thrombosis formation followed by platelet adhesion and activation. In formulation of the blood contacting membrane the main obstacle is the self-induced thrombosis [166]. The degree of thrombus detected by using whole blood and the results are shown in Figure 5.13. Amount of thrombus formed on the CA membrane has showed a thrombosis high value due to minimum number of functional groups. 5±0.15% thrombus formed on the CA-PVA 1% membrane due to increase in hydroxyl group. CA-PVA 1.5% indicated the thrombus formation of 6±0.15% due to more adsorption of protein in plasma. However, it concluded that thrombus formation gradually decreases on blend membranes surface as the concentration of PVA increases. PEG is the pore forming agent. It enhances the characteristics and performance of membrane by effecting its morphology [167]. Hydroxyl group and carboxyl group on the cellulosic membrane is responsible for complement activation. Hydrophilicity increases due to PVA which prevents the complement activation taking place on the membranes surface. Biocompatibility results revealed that the addition of PVA blended CA membrane the thrombus formation reduces to some limit due to less adsorption of plasma protein, then adhesion and resulting in platelet activation during hemodialysis.

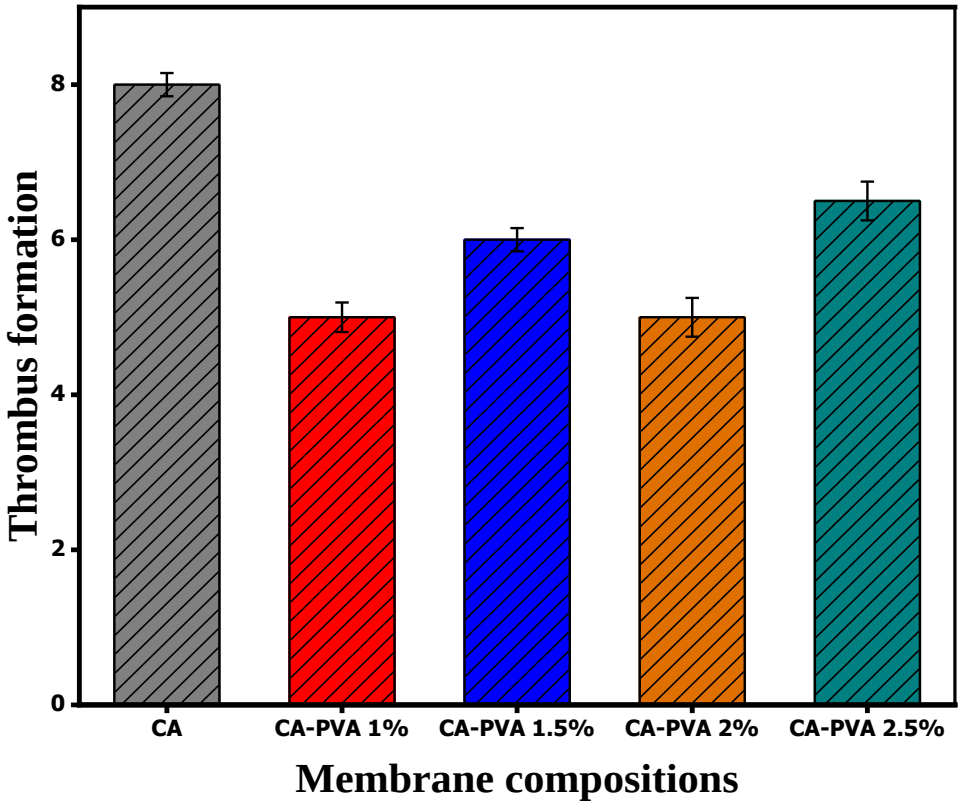


Figure 5.13 Thrombus formation comparison CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%;CA-PVA 2.5% blend membranes.

5.13. Hemolysis ratio

Most important aspect of haematology is hemolysis ratio (HR). It is used to investigate the damage done to erythrocytes caused by artificial materials. For safe biomaterials HR should be less than 5% [168]. Figure 5.14 elaborates CA and CA-PVA 1% membranes shows the HR more than 9.8±0.15% and 5.9±0.19% which is beyond the safety level of biomaterials. After 1 wt.% composition the quantity of PVA increase which shows the decreasing trend in hemolysis ratio. CA-PVA 1.5%, CA-PVA 2%, CA-PVA 2.5% has the hemolysis ratio value of 4±0.15, 3.2±0.25 and 3.5±0.25, respectively. It concluded that as the PVA added hydrophilicity and electronegativity increase due to which the hemolysis ratio of the samples becomes less the 5%. CA-PVA blend membranes are nontoxic and reduces the damage to erythrocytes in addition to preventing platelet attachemnt and blood clotting.

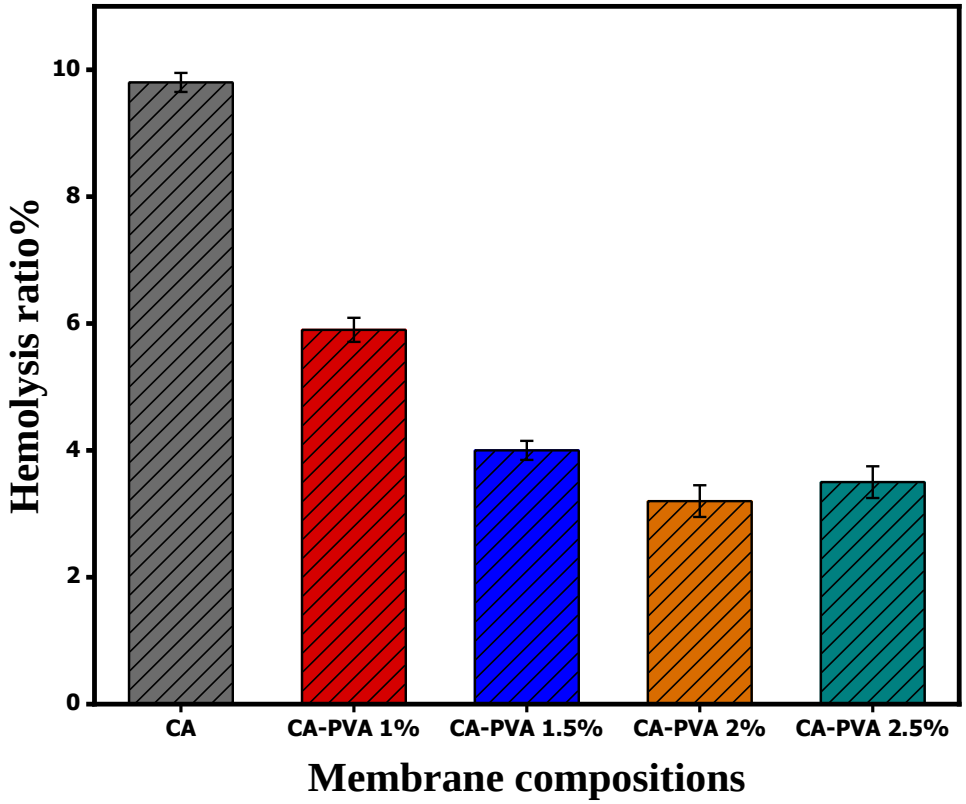


Figure 5.14 Effect of addition of PVA to CA membranes on their hemolysis ratio

5.14. Plasma recalcification time

Partial thrombo plastic time (PRT) is another name for the plasma recalcification time test. It determined the blood clotting time, and the insufficiency of factor causes clotting. If the coagulation factor VII activated Thrombin will be formed from thrombinogen by the stepped active process [145]. The blood coagulation cascade usually includes internal, external, and common pathway [155].

The CA membrane exhibited shorter recalcification time (220±3s). Figure 5.15 indicated that PVA 1-2.5wt% shows the increment in the plasma recalcification time from 240±5 to 300±3 respectively with change in composition. When the blood inContact the presence of Ca^{-2}, fibrous protein crosslinked with each other lead to the formation of thrombus. Thrombus formation time depends upon the hydrophilicity and presence of hydroxyl, carboxyl groups. Concludes that PVA considered as hydrophilic and biocompatible material which is the main cause of increment in the recalcification time. As the functional groups increases plasma slowly forms the adsorptive layer on surface resulting in enhances biocompatibility of the hemodialysis membranes.

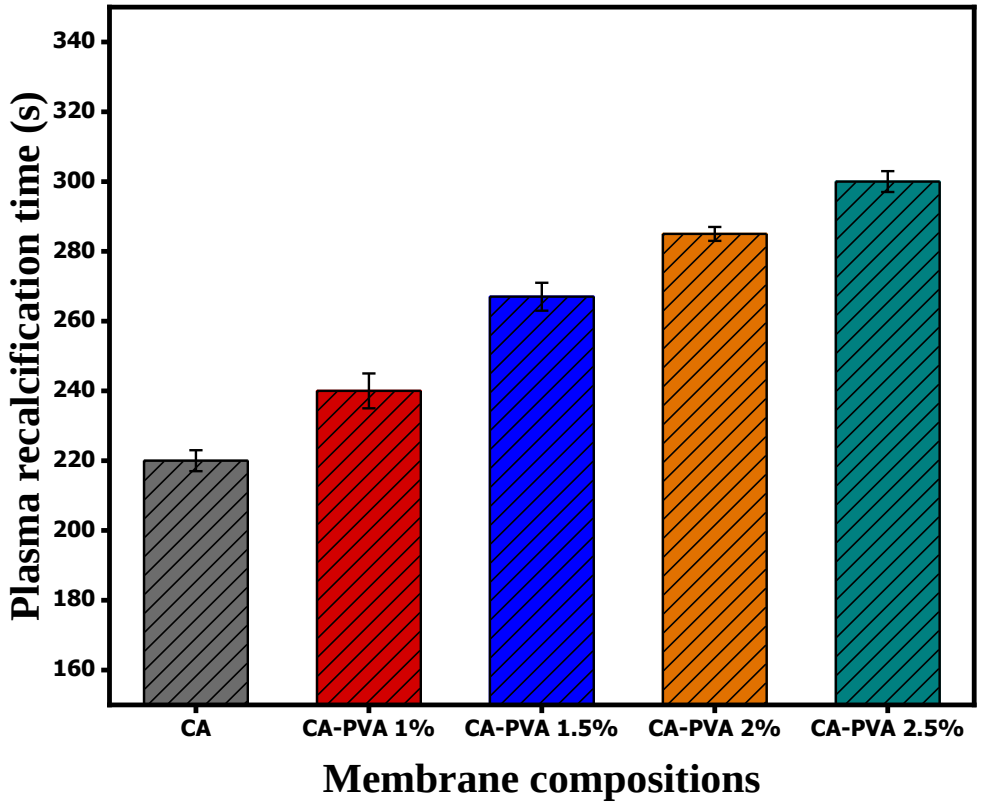


Figure 5.15 Plasma recalcification time of CA; CA-PVA1%; CA-PVA 1.5%; CA-PVA 2%; CA-PVA 2.5% blend membranes.

Conclusion

The purpose of this study is to fabricate the hemodialysis membrane that have optimized pore radius, distribution, density, and size to remove the toxic waste from human blood efficiently and effectively. For the less inflammatory and coagulation factor activation on the membrane surface the membrane morphology should be biocompatible.Firstly, the CA was blended with PEG and PVA to have required pore size to achieve good flux and permeability. Removes urea and creatinine from the blood while retaining BSA protein. The membranes were characterized by the SEM, FTIR and AFM. The average pore size increases with the increase in weight percent of PVA keeping CA and PEG. The large pore size is observed which is required for the solute removal and protein rejection. FTIR supports the results and showed the bonds of CA-PEG-PVA justified the homogenous mixing of the polymers in the solvent. It supports the AFM by showing the roughness trend. The roughness decrease of the CA-PVA blend membranes is less than the CA membranes. the smooth surface provides better results for the flux of the CA-PVA membranes.haracterization results supports the performance results which shows the same trend. The maximum pure water flux, BSA rejection, urea and creatine clearance obtained is 42.4±2 L/m^2h, 95±1.023%, 93±1.023% and 89±1.023% respectively. the membranes become more hydrophilic due to increment in hydroxyl groups indicated by the contact angle measurement. As the porosity increases the stress and strain values also decreases.The synthesized membranes biocompatibility testing was done to observe the interaction of membrane with blood. The results revealed that PVA incorporated membranes are biocompatible in nature because of material properties. Plasma adsorbed on the surface slowly reducing the platelet adhesion and thrombosis formation. Hemolysis ratio of the CA-PVA membranes is less than the required percentage indicating that the membrane is non-toxic. It is reasonable to predict that fabricated membrane had the potential to be used in blood purification fields, such as hemodialysis and plasma separation, and the study thus provide the useful information practical application of the membranes. The CA-PVA 1.5% gives the best results in comparison to other compositions. It mimics the kidney function in separating the solutes and proteins from the blood. These results are attractive for the hemodialysis membrane to commercialize.

Future outlook

In the recent research more inorganic additives such as nanoparticles, zeolites, MWCNTs and MOF’s can be incorporated in the membranes so they can enhance the protein adsorption with more efficient middle size toxins removal. The membrane should be hemocompatible with the blood. Hemodialysis materials and their modifications will be optimized to gain high blood compatibility and higher performing dialysis.

Reference

[1] L. A. Stevens, J. Coresh, T. Greene, and A. S. Levey, “Assessing kidney function - Measured and estimated glomerular filtration rate,” N. Engl. J. Med., vol. 354, no. 23, pp. 2473–2483, 2006, doi: 10.1056/NEJMra054415.

[2] D. F. Stamatialis et al., “Medical applications of membranes: Drug delivery, artificial organs and tissue engineering,” J. Memb. Sci., vol. 308, no. 1–2, pp. 1–34, 2008, doi: 10.1016/j.memsci.2007.09.059.

[3] N. A. Hoenich, “Update on the biocompatibility of hemodialysis membranes,” Hong Kong J. Nephrol., vol. 6, no. 2, pp. 74–78, 2004, doi: 10.1016/S1561-5413(09)60162-9.

[4] R. Tanaka et al., “Clinical Therapeutics Characterization of The Structure of Human Serum Albumin In Patients With End Stage Renal Disease After Kidney Transplantation Effect of Cyp2d6 Genetic Polymorphism on The Pharmacokinetics of Multiple-Dose Metoclopramide Relationship,” Clin. Ther., vol. 37, no. 8, p. e58, doi: 10.1016/j.clinthera.2015.05.171.

[5] C. M. Kee and A. Idris, “Permeability performance of different molecular weight cellulose acetate hemodialysis membrane,” Sep. Purif. Technol., vol. 75, no. 2, pp. 102–113, 2010, doi: 10.1016/j.seppur.2010.08.013.

[6] B. Lisowska-Myjak, “Uremic toxins and their effects on multiple organ systems,” Nephron - Clin. Pract., vol. 128, pp. 303–311, 2014, doi: 10.1159/000369817.

[7] J. Li et al., “Improved dialysis removal of protein-bound uremic toxins by salvianolic acids,” Phytomedicine, vol. 57, pp. 166–173, 2019, doi: 10.1016/j.phymed.2018.12.018.

[8] S. D. Rodrigues et al., “Uremic toxins promote accumulation of oxidized protein and increased sensitivity to hydrogen peroxide in endothelial cells by impairing the autophagic flux,” Biochem. Biophys. Res. Commun., vol. 523, no. 1, pp. 123–129, 2020, doi: 10.1016/j.bbrc.2019.12.022.

[9] “US Renal Data System 2015 Annual Data Report: Epidemiology of Kidney

Disease in the United States," Am. J. Kidney Dis., vol. 67, no. 3, p. A4, 2016, doi: 10.1053/j.ajkd.2015.12.015.

[10] S. L. Goldstein et al., "A prospective multi-center quality improvement initiative (NINJA) indicates a reduction in nephrotoxic acute kidney injury in hospitalized children," Kidney Int., vol. 97, no. 3, pp. 580–588, 2020, doi: 10.1016/j.kint.2019.10.015.

[11] B. Munksgaard, B. Munksgaard, B. L. Kasiske, J. J. Snyder, and T. David, "Cancer after Kidney Transplantation in the United States," no. 7, pp. 905–913, 2004, doi: 10.1111/j.1600-6143.2004.00450.x.

[12] G. Garcia and P. Harden, "The Global Role of Kidney Transplantation," pp. 299–304, 2012, doi: 10.1159/000337044.

[13] R. Gokal and N. P. Mallick, "Peritoneal dialysis," vol. 353, 1999.

[14] O. Balafa, N. Halbesma, D. G. Struijk, F. W. Dekker, and R. T. Krediet, "Peritoneal albumin and protein losses do not predict outcome in peritoneal dialysis patients," Clin. J. Am. Soc. Nephrol., vol. 6, no. 3, pp. 561–566, 2011, doi: 10.2215/CJN.05540610.

[15] P. K. Li et al., "ISPD GUIDELINES / RECOMMENDATIONS," vol. 30, no. February, pp. 393–423, 2010, doi: 10.3747/pdi.2010.00049.

[16] V. A. Online, A. Roy, and S. Dhara, "RSC Advances," 2014, doi: 10.1039/C4RA13460E.

[17] J. Q. Jaeger and R. L. Mehta, "Assessment of dry weight in hemodialysis: An overview," J. Am. Soc. Nephrol., vol. 10, no. 2, pp. 392–403, 1999.

[18] M. H. Sigler and B. P. Teehan, "Solute transport in continuous hemodialysis : A new treatment for acute renal failure," Kidney Int., vol. 32, no. 4, pp. 562–571, 1987, doi: 10.1038/ki.1987.245.

[19] X. Yu et al., "High performance thin-film nanofibrous composite hemodialysis membranes with efficient middle-molecule uremic toxin removal," J. Memb. Sci., vol. 523, no. May 2016, pp. 173–184, 2017, doi: 10.1016/j.memsci.2016.09.057.

[20] E. Klein, F. F. Holland, A. Donnaud, A. Lebeouf, and K. Eberle, “Diffusive and hydraulic permeabilities of commercially available cellulosic hemodialysis films and hollow fibers,” J. Memb. Sci., vol. 2, no. C, pp. 349–364, 1977, doi: 10.1016/S0376-7388(00)83262-7.

[21] “basic-statistics-2020.” .

[22] C. R. Blagg, “A brief history of home hemodialysis.,” Adv. Ren. Replace. Ther., vol. 3, no. 2, pp. 99–105, 1996, doi: 10.1016/S1073-4449(96)80048-3.

[23] H. Waheed, A. Hussain, and S. Farrukh, “Fabrication , characterization and permeation study of ultrafiltration dialysis membranes,” vol. 3994, no. February, 2016, doi: 10.1080/19443994.2016.1149108.

[24] V. Jha, “Current status of end-stage renal disease care in India and Pakistan,” Kidney Int. Suppl., vol. 3, no. 2, pp. 157–160, 2013, doi: 10.1038/kisup.2013.3.

[25] A. Boschetti-De-Fierro, M. Voigt, M. Storr, and B. Krause, “MCO Membranes: Enhanced Selectivity in High-Flux Class,” Sci. Rep., vol. 5, no. December, 2015, doi: 10.1038/srep18448.

[26] S. Schmaldienstand and W. H. Hörl, “The biology of hemodialysis,” no. 5, pp. 157–158, 2004.

[27] C. M. Kjellstrand, “A Brief History of Daily Hemodialysis,” no. 3, 1998.

[28] C. Ronco, “The Rise of Expanded Hemodialysis,” 2017, doi: 10.1159/000476012.

[29] “No Title.”

[30] I. Van Tricht, D. De Wachter, J. Tordoir, and P. Verdonck, “Hemodynamics and complications encountered with arteriovenous fistulas and grafts as vascular access for hemodialysis: A review,” Ann. Biomed. Eng., vol. 33, no. 9, pp. 1142–1157, 2005, doi: 10.1007/s10439-005-5367-X.

[31] R. Vanholder, N. Hoenich, and S. Ringoir, “Morbidity and mortality of central venous catheter hemodialysis: A review of 10 years’ experience,” Nephron, vol. 47, no. 4, pp. 274–279, 1987, doi: 10.1159/000184523.

[32] J. G. Speight, Ebooks Chemical Engineering. 2010.

[33] C. Ronco, N. Marchionna, A. Brendolan, M. Neri, A. Lorenzin, and A. J. Martínez Rueda, “Expanded haemodialysis: From operational mechanism to clinical results,” Nephrol. Dial. Transplant., vol. 33, pp. iii41–iii47, 2018, doi: 10.1093/ndt/gfy202.

[34] R. W. Baker, “Overview of Membrane Science and Technology,” Membr. Technol. Appl., pp. 1–14, 2012, doi: 10.1002/9781118359686.ch1.

[35] M. Leung, J. Jung, W. Lau, M. Kiaii, and B. Jung, “Best Possible Medication History for Hemodialysis Patients Obtained by a Pharmacy Technician,” vol. 62, no. 5, pp. 386–391, 2009.

[36] T. M. Liu, X. Z. Wu, and Y. R. Qiu, “Enhanced biocompatibility and antibacterial property of polyurethane materials modified with citric acid and chitosan,” J. Biomater. Sci. Polym. Ed., vol. 27, no. 12, pp. 1211–1231, 2016, doi: 10.1080/09205063.2016.1181375.

[37] F. Ding and H. D. Humes, “The bioartificial kidney and bioengineered membranes in acute kidney injury,” Nephron - Exp. Nephrol., vol. 109, no. 4, 2008, doi: 10.1159/000142936.

[38] S. Koter, “Determination of the parameters of the Spiegler-Kedem-Katchalsky model for nanofiltration of single electrolyte solutions,” Desalination, vol. 198, no. 1–3, pp. 335–345, 2006, doi: 10.1016/j.desal.2006.02.009.

[39] A. Kargol, “Modified Kedem-Katchalsky equations and their applications,” J. Memb. Sci., vol. 174, no. 1, pp. 43–53, 2000, doi: 10.1016/S0376-7388(00)00367-7.

[40] N. Shahgholian and H. Yousefi, “Supporting hemodialysis patients: A phenomenological study,” vol. 20, no. 5, pp. 0–7, 2015, doi: 10.4103/1735-9066.164514.

[41] M. C. Mariotti, J. Gastão, and R. D. E. Carvalho, “Improving quality of life in hemodialysis : impact of an occupational therapy program,” no. April 2010, pp. 172–179, 2014, doi: 10.3109/11038128.2010.488271.

[42] G. Kaur, S. Prinja, R. Ramachandran, P. Malhotra, K. L. Gupta, and V. Jha, “Cost of hemodialysis in a public sector tertiary hospital of India,” vol. 11, no. 5, pp. 726–733, 2018, doi: 10.1093/ckj/sfx152.

[43] M. Education, “End-stage renal disease in India and Pakistan : Burden of disease and management issues,” vol. 63, pp. 115–118, 2003.

[44] J. Himmelfarb, R. Vanholder, and M. Tonelli, “The current and future landscape of dialysis,” Nat. Rev. Nephrol., doi: 10.1038/s41581-020-0315-4.

[45] P. Susantitaphong and B. L. Jaber, “Methods and Complications of Dialyzer Reuse,” Handb. Dial. Ther. Fifth Ed., pp. 144-151.e1, 2017, doi: 10.1016/B978-0-323-39154-2.00011-4.

[46] C. P. Kovesdy et al., “Serum and dialysate potassium concentrations and survival in hemodialysis patients,” Clin. J. Am. Soc. Nephrol., vol. 2, no. 5, pp. 999–1007, 2007, doi: 10.2215/CJN.04451206.

[47] S. Mitra and N. Mitsides, “Technical aspects of hemodialysis,” Core Concepts Dial. Contin. Ther., pp. 15–26, 2016, doi: 10.1007/978-1-4899-7657-4_2.

[48] B. A. Warady, F. Schaefer, and S. R. Alexander, “Pediatric dialysis, second edition,” Pediatr. Dial. Second Ed., pp. 1–825, 2012, doi: 10.1007/978-1-4614-0721-8.

[49] F. Maduell, “Hemodiafiltration versus conventional hemodialysis: Should ‘conventional’ be redefined?,” Semin. Dial., vol. 31, no. 6, pp. 625–632, 2018, doi: 10.1111/sdi.12715.

[50] L. G. F. Orni, “C Ontinuous H Emofiltration in the T Reatment of a Cute R Enal F Ailure,” vol. 336, p. 1303, 1997.

[51] G. Mussardo, “済無No Title No Title,” Stat. F. Theor, vol. 53, no. 9, pp. 1689–1699, 2019, doi: 10.1017/CBO9781107415324.004.

[52] F. Locatelli et al., “Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters,” Kidney Int., vol. 50, no. 4, pp. 1293–1302, 1996, doi: 10.1038/ki.1996.441.

[53] A. K. Cheung et al., “Effects of High-Flux Hemodialysis on Clinical Outcomes: Results of the HEMO Study,” J. Am. Soc. Nephrol., vol. 14, no. 12, pp. 3251–3263, 2003, doi: 10.1097/01.ASN.0000096373.13406.94.

[54] B. Canaud et al., “Response to ‘Mortality risk for patients receiving hemodiafiltration versus hemodialysis’ [4],” Kidney Int., vol. 70, no. 8, pp. 1524–1525, 2006, doi: 10.1038/sj.ki.5001771.

[55] E. Vilar, A. C. Fry, D. Wellsted, J. E. Tattersall, R. N. Greenwood, and K. Farrington, “Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: A comparative analysis,” Clin. J. Am. Soc. Nephrol., vol. 4, no. 12, pp. 1944–1953, 2009, doi: 10.2215/CJN.05560809.

[56] C. Ronco, A. Brendolan, A. Lupi, G. Metry, and N. W. Levin, “Effects of a reduced inner diameter of hollow fibers in hemodialyzers,” Kidney Int., vol. 58, no. 2, pp. 809–817, 2000, doi: 10.1046/j.1523-1755.2000.00230.x.

[57] J. R. Prowle and R. Bellomo, “Continuous renal replacement therapy: Recent advances and future research,” Nat. Rev. Nephrol., vol. 6, no. 9, pp. 521–529, 2010, doi: 10.1038/nrneph.2010.100.

[58] O. Paper, “Is Expanded Hemodialysis an Option to Online Hemodiafiltration for Small- and Middle-Sized Molecules Clearance ?,” pp. 1–6, 2018, doi: 10.1159/000493910.

[59] J. K. Leypoldt, A. K. Cheung, T. Chirananthavat, J. F. Gilson, C. D. Kamerath, and R. Barry Deeter, “Hollow fiber shape alters solute clearances in high flux hemodialyzers,” ASAIO J., vol. 49, no. 1, pp. 81–87, 2003, doi: 10.1097/00002480-200301000-00013.

[60] C. Ronco et al., “A new scintigraphic method to characterize ultrafiltration in hollow fiber dialyzers,” Kidney Int., vol. 41, no. 5, pp. 1383–1393, 1992, doi: 10.1038/ki.1992.203.

[61] P. Number, “Patent Number : Date of Patent : U . S . Patent Jun . 3 , 1986 Sheetl of2,” no. 19, 1984.

[62] J. Diani and K. Gall, “Finite Strain 3D Thermoviscoelastic Constitutive Model,”

Society, pp. 1–9, 2006, doi: 10.1002/pen.

[63] National Kidney Foundation, “A Clinical Update on Dialyzer Membranes State-of-the-Art Considerations for Optimal Care in Hemodialysis,” Natl. Kidney Found., p. 16, 2014, [Online]. Available: https://www.kidney.org/sites/default/files/02-10-6050_FBD_Clinical_bulletin.pdf.

[64] K. Oshvandi et al., “Comparison the effect of high flux and low flux dialyzer on quality of life in hemodialysis patients; A clinical trial,” J. Ren. Inj. Prev., vol. 8, no. 2, pp. 98–105, 2019, doi: 10.15171/jrip.2019.19.

[65] A. Santoro et al., “The Effect of On-line High-flux Hemofiltration Versus Low-flux Hemodialysis on Mortality in Chronic Kidney Failure: A Small Randomized Controlled Trial,” Am. J. Kidney Dis., vol. 52, no. 3, pp. 507–518, 2008, doi: 10.1053/j.ajkd.2008.05.011.

[66] T. B. Pifer et al., “Mortality risk in hemodialysis patients and changes in nutritional indicators: DOPPS,” Kidney Int., vol. 62, no. 6, pp. 2238–2245, 2002, doi: 10.1046/j.1523-1755.2002.00658.x.

[67] D. H. Krieter and B. Canaud, “High permeability of dialysis membranes: What is the limit of albumin loss?,” Nephrol. Dial. Transplant., vol. 18, no. 4, pp. 651–654, 2003, doi: 10.1093/ndt/gfg054.

[68] F. Garzotto and R. Clark, “Multidimensional Classification of,” vol. 191, pp. 115–126, 2017, doi: 10.1159/000479260.

[69] B. J. G. Pereira, A. J. King, D. D. Poutsiaka, J. A. Strom, and C. A. Dinarello, “Comparison of First Use and Reuse of Cuprophan Membranes on Interleukin-1 Receptor Antagonist and Interleukin-1β Production by Blood Mononuclear Cells,” Am. J. Kidney Dis., vol. 22, no. 2, pp. 288–295, 1993, doi: 10.1016/S0272-6386(12)70320-7.

[70] D. Falkenhagen, T. Bosch, G. S. Brown, B. Schmidt, M. Holtz, and U. Baurmeister, “A Clinical Study on Different Cellulosic Dialysis Membranes,” Nephrol. Dial. Transplant., 1987, doi: 10.1093/oxfordjournals.ndt.a091596.

[71] P. R. Craddock, J. Fehr, A. P. Dalmasso, K. L. Brighan, and H. S. Jacob, “Hemodialysis leukopenia. Pulmonary vascular leukostasis resulting from complement activation by dialyzer cellophane membranes,” J. Clin. Invest., vol. 59, no. 5, pp. 879–888, 1977, doi: 10.1172/JCI108710.

[72] K. Yamazaki, M. Matsuda, K. Yamamoto, T. Yakushiji, and K. Sakai, “Internal and surface structure characterization of cellulose triacetate hollow-fiber dialysis membranes,” J. Memb. Sci., vol. 368, no. 1–2, pp. 34–40, 2011, doi: 10.1016/j.memsci.2010.11.008.

[73] O. Stress, “Hemodialysis Impairs Endothelial Function,” pp. 1002–1007, 2015.

[74] J. L. Lebowitz and H. Spohn, “Microscopic basis for Fick’s law for self-diffusion,” J. Stat. Phys., vol. 28, no. 3, pp. 539–556, 1982, doi: 10.1007/BF01008323.

[75] N. Ferraz and A. Leschinskaya, “Membrane characterization and solute diffusion in porous composite nanocellulose membranes for hemodialysis,” pp. 2959–2970, 2013, doi: 10.1007/s10570-013-0045-x.

[76] R. Zevenhoven, Mass transfer , Mass transfer ,. 2012.

[77] B. Y. L. Kahlekberg, “On t h e nature o f t h e process of osmosis and osmotic pressure with observations cokcerning dialysis’,” vol. I, 1887.

[78] R. Hughes, 済無No Title No Title, vol. 53, no. 9. 2008.

[79] J. M. Allan, “T ? EH = (^),” no. 19.

[80] C. S. C. Bouman, R. W. Van Olden, and C. P. Stoutenbeek, “Cytokine filtration and adsorption during pre- and postdilution hemofiltration in four different membranes,” Blood Purif., vol. 16, no. 5, pp. 261–268, 1998, doi: 10.1159/000014343.

[81] P. Valette and M. Thomas, “Adsorption of low molecular weight proteins to hemodialysis membranes : experimental results and simulations,” vol. 20, 1999.

[82] M. Reyes, J. N. Fuertes, M. T. Moore, G. J. Punnakudiyil, L. Calvo, and S. Rubinstein, “Psychological and relational factors in ESRD hemodialysis

treatment in an underserved community," Patient Educ. Couns., vol. 104, no. 1, pp. 149–154, 2021, doi: 10.1016/j.pec.2020.06.002.

[83] W. R. Clark, M. Neri, and C. Ronco, "Solute Transport in Hemodialysis : Advances and Limitations of Current Membrane Technology," vol. 191, pp. 84–99, 2017, doi: 10.1159/000479258.

[84] A. Mollahosseini, A. Abdelrasoul, and A. Shoker, "Challenges and Advances in Hemodialysis Membranes."

[85] A. G. T. Fane, R. Wang, and Y. Jia, Membrane Technology: Past, Present and Future, vol. 13. .

[86] N. Alwall, "Historical Perspective on the Development of the Artificial Kidney," vol. 10, no. 2, pp. 86–99, 1986.

[87] S. Antonio, "From the rotating drum dialyzer to the personal hemodialysis system : a brief history of hemodialysis technology," vol. 23, no. 12, pp. 791–797, 2000.

[88] H. D. Humes, W. H. Fissell, and K. Tiranathanagul, "The future of hemodialysis membranes," Kidney Int., vol. 69, no. 7, pp. 1115–1119, 2006, doi: 10.1038/sj.ki.5000204.

[89] J. Kooman et al., "Mixed Matrix Membranes : A New Asset for Blood Purification Therapies," pp. 1–3, 2014, doi: 10.1159/000356226.

[90] W. Y. Chuang, T. H. Young, and W. Y. Chiu, "The effect of acetic acid on the structure and filtration properties of poly(vinyl alcohol) membranes," J. Memb. Sci., vol. 172, no. 1–2, pp. 241–251, 2000, doi: 10.1016/S0376-7388(00)00336-7.

[91] S. H. Ye, J. Watanabe, Y. Iwasaki, and K. Ishihara, "In situ modification on cellulose acetate hollow fiber membrane modified with phospholipid polymer for biomedical application," J. Memb. Sci., vol. 249, no. 1–2, pp. 133–141, 2005, doi: 10.1016/j.memsci.2004.10.006.

[92] A. Idris and L. K. Yet, "The effect of different molecular weight PEG additives on cellulose acetate asymmetric dialysis membrane performance," J. Memb.

Sci., vol. 280, no. 1–2, pp. 920–927, 2006, doi: 10.1016/j.memsci.2006.03.010.

[93] Z. Li, J. Ren, A. G. Fane, D. F. Li, and F. S. Wong, "Influence of solvent on the structure and performance of cellulose acetate membranes," J. Memb. Sci., vol. 279, no. 1–2, pp. 601–607, 2006, doi: 10.1016/j.memsci.2005.12.054.

[94] W. L. Chou, D. G. Yu, M. C. Yang, and C. H. Jou, "Effect of molecular weight and concentration of PEG additives on morphology and permeation performance of cellulose acetate hollow fibers," Sep. Purif. Technol., vol. 57, no. 2, pp. 209–219, 2007, doi: 10.1016/j.seppur.2007.04.005.

[95] E. Saljoughi and T. Mohammadi, "Cellulose acetate (CA)/polyvinylpyrrolidone (PVP) blend asymmetric membranes: Preparation, morphology and performance," Desalination, vol. 249, no. 2, pp. 850–854, 2009, doi: 10.1016/j.desal.2008.12.066.

[96] A. Idris, K. Y. Hew, and M. K. Chan, "Preparation Of Cellulose Acetate Dialysis Membrane Using D–Glucose Monohydrate As Additive," J. Teknol., vol. 51, no. 1, 2009, doi: 10.11113/jt.v51.147.

[97] F. Yasar, M. Æ. Sacide, and A. Altinkaya, "The effects of urease immobilization on the transport characteristics and protein adsorption capacity of cellulose acetate based hemodialysis membranes," pp. 2167–2179, 2009, doi: 10.1007/s10856-009-3776-3.

[98] E. Saljoughi, M. Amirilargani, and T. Mohammadi, "Asymmetric Cellulose Acetate Dialysis Membranes : Synthesis , Characterization , and Performance," vol. 116, pp. 2251–2259, 2010, doi: 10.1002/app.

[99] E. Saljoughi, M. Amirilargani, and T. Mohammadi, "Effect of PEG additive and coagulation bath temperature on the morphology, permeability and thermal/chemical stability of asymmetric CA membranes," Desalination, vol. 262, no. 1–3, pp. 72–78, 2010, doi: 10.1016/j.desal.2010.05.046.

[100] S. Yu et al., "Cellulose acetate hollow fiber nanofiltration membrane with improved permselectivity prepared through hydrolysis followed by carboxymethylation," J. Memb. Sci., vol. 434, pp. 44–54, 2013, doi: 10.1016/j.memsci.2013.01.044.

[101] B. Han, D. Zhang, Z. Shao, L. Kong, and S. Lv, “Preparation and characterization of cellulose acetate/carboxymethyl cellulose acetate blend ultrafiltration membranes,” Desalination, vol. 311, pp. 80–89, 2013, doi: 10.1016/j.desal.2012.11.002.

[102] H. Waheed and A. Hussain, “Fabrication of Cellulose Acetate/Polyaziridine Blended Flat Sheet Membranes for Dialysis Application,” Bionanoscience, vol. 9, no. 2, pp. 256–265, 2019, doi: 10.1007/s12668-019-0600-5.

[103] K. H. Chan, E. T. Wong, M. I. Khan, A. Idris, and N. M. Yusof, “Fabrication of polyvinylidene difluoride nano-hybrid dialysis membranes using functionalized multiwall carbon nanotube for polyethylene glycol (hydrophilic additive) retention,” J. Ind. Eng. Chem., vol. 20, no. 5, pp. 3744–3753, 2014, doi: 10.1016/j.jiec.2013.12.074.

[104] H. R. Ahn, T. M. Tak, and Y. N. Kwon, “Preparation and applications of poly vinyl alcohol (PVA) modified cellulose acetate (CA) membranes for forward osmosis (FO) processes,” Desalin. Water Treat., vol. 53, no. 1, pp. 1–7, 2015, doi: 10.1080/19443994.2013.834516.

[105] A. Bernal-Ballén, I. Kuritka, and P. Saha, “Preparation and Characterization of a Bioartificial Polymeric Material: Bilayer of Cellulose Acetate-PVA,” Int. J. Polym. Sci., vol. 2016, 2016, doi: 10.1155/2016/3172545.

[106] X. Yu et al., “High performance thin-film nanofibrous composite hemodialysis membranes with efficient middle-molecule uremic toxin removal,” J. Memb. Sci., vol. 523, no. May 2016, pp. 173–184, 2017, doi: 10.1016/j.memsci.2016.09.057.

[107] H. Waheed and A. Hussain, “Preparation and Solvents Effect Study of Asymmetric Cellulose Acetated/Polyethyleneimine Blended Membranes for Dialysis Application,” Int. J. Heal. Med., vol. 2, no. 4, p. 5, 2017, doi: 10.24178/ijhm.2017.2.4.05.

[108] A. Hayder, A. Hussain, A. N. Khan, and H. Waheed, “Fabrication and characterization of cellulose acetate/hydroxyapatite composite membranes for the solute separations in Hemodialysis,” Polym. Bull., vol. 75, no. 3, pp. 1197–

1210, 2018, doi: 10.1007/s00289-017-2084-1.

[109] H. Waheed, F. T. Minhas, and A. Hussain, “Cellulose acetate/sericin blend membranes for use in dialysis,” Polym. Bull., vol. 75, no. 9, pp. 3935–3950, 2018, doi: 10.1007/s00289-017-2238-1.

[110] Y. Raharjo and Z. Fahmi, “Primary study of cellulose acetate hollow fiber as a green membrane applied to hemodialysis PRIMARY STUDY OF CELLULOSE ACETATE HOLLOW FIBER,” no. January, 2017.

[111] A. Idris, K. Lee, M. Noordin, and M. Chan, “Response surface methodology approach to study the influence of PEG and water in cellulose acetate dialysis membranes,” J. Teknol. F, no. 49F, pp. 39–49, 2008.

[112] A. A. Seddik et al., “Challenges in management of diabetic ketoacidosis in hemodialysis patients, case presentation and review of literature,” Diabetes Metab. Syndr. Clin. Res. Rev., vol. 13, no. 4, pp. 2481–2487, 2019, doi: 10.1016/j.dsx.2019.06.022.

[113] J. Martin-Navarro et al., “Reactions to Synthetic Membranes Dialyzers: Is there an Increase in Incidence?,” Kidney Blood Press. Res., vol. 44, no. 5, pp. 907–914, 2019, doi: 10.1159/000501035.

[114] R. A. Lusiana, G. A. Pambudi, F. N. Sari, D. S. Widodo, and K. Khabibi, “Grafting of heparin on blend membrane of citric acid crosslinked chitosan/polyethylene glycol-poly vinyl alcohol (PVA-PEG),” Indones. J. Chem., vol. 19, no. 1, pp. 151–159, 2019, doi: 10.22146/ijc.30861.

[115] H. Waheed and A. Hussain, “Effect of Polyvinyl Pyrolidone on Morphology and Performance of Cellulose Acetate Based Dialysis Membrane,” Eng. Technol. Appl. Sci. Res., vol. 9, no. 1, pp. 3744–3749, 2019, doi: 10.5281/zenodo.2576267.

[116] Y. Raharjo, Z. Fahmi, and A. A. Widati, “Jurnal Teknologi INCORPORATION OF IMPRINTED-ZEOLITE TO POLYETHERSULFONE / CELLULOSE ACETATE MEMBRANE FOR CREATININE REMOVAL IN,” no. June, 2019, doi: 10.11113/jt.v81.13075.

[117] H. Orelma, A. Hokkanen, I. Leppänen, K. Kammiovirta, M. Kapulainen, and A. Harlin, “Optical cellulose fiber made from regenerated cellulose and cellulose acetate for water sensor applications,” Cellulose, vol. 27, no. 3, pp. 1543–1553, 2020, doi: 10.1007/s10570-019-02882-3.

[118] M. A. Wsoo, S. Shahir, S. P. Mohd Bohari, N. H. M. Nayan, and S. I. A. Razak, A review on the properties of electrospun cellulose acetate and its application in drug delivery systems: A new perspective, vol. 491. Elsevier Ltd, 2020.

[119] S. Nishigochi et al., “Improvement of Antifouling Properties of Polyvinylidene Fluoride Hollow Fiber Membranes by Simple Dip Coating of Phosphorylcholine Copolymer via Hydrophobic Interactions,” 2014.

[120] L. W. McKeen, “Renewable Resource and Biodegradable Polymers,” Film Prop. Plast. Elastomers, pp. 353–378, 2012, doi: 10.1016/b978-1-4557-2551-9.00014-1.

[121] S. N. Goyanes and N. B. D’Accorso, “Industrial applications of renewable biomass products: Past, present and future,” Ind. Appl. Renew. Biomass Prod. Past, Present Futur., no. August, pp. 1–332, 2017, doi: 10.1007/978-3-319-61288-1.

[122] R. Nagarkar and J. Patel, “Polyvinyl Alcohol : A Comprehensive Study,” Acta Sci. Pharm. Sci., vol. 3, no. 4, pp. 34–44, 2019.

[123] M. Julinová, L. Vaňharová, and M. Jurča, “Water-soluble polymeric xenobiotics – Polyvinyl alcohol and polyvinylpyrrolidon – And potential solutions to environmental issues: A brief review,” J. Environ. Manage., vol. 228, no. April, pp. 213–222, 2018, doi: 10.1016/j.jenvman.2018.09.010.

[124] A. Timofejeva, M. D’Este, and D. Loca, “Calcium phosphate/polyvinyl alcohol composite hydrogels: A review on the freeze-thawing synthesis approach and applications in regenerative medicine,” Eur. Polym. J., vol. 95, pp. 547–565, 2017, doi: 10.1016/j.eurpolymj.2017.08.048.

[125] S. A. Salman and N. A. Bakr, “Section C: Physical Sciences DSC and TGA Properties of PVA Films Filled with Na 2 S 2 O 3 .5H 2 O Salt,” J. Chem. Biol. Phys. Sci., no. March, 2018, doi: 10.24214/jcbps.C.8.2.00111.

[126] A. Muhammed and E. Hashash, “Polyvinyl Alcohol-Cellulose Acetate Composite Reverses Osmosis Membranes: I. Synthesis and Characterization,” Hydrol. Curr. Res., vol. 03, no. 02, 2012, doi: 10.4172/2157-7587.1000131.

[127] F. M. Ali, R. M. Kershi, M. A. Sayed, and Y. M. AbouDeif, “Evaluation of structural and optical properties of Ce3+ ions doped (PVA/PVP) composite films for new organic semiconductors,” Phys. B Condens. Matter, vol. 538, no. May, pp. 160–166, 2018, doi: 10.1016/j.physb.2018.03.031.

[128] K. Ghedira et al., “The PEG-responding desiccome of the alder microsymbiont Frankia alni,” Sci. Rep., vol. 8, no. 1, 2018, doi: 10.1038/s41598-017-18839-0.

[129] V. Sirolli et al., “Biocompatibility and functional performance of a polyethylene glycol acid-grafted cellulosic membrane for hemodialysis,” vol. 23, no. 6, pp. 356–364, 2000.

[130] L. Benedini, P. V. Messina, S. D. Palma, D. A. Allemandi, and P. C. Schulz, “The ascorbyl palmitate-polyethyleneglycol 400-water system phase behavior,” Colloids Surfaces B Biointerfaces, vol. 89, no. 1, pp. 265–270, 2012, doi: 10.1016/j.colsurfb.2011.09.030.

[131] W. Zhou, R. Apkarian, Z. L. Wang, and D. Joy, “Fundamentals of scanning electron microscopy (SEM),” Scanning Microsc. Nanotechnol. Tech. Appl., pp. 1–40, 2007, doi: 10.1007/978-0-387-39620-0_1.

[132] M. Abd Mutalib, M. A. Rahman, M. H. D. Othman, A. F. Ismail, and J. Jaafar, Scanning Electron Microscopy (SEM) and Energy-Dispersive X-Ray (EDX) Spectroscopy. Elsevier B.V., 2017.

[133] S. Sakthivel, T. Alagesan, S. Muthu, C. S. Abraham, and E. Geetha, “Quantum mechanical, spectroscopic study (FT-IR and FT - Raman), NBO analysis, HOMO-LUMO, first order hyperpolarizability and docking studies of a non-steroidal anti-inflammatory compound,” J. Mol. Struct., vol. 1156, no. 2018, pp. 645–656, 2018, doi: 10.1016/j.molstruc.2017.12.024.

[134] R. Splinter, “Action potential transmission and volume conduction,” Handb. Phys. Med. Biol., vol. 56, no. 9, pp. 5-1-5–9, 2010, doi: 10.1201/9781420075250.

[135] Z. Jia and C. Tian, “Quantitative determination of polyethylene glycol with modified Dragendorff reagent method,” Desalination, vol. 247, no. 1–3, pp. 423–429, 2009, doi: 10.1016/j.desal.2008.09.004.

[136] Z. K. Xu, F. Q. Nie, C. Qu, L. S. Wan, J. Wu, and K. Yao, “Tethering poly(ethylene glycol)s to improve the surface biocompatibility of poly(acrylonitrile-co-maleic acid) asymmetric membranes,” Biomaterials, vol. 26, no. 6, pp. 589–598, 2005, doi: 10.1016/j.biomaterials.2004.03.008.

[137] A. Gugliuzza, A. Politano, and E. Drioli, “The advent of graphene and other two-dimensional materials in membrane science and technology,” Curr. Opin. Chem. Eng., vol. 16, pp. 78–85, 2017, doi: 10.1016/j.coche.2017.03.003.

[138] S. Mansur et al., “Investigation on the effect of spinning conditions on the properties of hollow fiber membrane for hemodialysis application,” J. Appl. Polym. Sci., vol. 133, no. 30, pp. 1–10, 2016, doi: 10.1002/app.43633.

[139] K. A. Gebru and C. Das, “Effects of solubility parameter differences among PEG, PVP and CA on the preparation of ultrafiltration membranes: Impacts of solvents and additives on morphology, permeability and fouling performances,” Chinese J. Chem. Eng., vol. 25, no. 7, pp. 911–923, 2017, doi: 10.1016/j.cjche.2016.11.017.

[140] D. Zhong, Z. Wang, J. Zhou, and Y. Wang, “Additive-free preparation of hemodialysis membranes from block copolymers of polysulfone and polyethylene glycol,” J. Memb. Sci., vol. 618, no. May 2020, p. 118690, 2021, doi: 10.1016/j.memsci.2020.118690.

[141] L. Zhu, F. Liu, X. Yu, A. Gao, and L. Xue, “Surface zwitterionization of hemocompatible poly (lactic acid) membranes for hemodia fi ltration,” J. Memb. Sci., vol. 475, pp. 469–479, 2015, doi: 10.1016/j.memsci.2014.11.004.

[142] T. Shionoya, “Studies in experimental extracorporeal thrombosis,” J. Exp. Med., vol. 46, no. 1, pp. 13–26, 1927, doi: 10.1084/jem.46.1.13.

[143] L. Ma et al., “Toward highly blood compatible hemodialysis membranes via blending with heparin-mimicking polyurethane: Study in vitro and in vivo,” J. Memb. Sci., vol. 470, pp. 90–101, 2014, doi: 10.1016/j.memsci.2014.07.030.

[144] Z. M. Ruggeri and G. L. Mendolicchio, “Adhesion mechanisms in platelet function,” Circ. Res., vol. 100, no. 12, pp. 1673–1685, 2007, doi: 10.1161/01.RES.0000267878.97021.ab.

[145] A. Gao, F. Liu, and L. Xue, “Preparation and evaluation of heparin-immobilized poly (lactic acid) (PLA) membrane for hemodialysis,” J. Memb. Sci., vol. 452, pp. 390–399, 2014, doi: 10.1016/j.memsci.2013.10.016.

[146] T. Rbcs, T. Znfinite, and N. Red, “Supplementary Information,” pp. 8–10, 2013.

[147] M. Sharma, Transdermal and Intravenous Nano Drug Delivery Systems. Elsevier Inc., 2019.

[148] A. Simple, “A Simple and Reliable Test to Monitor Heparin Therapy.”

[149] W. W. Yue, H. J. Li, T. Xiang, H. Qin, S. D. Sun, and C. S. Zhao, “Grafting of zwitterion from polysulfone membrane via surface-initiated ATRP with enhanced antifouling property and biocompatibility,” J. Memb. Sci., vol. 446, pp. 79–91, 2013, doi: 10.1016/j.memsci.2013.06.029.

[150] J. Yin, H. Fan, and J. Zhou, “Cellulose acetate/poly(vinyl alcohol) and cellulose acetate/crosslinked poly(vinyl alcohol) blend membranes: preparation, characterization, and antifouling properties,” Desalin. Water Treat., vol. 57, no. 23, pp. 10572–10584, 2016, doi: 10.1080/19443994.2015.1040846.

[151] Y. Liang et al., “Regulation of Polyvinyl Alcohol/Sulfonated Nano-TiO 2 Hybrid Membranes Interface Promotes Diffusion Dialysis,” 2021.

[152] M. Bilal, K. Niazi, Z. Jahan, S. S. Berg, and Ø. W. Gregersen, “Mechanical , thermal and swelling properties of phosphorylated Nanocellulose fibrils / PVA nanocomposite membranes,” Carbohydr. Polym., 2017, doi: 10.1016/j.carbpol.2017.08.125.

[153] P. S. Thomas, J. Guerbois, G. F. Russell, and B. J. Briscoe, “FTIR STUDY OF THE THERMAL DEGRADATION OF POLY (VINYL ALCOHOL),” vol. 64, no. 2001, pp. 501–508, 2007.

[154] D. F. Stamatialis, C. R. Dias, and M. N. De Pinho, “Atomic force microscopy of dense and asymmetric cellulose-based membranes,” vol. 160, pp. 235–242,

1999.

[155] S. Senthilkumar, S. Rajesh, A. Jayalakshmi, and D. Mohan, “Biocompatibility and separation performance of carboxylated poly (ether – imide) incorporated polyacrylonitrile membranes,” Sep. Purif. Technol., vol. 107, pp. 297–309, 2013, doi: 10.1016/j.seppur.2013.01.041.

[156] S. Velu, K. Rambabu, and L. Muruganandam, “Development , Characterization and Application Studies of Cellulose acetate – activated Carbon blend Ultra Filtration Membranes,” vol. 6, no. 1, pp. 565–577, 2014.

[157] L. L. S. Silva, C. G. Moreira, B. A. Curzio, and F. V Fonseca, “Micropollutant Removal from Water by Membrane and Advanced Oxidation Processes — A Review,” pp. 411–431, 2017, doi: 10.4236/jwarp.2017.95027.

[158] C. Feng, R. Wang, B. Shi, G. Li, and Y. Wu, “Factors affecting pore structure and performance of poly (vinylidene fluoride- co -hexafluoro propylene) asymmetric porous membrane,” vol. 277, pp. 55–64, 2006, doi: 10.1016/j.memsci.2005.10.009.

[159] H. Eustache, M. Using, P. Membranes, and G. Spencer, “United States Patent (19),” no. 19, 1992.

[160] P. I. Morgado, A. Aguiar-Ricardo, and I. J. Correia, “Asymmetric membranes as ideal wound dressings: An overview on production methods, structure, properties and performance relationship,” J. Memb. Sci., vol. 490, pp. 139–151, 2015, doi: 10.1016/j.memsci.2015.04.064.

[161] Y. C. Ko, B. D. Ratner, and A. S. Hoffman, “Characterization of Hydrophilic-Hydrophobic Polymeric Surfaces by Contact Angle Measurements,” vol. 82, no. 1, 1981.

[162] M. Kumar et al., “Three-dimensional cellulose sponge : Fabrication , characterization , biomimetic mineralization , and in vitro cell infiltration,” Carbohydr. Polym., vol. 136, pp. 154–162, 2016, doi: 10.1016/j.carbpol.2015.09.018.

[163] M. M. Amiji, “Journal of Biomaterials Science , Surface modification of

chitosan membranes by of anionic polysaccharides for improved blood compatibility in hemodialysis," no. December 2012, pp. 37–41.

[164] M. Nidzhom, Z. Abidin, P. S. Goh, N. Said, and A. Fauzi, "Applications of Polymer , Composite , and Coating Materials Co-adsorptive removal of creatinine and urea by a three-component dual layer hollow fiber membrane," 2020, doi: 10.1021/acsami.0c08947.

[165] L. Zhu, F. Liu, X. Yu, and L. Xue, "Poly(Lactic Acid) Hemodialysis Membranes with Poly(Lactic Acid)- block -Poly(2-Hydroxyethyl Methacrylate) Copolymer As Additive: Preparation, Characterization, and Performance," 2015, doi: 10.1021/acsami.5b03951.

[166] J. Rivera, M. L. Lozano, L. Navarro-núñez, and V. Vicente, "Fe rra ta St or ti Fo u nd at io n Fe rra ta St or ti Fo u," no. Figure 1, doi: 10.3324/haematol.2008.003178.

[167] T. Saito and Y. Miyamoto, "The effect of poly ethylene glycol additive on the characteristics and performance of cellulose acetate ultrafiltration membrane for removal of Cr (III) from aqueous solution The effect of poly ethylene glycol additive on the characteristics and perform," no. Iii, doi: 10.1088/1757-899X/352/1/012051.

[168] Z. Shi, H. Ji, H. Yu, X. Huang, and W. Zhao, "Engineering polyethersulfone hollow fiber membrane with improved blood compatibility and antibacterial property," pp. 441–453, 2016, doi: 10.1007/s00396-015-3801-7.