Fabrication and characterization of Poly-sulfone/Zeolite Hemodialysis membrane for protein bound and water-soluble toxins rejection capacity

By

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Fabrication and characterization of Poly-sulfone/Zeolite Hemodialysis membrane for protein bound and water-soluble toxins rejection capacity

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Dedication

I, with great pleasure and reverence, dedicate this work to the Holy Prophet (S.A.W) who inspired me through His saying “Learn from cradle to grave”.

Acknowledgements

I have no words to express my humble gratitude to Almighty Allah, Who, bestowed on me the shower of His countless blessings since my birth as a Muslim and in the Ummah of the beloved Holy Prophet (S.A.W) and enabled me to complete this tedious yet thrilling work with the lofty ideals ahead.

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Abstract

Hemodialysis membranes have been used widely for the end stage renal disease patients. In hemodialysis, the solute molecules based on their molecular weights are separated by using a semi-permeable membrane. Decreasing the therapy time and efficient removal of toxin materials from the blood are the key for the optimized hemodialysis process. Membranes containing zeolites have the tendency to remove uremic toxins via molecular sieving while performing the blood dialysis. The addition of various pore-gen and adsorbent in the membrane can certainly impact the membrane production along with creatinine adsorption but it is not directed which pore-gen along with zeolite leads to better performance. The research was aimed at reducing the adsorption of protein bound and uremic toxins by using mordenite zeolite as an adsorbent while polyethylene glycol and cellulose acetate as pore generator. Membranes were cast by phase-inversion technique which is cheap and easy to handle as compared to electro-spinning technique. Through this strategy, the ability to adsorb creatinine and solute rejection percentage were measured and compared against the pristine PSF, when only PEG used as a pore-gen and when PEG along with CA was used as a pore-gen along with different concentration of zeolite. The experiments revealed that PEG membranes can give a better solute rejection percentage (93%) but with a low creatinine adsorption capacity that is 7654 µg/g and low bio-compatibility (PRT 392s, HR 0.46 %). However, PEG/CA membranes give maximum creatinine adsorption that is 9643 µg/g and also better biocompatibility (PRT 490s, HR 0.37%) but with the low BSA rejection (72%) as compared to the pristine PSF and PEG membranes. The present study concluded that large pore size decreases solute rejection percentage but increases creatinine uptake level and concentration of zeolite also affects membrane performance during hemodialysis.

Key Words: *Hemodialysis membrane, Poly-sulfone, Polyethylene glycol, Urea clearance, Creatinine Adsorption, BSA rejection, Biocompatibility*

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List of Abbreviations

CRF	Chronic renal failure
HFD	High flux dialysis
CA	Cellulose Acetate
PEG	Polyethylene Glycol
PSF	Poly-Sulfone
SEM	Scanning electron microscopy
FTIR	Fourier transform infrared spectroscopy
PWP	Pure water permeation
PRP	Platelet rich plasma
PBS	Phosphate buffer solution
PPP	Plasma poor plasma
PRT	Plasma Recalcification Time
AFM	Atomic force microscopy

Chapter No. 1

Introduction

Kidney diseases are gradually increasing in south Asian countries. In Pakistan ranked 8th nearly 20,000 people die every year because of kidney disease. Nearly 220,000275,000 new patients were reported for the renal therapy. The greatest communal reason of End-Stage-Renal-Disease (ESRD) obstructive uropathy affecting 22% of children, shadowed by reflux nephropathy (13% of the population) and chronic glomerulonephritis (11% of the population) in Pakistan [1]. The cure of kidney failure can be a kidney transplant or hemodialysis. The option of kidney transplant is not affordable by every patient. Furthermore, it is a risky procedure. Hemodialysis is an excellent alternative cure, but still advancement in the membrane is required for the better toxin rejections. Certain clinical upgradation is required, and some uremic solute molecules are still unresolved such as indoxyl sulfate, p-cresol. Hemodialysis is the new emerging innovation, which can solve Chronic Kidney Disease (CKD) Work should be done on hemodialysis to make it cost effective. Almost 7 million people are suffering from renal failure in Pakistan according to the 2018 report [2]. Worldwide, more than 2 million are receiving renal replacement treatment to stay alive, while this is the representation of 10% of those who need it.

After the malfunctioning of the kidney, hemodialysis is the only economic method of treatment to maintain the health of patient and breathing. Semi-permeable membranes are used for the exclusion of waste and excess water from the blood into the glucose solution called as dialyzate. Among all the kidney disease patents 42% of the patients are on traditional hemodialysis in Pakistan [3]. While 71% of the patients are on traditional hemodialysis having kidney failure in USA.

1.1. Background & Scope

The current hemodialysis procedure contains diffusion and convection with low/high flux dialyzer used for the solute clearance. However, these current procedures are not much efficient to remove certain toxins that are connected to proteins (such as, pcersol, creatinine and indoxyl sulfate) with high percentages. As these toxins are responsible

of the increase in the mortality rates and also convert this kidney disease into CKD (Chronic kidney disease) [1]. Toxins such as small and water-soluble toxin i.e., Urea (75-86% reduction) are easily cleaned from the blood of the dialysis patient. However, latent uremic toxins such as indoxyl sulphate (35 percent), 3 cardoxy4methyl-5-propyl2furanoproprionic acid (32 percent), and p-cresol (29 percent), as well as middle-sized toxins such as 2 microglobulin (0.7-6.8%), are washed to a lesser degree [4].

A study by Davenports showed that the removal of water-soluble toxins greatly effects the small (measured in days), medium (measured in months) survival of the kidney disease patients. However, for to increase the patient's life also said as long term (years and decades) survival involves optimized removal of protein bound toxins [4][5].

The toxins that are reported and are responsible for the increased risk of deaths in kidney disease patients are as follows phosphate, 2 microglobulin, indoxyl sulfate and p-cresol.

Eknoyan et al. undertook 5 years randomized clinical research with 1864 patients experiencing hemodialysis three times in a week. This study revealed that no deaths and ill health were affected even by using high-flux membranes in short term hemodialysis. However this research recommended that for the patients undergoing hemodialysis for 3.7 years must use high-flux membranes [5].

So, the major motivation of this research is to create such type of membrane that can eliminate all sized toxins (small, Medium and large) during the hemodialysis procedure so that the kidney disease patient may never reach to CKD (Chronic Kidney Disease).

1.2. Motivation.

In this thesis, the major motivation is to fabricate a membrane that has the ability to remove the uremic toxins along with the middle toxins much better as compare to the traditional hemodialysis membranes. The waste materials can also be removed faster by using this membrane hence it will decrease the time of hemodialysis which currently takes 3 to 4 hours. Aside from the diffusion and convection mechanisms for toxin elimination, this membrane may also use an adsorption strategy to remove protein-bound toxins.

There are certain ways to adsorb both the toxins and these biological waste molecules. Like Tijink used active carbons for to develop the modified composite membranes, as carbon has the non-selective adsorbing property to adsorb such protein-bound toxins [6]. Another potentially optimized method is to fabricate the modified composite membrane with nano-particles to achieve all these purposes.

The hemodialysis method can remove only 30% of the protein-bound toxins because they are bind with albumin. However, it can clear more than 60% of urea & creatinine [22]. The kidney damage and uremic cardiovascular disease are responsible for the most functional failure, as because these toxins especially creatinine are responsible for their roles in vascular and renal disease continuation. As the pure PSF membrane is hydrophobic in nature that are responsible for the adsorption of proteins during the hemodialysis process hence it activate some alternative pathways which is a serious life-threatening complication [23]. The membrane rejection performance and the permeability also lessened because of the removal of the protein on the membrane.

Through the study of the previous literature it was depicted that the researches utilized large sized adsorbents which lead to decrease surface area and reducing the adsorption of protein bound toxin [23]. So this study worked on the gap highlighted above by using mordenite zeolite with spherical shape and size which is less than 48 nm provides more surface area considered as the best adsorbent into the dialysis membrane as it can adsorb more protein-bound toxins onto the porous particle hence also decreasing the risk of cardiovascular disease [25]. PEG and CA as an additive that ae highly hydrophilic, non-toxic polymer with optimized strength and antifouling properties for the platelet and plasma proteins can enhance the hemo-compatibility, hydrophobicity and biocompatibility of PSF.

Hence, main motivation of this research is to make a composite membrane by using the phase inversion method which is also a cheap method and is associated with mild handling as compared to the hard handling of electro-spinning technique. This strategy directs towards the easy fabrication of hemodialysis membrane. In addition, the adsorbent particles of perfect four-dimensional shape were used and their size was also smaller than 50 nm hence providing more adsorption sites when incorporated inside the membrane. Maximum tests were conducted to find out the performance and

biocompatibility of the membrane while changing the concentration of mordenite zeolite. The ability to adsorb creatinine and solute rejection percentage were measured and compared against the pristine PSF, when only PEG used as a pore-gen and when PEG along with CA was used as a pore-gen in terms of urea clearance and BSA rejection and that can also eliminate the protein-bound toxins.

1.3. Importance of Motivation.

Literature showed that renal damage is chief basis of death in the world now days. Still increasing kidney failure patients by growing population and the number of diabetes and hypertension patients. 600 million patients have kidney problems worldwide and the worst part is number of patients are still increasing 6-7% yearly [7]. This reveals that there is stillroom of improvement in the current ongoing kidney replacement treatment for the betterment of the patient's life.

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 an extensive range of molecular weight. After the treatment, the patients have higher level of middle and large molecule toxins in the plasma [8]. Therefore, the membrane should be closer to natural glomerular membrane in the kidney. So that the kidney disease may not convert into Chronic Kidney Disease (CKD) which is the main case of increase in the mortality rate.

Existing gap between natural kidney and synthetic membranes is the biocompatibility and permeability. During the last decade, work on membrane permeability is the main focus for the performance of the membrane with biocompatibility. More work is required to increase the permeability and make the membrane biocompatible with blood for the betterment of the patient [9]. Another major issue is the time for treatment. Minimum 4 hours, three times in a week is required for the process to complete which is painful and hectic for the patient [10].

The current requirement is to fabricate a membrane that mimics the natural kidney. It should have lager pore sizes that removes large toxins and have biocompatibility with blood. In peritoneal dialysis nearly 21-42g/1.73m^2 bovine serum albumin loss on

weekly basis [11]. Therefore, maximum bovine serum albumin must retain by membrane.

1.4. Thesis Layout

The thesis has been mainly designed as follows, In Chapter 2, the study of kidney failure, kidney diseases, hemodialysis and the main principles used in hemodialysis process and mechanisms responsible for the removal of toxins such as hemoperfusion and wearable kidney were discussed. The types of toxins and zeolites that can be used then for the adsorption of middle toxin such as creatinine is also explained.

A review of the literature on renal medical therapies that use adsorption processes to remove toxins was published in Chapter 3. Among all the synthesized hemodialysis membranes, poly-sulfone along with cellulose acetate and PEG as polymer representatives is selected, so their use is also reviewed in hemodialysis

The methodology for the membrane casting along with the phase inversion technique is elaborated in Chapter 4. Then all the methods for the characterizations and testing for to justify that this fabricated membrane is useful for hemodialysis process is explained.

In Chapter 5, all of the outcomes and results of the characterization and membrane testing also to adsorb creatinine and solute rejections are explained.

At the end the conclusion of this research and future guidelines of research are given.

Chapter No. 2

Background, Hemodialysis membranes, Zeolites

In this chapter, the widespread framework understanding about kidney, its failure, hemodialysis, hemoperfusion, wearable kidney, membranes, uremic toxins and methods to synthesize hemodialysis membranes are introduced. Since membranes also contains zeolite particles used as adsorbent, so at the end a complete brief on zeolites is also discussed.

2.1. Kidney and Medical Treatments

In sustaining human health, the kidneys play a significant function. They ensure the balance of minerals and water, clear waste from acidic digestion and act as part of the endocrine system. To keeps a person alive, medical procedure are required when kidneys breakdown to eliminate toxins and waste from the body. Hemodialysis is the most common therapy method. Before a donor kidney is accessible, many patients spend time on hemodialysis.

2.1.1. Kidney.

The kidneys are about 11 cm long, 5-6 cm in diameter, and 3-4 cm in thickness, beanshaped organs. Each kidney is 120-160 g in weight [1]. The structure of kidney is illustrated in Fig. 2.1. The role of a normal kidney includes the hormones erythropoietin, detoxification, blood volume regulation, accretion of urine and disposal of it by urinary tract, maintaining blood pressure and acid-base regulation of the blood, maintaining production of vitamin D level in addition to endocrine functions, sodium and potassium level adjustment [12]. It is important to limit uremic toxins and to get a balanced diet and drink the proper portion of water for a healthy kidney. The leading causes of renal dysfunction are diseases, high blood pressure (hypertension), diabetes and the widespread usage of medicine [12]. The daily waste that is removed by the kidney are illustrated in Table 2.1

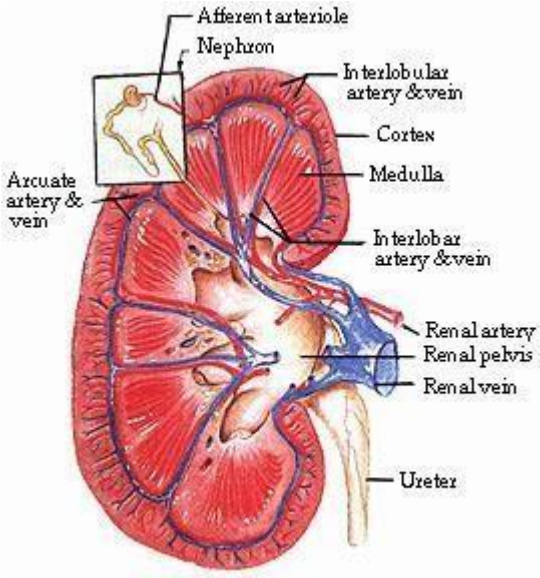


Figure 2. 1 Structure of Kidney [1]

Table 2. 1 Daily Waste Production by a Human [12]

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

2.1.2. Kidney Collapse.

The semi or complete loss of normal kidney processes is kidney failure. This is identified by the failure to extract from the body excess water and metabolic waste products. Eventually, this influences blood pressure, volume of blood, and blood

content. Kidney damage, depending on the cause, is categorized into acute kidney injury (AKI) and chronic renal failure (CRF).

The Acute kidney failure raises a drastic failure in kidney function within 48 hours. This happens due to the 0.3 mg/ML which is less or equal to surge in serum creatinine (approximately 26.4 μmol/L). A fraction rise in serum creatinine greater than or equal to 50% (1.5 times the baseline) and a decrease in urine production (recorded oliguria less than 0.5 mL/kg per hour for more than 6 hours is also said to as AKF (Acute Kidney Failure) [13].

Below 60 mL/min/1.73 m2 of body mass of filtration rate of urine for at least three months the National Kidney Foundation says such patients are suffering from CRF or either kidney failure or Glomerular Filtration Rate. Further classification stage of chronic kidney disease is shown in table 2.2.

Table 2. 2 Classification phases of acute kidney disease [14]

Stage	**Description**	**Glomerulus Filtration Rate (GFR) (mLl/min/1.73m^2)**
1	Kidney damage with normal or increase GFR	≥90
2	Kidney damage with mild decrease GFR	60-89
3	Moderate decrease GFR	30-59
4	Severe decrease GFR	15-29
5	Kidney failure	<15 or Dialysis

2.1.3. Medical Treatment.

When a kidney fails, there are certain possibilities for recovery.

(1). Kidney Transplant.

(2). Hemodialysis.

(3). Hemoperfusion

(4). Wearable Kidney

Hemodialysis is the most prevalent treatment method as compare to all of the methods. Kidney transplant is the other recommended treatment, but available donated kidneys are restricted. For patients, hemodialysis process act as a "bridge to transplant" before a donor kidney is made accessible to support the life of the patient.

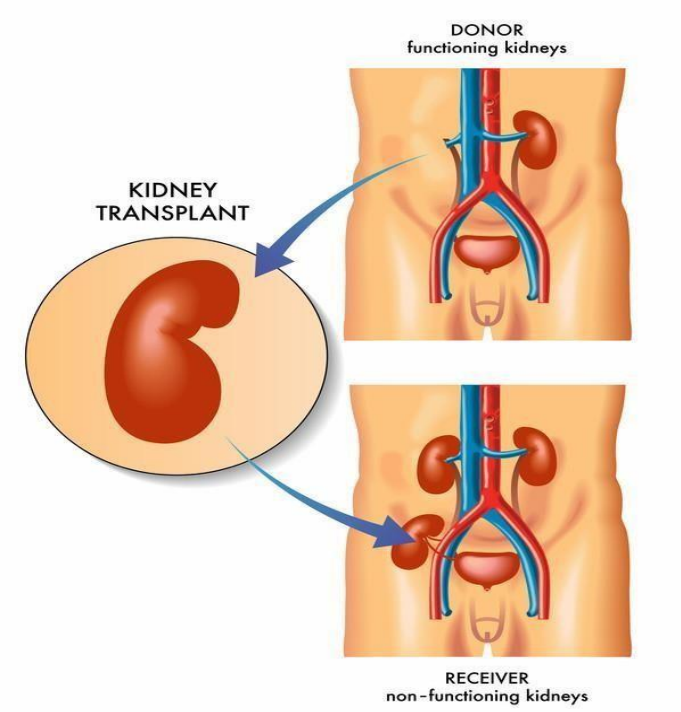


Figure 2. 2 Kidney Transplant [15]

2.1.3.1. Hemoperfusion

Hemoperfusion (HP) technique which was introduced in the 1940s is utilized for the treatment of over dosage of drug and poisoning [16]. In 1970s and 1980s it was adapted in clinics [16] [17] for acute intoxication treatment [18]. Fig. 2.3 shows a typical hemoperfusion system. It is composed of a blood circuit having pressure monitors, blood pumps that are like hemodialysis, along with a cartridge having adsorbents such as charcoal, resin or activated carbon. From the cartridge the anticoagulated blood is pumped. The toxins are removed by the process of adsorption. Table 2.3 illustrates several adsorption cartridges [19]. Hemoperfusion can lead to several medical complicated diseases, including thrombocytopenia, leukopenia, hypocalcemia, and hypoglycemia. The use of such mechanism is reduced because of the discovery of high-flux hemodialysis. As the high-flux hemodialysis contains lower cost and have very

fewer medical complications. However, for the low concentrated poisons distributions and high degree of protein bindings hemoperfusion is still a valid other way [20]

Table 2. 3 Devices for Hemoperfusion.

Manufacturer	Device	Sorbent Type
Clark	Biocompatible system	Carbon
Gambro	Adsorba	Norit Carbon
Nextron Medical	Hemosorba Ch-350	Petroleum bead carbon

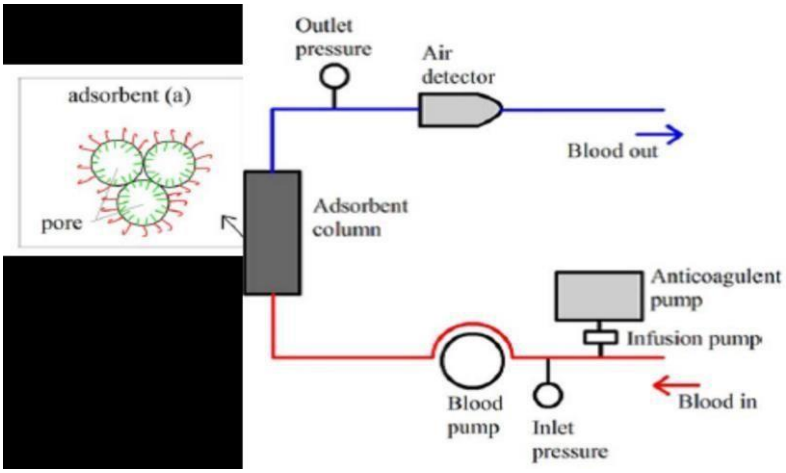


Figure 2. 3 Simplified form of a typical hemoperfusion system [21].

2.1.3.2. Wearable Kidney

Large portion of hemodialysis fluid named as dialysate passed through the system in single time pass in the present hemodialysis process. If the amount of the fluid is reduced in one time pass through the hemodialysis process the size of the hemodialysis system can be cut down remarkably. This can be attained by regenerating the dialysate by using an adsorbent system [22] [23].

Since there are certain techniques used for the treatment of kidney disease wearable kidney is a small-scale hemodialysis system that the patient can wear around his belly and can also move around. This device uses very less volume of dialysate in a closedloop system by reusing and regenerating techniques. This small wearable kidney system is helpful for non-continuous hemodialysis and important for patient mobility as this system can remove long term hemodialysis issues. So, the dialyzer is the key

component of the hemodialysis system, however the models of WAK may vary from each other.

Many well-known designs of WAKs that mainly use adsorbents to formulate dialysate are Yoshida, Henne, Davankov, Granger, and Gura [24]. A simplified diagram of a WAK is shown in Fig. 2.4 (a) while a model is shown in Fig. 2.4 (c). The most feasible design from all the wearable kidney designs is Gura WAK which is undergoing clinical proceedings for the regeneration of cartridges [24]. The most predominantly model used in Australian hospitals is the REDY models of regeneration cartridge, it was the first moveable hemodialysis system based on sorbent and enzymatic technology [16]. The cleanliness of the recycled hemodialysis fluid was done by this type of cartridge. This cartridge contains urease layer that is used to convert urea, for the adsorption of non-urea organic wastes activated carbon layer is present, zirconium phosphate to bind potassium and (urease-generated) ammonium, and zirconium oxide & zirconium carbonate layer to confiscate phosphate [24]. The WAK that were developed by Davenport et al consist of the joining of sorbents and urease that created the basis [24]. Table 2.4 gives the key components, usage and therapies in terms of mechanism for the treatment of kidney failure.

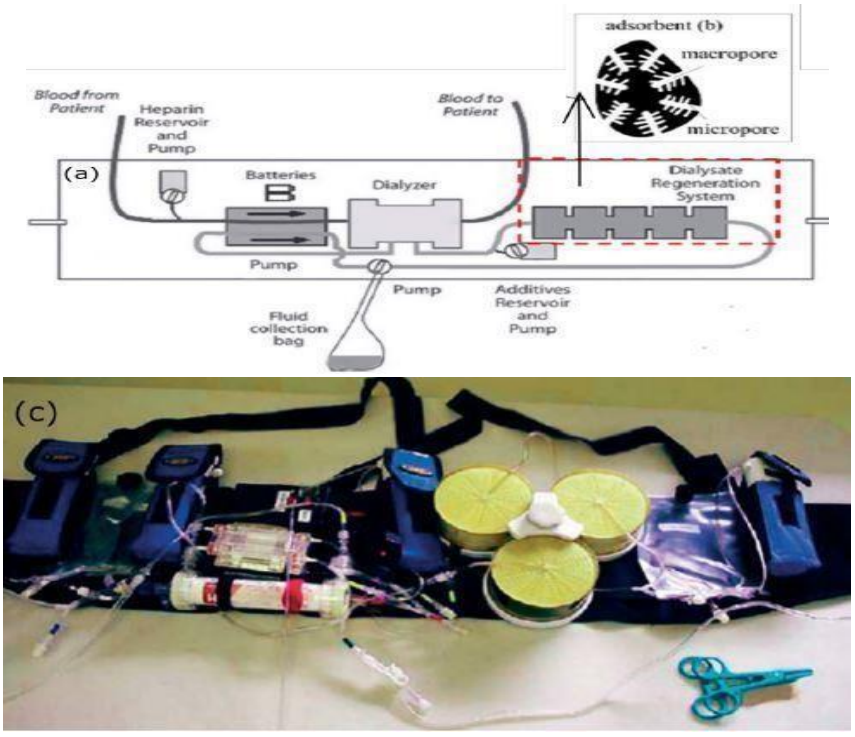


Figure 2. 4 (a) Simplified form of a wearable kidney the adsorbent, (c) Gura wearable kidney [24] [25].

Table 2. 4 Comparison of hemoperfusion, hemodialysis and wearable kidney.

Categories	Hemoperfusion	Hemodialysis	Wearable Kidney
Mechanism	Adsorption	Diffusion convection	Diffusion
Usage	Poisoning/Over dose	Kidney failure	Kidney failure
Key parts	Adsorption cartridge	Dialyzer/Dialysate	Dialyzer/Adsorption cartridge

2.2. Hemodialysis process components

The extra water and waste products from the blood can be eliminated via hemodialysis and is used mainly in patients with kidney failure as an artificial substitute. Fig. 2.5 shows the method of hemodialysis. Patient's blood is transferred into the blood section of a dialyzer in hemodialysis, consisting of a roll of semi-permeable hollow fiber or flat sheet membranes. Then it runs into the hollow fiber membrane while the dialysate flows in the space that surrounds the hollow fibers. The waste products from the blood thus go through convection and diffusion to the dialysate. Purified blood would then be redirected to the patient. The membrane is the most essential element in this process, because the membrane's opening size chooses which molecules are allowed from the membranes. The important tool in this phase to remove toxic substances from blood is Dialysate. Pure water, sodium bicarbonate, potassium chloride, sodium chloride, magnesium chloride and calcium chloride are usually included. Our body comprises of different types of membranes but they follow the same membrane principles, such as skin, cell membranes and peritoneal membranes. Numerous illnesses, such as artificial transplant organs, are resolved by extracorporeal membranes. In hemodialysis, hemodiafiltration, hemofiltration, blood oxygenation and plasmapheresis, membrane technology is highly advised for the extraction of exogenous and endogenous metabolites from the blood.[26].

Kedem-Katchalsky proposed a friction model that describes the phenomenon of membrane transport through the capillary network. Because of the existence of

gradient concentration in the membrane system, passive transport is formed. It is also described that the major components obtained as retentate and permeate, respectively, are the dialysate flux and blood flux. The membrane flux is dependent on the osmotic pressure difference and the difference in hydrostatic pressure. For the study of the mechanism in which boundary layers played a crucial role, the derived KK equation may be used [25].

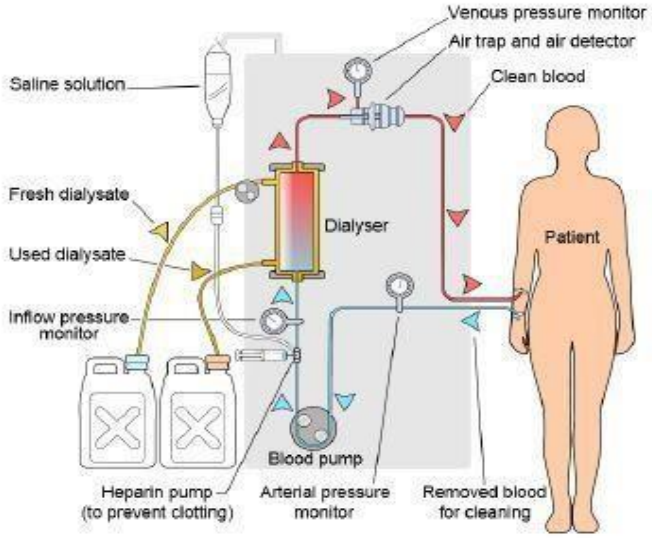


Figure 2. 5 Drawing of a hemodialysis procedure (YassineMrabet).

2.2.1. Hemodialysis Machine Working Principle.

2.2.1.1. 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.

2.2.1.2. Dialyzer

During the early 1960's dialyzer has been practiced in United States [27]. The motivation to use dialyzers facility 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. Wastes are percolate into the dialysate that come from the blood by diffusion gradient.

Dialysate having waste products leaves the dialyzer and washed out. Then clean blood goes back into the human body [27]. They are classified based on permeability, surface area, membrane composition, geometry design and biocompatibility [27].

2.2.1.3. Dialysate

The solution of electrolytes, pure water, salts e.g., sodium and bicarbonates also called as dialysis fluid, solution, or bath. The function of the dialysate is to extract the toxin wastes from the blood through the diffusion procedure. 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. According to estimation over 300 liters water used to treat the hemodialysis patient.

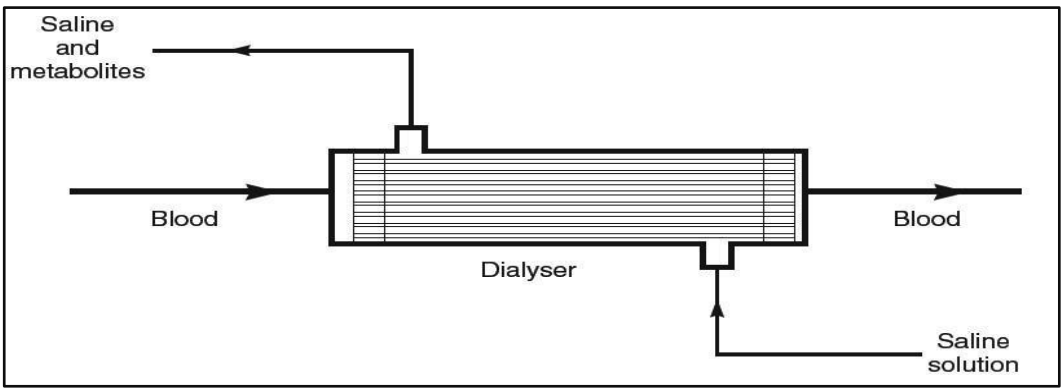


Figure 2. 6 Schematic Diagram of Dialyzer [28]**.**

2.2.2. Basic Principle of Hemodialysis membrane transportation.

Hemodialysis ensures that the blood electrolytes are balance-size through a semipermeable membrane through an exchange of blood and dialysis between a wide variety of uremic toxins. Transportation processes in the most recent hemodialysis are convection and diffusion. Osmosis, ultra-filtration and hemodialysis therapy all have essential adsorption mechanisms. They are all explained as follows.

2.2.2.1. Diffusion.

Diffusion, by the Brownian movement, largely destroys the small molecules [13]. The solutes pass from the top to the floor. Fig. 2.7 describes the underlying mechanism. The urea that is in the blood diffused in the dialysate due to the gradient level, and

dialysis travels in the reverse direction in order to reduce the elimination of toxins [14]. Diffusion relies on blood dialysis level, blood dialysate fluid, thickness, temperature, surface and conductivity or membrane structure. The gradient between the fluids was very dependent on keeping all the other component in the process constant [13]. The rule of Fick also draughts the framework for diffusion [15].

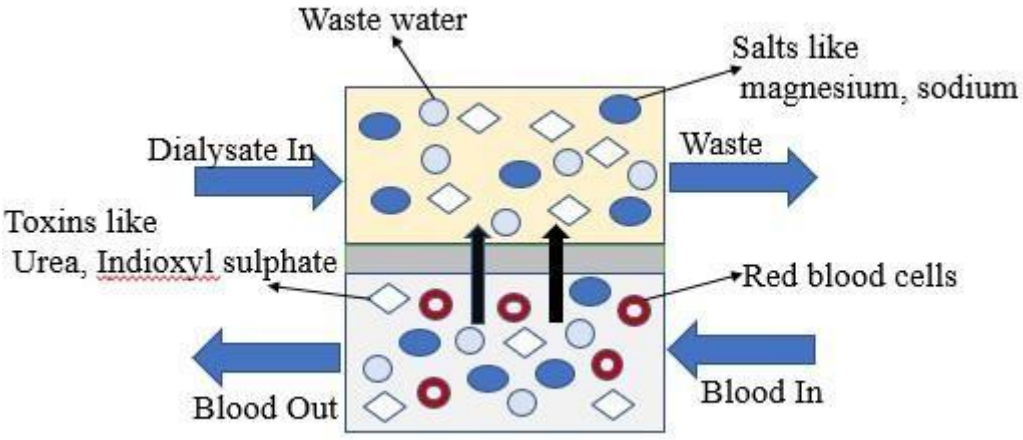


Figure 2. 7 Diffusion process in hemodialysis

2.2.2.2. Convection.

Convection stands for the movement of the fluid from denser layer to lighter region due to temperature. Due to the differential pressure, the combined transfer of solute and water is the convection phase of hemodialysis from blood to through membranes. The hydraulic penetrability, the solute coefficient, the area of the membrane, the aggregation of solutes in the blood, and the acclivity of pressure across the membrane are used to measure the convection rate. [29]. Fig. 2.8 illustrate the whole mechanism.

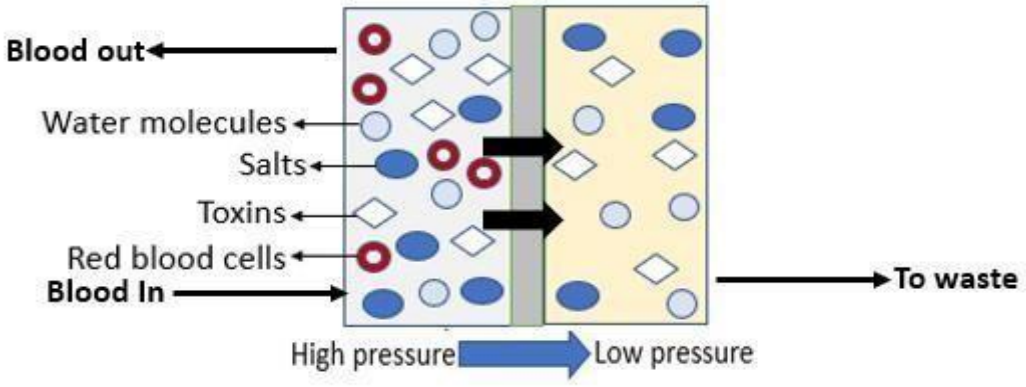


Figure 2. 8 Convection process in hemodialysis

2.2.2.3. Osmosis.

Osmosis is the random net migration of the solvent along an area of higher solute concentration across semi-permeable membranes in order to maintain an equilibrium of concentration. The driving force of osmosis is the gradient of concentration. Fig. 2.9 shows the process. In hemodialysis, osmosis describes the flow of water into blood plasma or interstitial fluid through cell membranes.

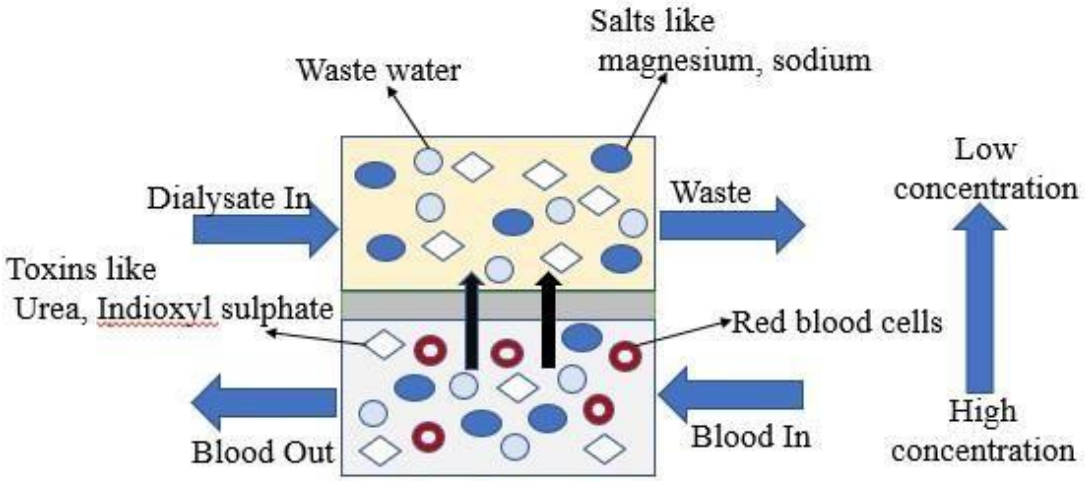


Figure 2. 9 Osmosis process in hemodialysis

2.2.2.4. Ultrafiltration.

Ultrafiltration is simply a method of excess water being extracted from the body. Based on the pressure differential, the water transfers from the blood plasma to the dialysate.

There is a greater pressure on the blood side, then the water travels to the lower pressure side, i.e., dialysate. The two essential variables that ultrafiltration relies on are hydrostatic blood pressure and membrane porosity. The patients are pre- and postweighted during the procedure to measure the performance of the membrane. The disparity in the patient's weight influences the membrane's efficacy. This medication was meant to kill medium-sized toxins, but it induces uremia. The Fig. 2.10 explain the process.

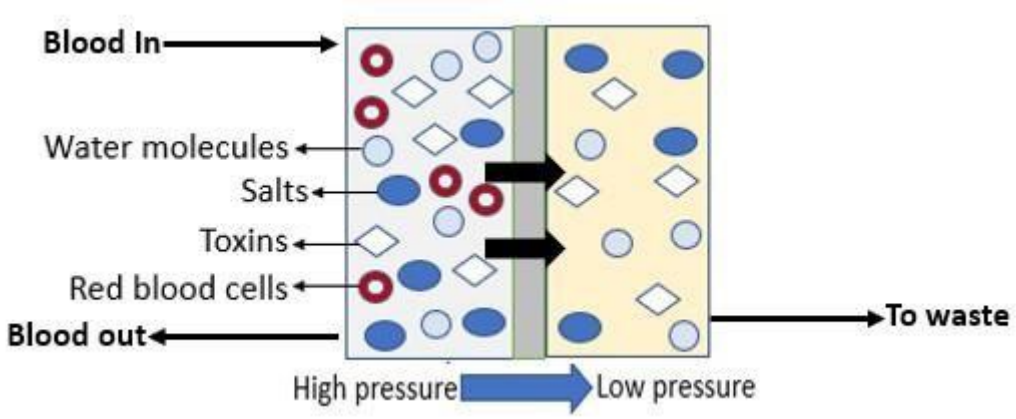


Figure 2. 10 Ultrafiltration process in hemodialysis

2.2.2.5. Adsorption

The binding of liquid, solid and gas to a surface by electrons, particles and molecules is defined as adsorption. Hemodialysis adsorption occurs as uremic toxins bind to or onto the adsorbents within the membranes on the surface of the semi-permeable hemodialysis membrane. As the solutes form bonds with the membrane surface, it is known as adsorption. In hemodialysis, the concept of adsorption is followed as the toxin can be removed by the adhesion with the membrane surface or the membrane adsorbent. The mechanism is explained in Fig. 2.11. The toxins whose isolation is very difficult they are named as P-cresol, peptides and Indoxyl-sulphate [16]. As they are ideally absorbed by adsorbing membrane surface or by adhesives added to the membrane adsorbent. On the membrane surface, certain protein which is significant for the body is also absorbed. By utilizing back flushing, they may be maintained.

The downside is that contaminants can quickly populate the membrane pores and reduce their effectiveness. It can be strengthened by the ability of adsorption of the membrane since the elimination of toxins is depended on the surface area.

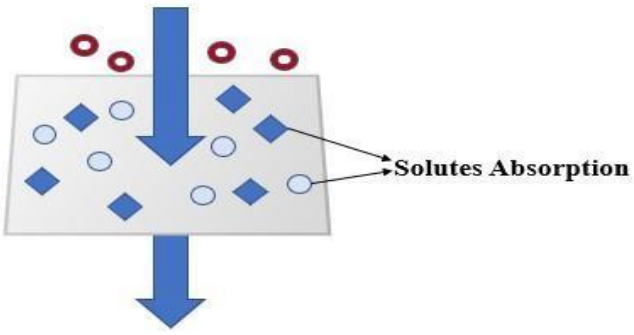


Figure 2. 11 Illustration of Adsorption process.

2.3. Hemodialysis Membrane classification

2.3.1. Symmetric or Asymmetric membranes.

The polymeric membranes comprise of 2 symmetric and asymmetric fiber structure forms. Symmetric membranes have a single sheet of polymer with a homogeneous, non-porous dense layer. They are produced without adding any additives from the polymers. These membranes are considerably thicker in comparison with the asymmetric membranes and offer low fluxes [17]. For the hollow fiber membranes outer and inner layers of the membrane wall, they can generate by cellulose or other synthetic polymer which helps in making similar-sized pores [30].

Dense porous membranes having high flux are asymmetric membranes. These membrane types are usually used for ultrafiltration, reverse osmosis and separation of gases. They have applications such as mechanical strength for high permeability, selectivity, and high-pressure [17]. Fig 2.12 explains the complete extracorporeal blood circuit.

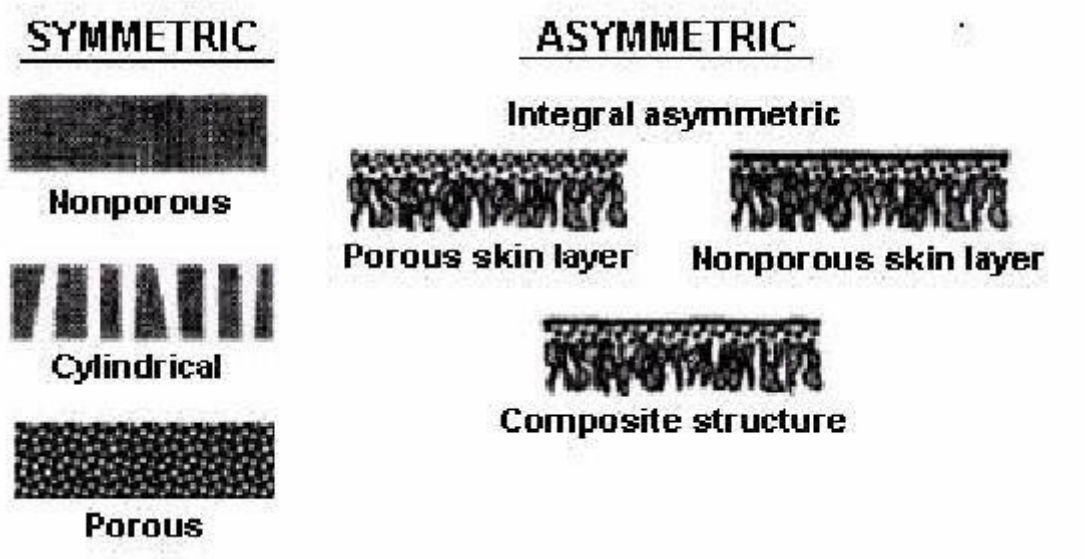


Figure 2. 12 Extracorporeal Blood Circuit [31]

2.3.2. High Flux v/s Low Flux Membranes.

High flux membranes give certain advantages to the treatment. This increases anaemia regulation, lowers cardiovascular disorders and decreases the need for erythropoietin [19]. The main distinction between them is that the sieving coefficient of the low flux membranes for β2-microglubulin is equivalent to 0 and the ultrafiltration is even less than 20 ml/mmHg. However, high flux membranes have ultrafiltration is more than

20ml/mmHg and sieving coefficient of β2-microglubulin is just about 33.90±2.94mg/dL [20]. Meanwhile, membranes showing high flux have more effective properties than membranes showing low flux these properties are high porosity, high adsorption capability and high molecular weight.

Using membranes with high flux lowers the risk of death if the patient has less than 40 g/l of serum albumin [21]. Serum albumin concentration is inversely proportional to the patient's mortality risk rate. It suggested that the patient's mortality did not depend on the material in the membrane [21]. High flux membranes fall into the processes of hemodialysis, hemofiltration, and hemodiafiltration and have the necessary permeation effect. The downside is that the high-performance dialyzer consists of a large pore scale that also extracts serum albumin with the toxic waste [22]. Loss of albumin in large amounts can result in adverse results for patients with renal function. Patients that are unable to bear protein deficiency must switch to traditional dialysis membranes or to low-flux membranes [22].

Albumin proteins drain from the kidney in certain renal patients. To cure any conditions in patients, this characteristic may be used. It can treat anaemia and help to eliminate end products of oxidative protein and glycation. The protein body begins to produce more albumin by extra or regulated removal and the development rate increases, resulting in better life for patients [22]. It is concluded that the membranes must be used as per the specifications of the patient.

2.3.3. Chemical Components of hemodialysis membrane

The membrane of hemodialysis is categorized into multidimensional criteria. These criteria specifically explain how dialysis membranes are useful in patients with renal failure. Important parameters are shown with the help of Fig. 2.13.

The toxins present in blood are removed by semi-permeable membrane while the dialysate is flowing on the other side of the membrane in hemodialysis process. The more the pores are present in the membrane that hemodialysis membrane is considered as more hydrophilic containing more semi-permeability. In addition, during and after the hemodialysis procedure, it affects the patients' biological response. Three groups can be categorized into readily accessible hemodialysis membranes: substituted cellulose, regenerated cellulose and synthetic polymers. (Table 2.5).

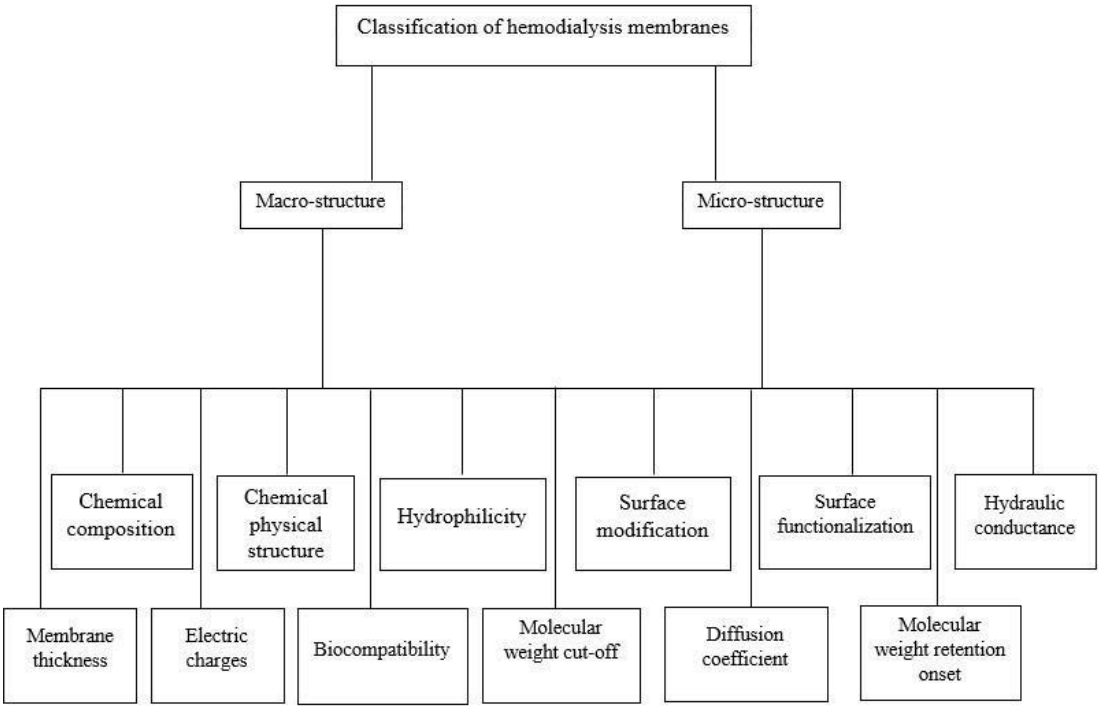


Figure 2. 13 Classification of Hemodialysis Membrane. [32]

2.3.3.1. Unmodified cellulose.

Cellulose membranes have been the most commonly used membranes for the exclusion of small molecules from the blood since the 1960s [7]. Cuprophan membranes are classified as unaltered cellulose membranes. Cuprophan membranes consider urea and creatinine toxins to be effectively isolated as the beginning of the artificial kidney. The minimum thickness, good mechanical properties, low cost, and consistent permeability make this material common.[33]. Cellulose is made from natural plants or cotton. Cellulose membranes are called hydrophilic since the cellulose monomer consists of large amounts of hydroxyl groups [9]. The main downside of this material is the flow of small-size impurities and preservation of medium molecules. It does not absorb impurities that are unwanted. These are regarded as a low flux unaltered cellulose membrane that, by stimulating the leukocytes and complementing the activation system, causes bio-incompatibility [34].

2.3.3.2. Exchanged Cellulose.

Substituted cellulose membranes are like membranes of cellulose, but later chemical modifications were made to eliminate the cellulose monomer from the hydroxyl group. The altered material is known as cellulose replacement and is more biocompatible than

the unmodified material. The acetyl residues of acetate, diacetate, or triacetate occupy the free space of the hydroxyl group [35]. Hemophan and vitamin E coated membrane was changed to enhances the bio-compatibility [12]. Substituted membranes have been calculated to provide more flux than previous membranes and to be considered more biocompatible. The downside of these membranes is the poor absorption permeability of larger molecules of toxins and still have a void to boost the characteristics of membranes [35].

2.3.3.3. Synthetic Membranes.

A variety of synthetic membranes, including AN 69 membranes, polyamide, polyamide (PA), polyacrylonitrile, polymethacrylate (PMMA) and polyethersulfone (PES) and polycarbonate occur from around the 1970s. These all membranes are also used in different applications [36]. Collectively, they are classified as synthetic membranes. With high-flux capacity, acceptable molecular weight cut-off and with different pore sizes and distributions these polymer membranes can be fabricated.

These membranes can provide outstanding biodegradability as well [36]. Mainly hydrophobic membranes can induce cell and protein adsorption on the membrane surfaces.

Table 2. 5 Commonly available hemodialysis membranes.

Cellulose	**Substituted Cellulose**	**Synthetic Polymers**
Cuprophan	Cellulose acetate	Polyacrylonitrile
	Cellulose diacetate	Polymethylmethacrylate
	Cellulose triacetate	AN69
	Hemophan	Poly-sulfone
	Vitamin E coated	Poly-ether-sulfone
		…

2.4. Challenges for the hemodialysis membranes

Despite improvements in the compatibility of blood purification membranes, high mortality rates have been recorded. Even though traditional hemodialysis has led to patients lasting longer lives, it also struggles to sustain their full essence of life [37].

Several immobilization methods have been applied, but no final better approach for surface modifications has been identified. Furthermore, not all of the membranes investigated were tested for hemocompatibility. In other words, few papers research articles reporting hemocompatibility aspects. While research wok reported hemocompatibility assessments with few factors. Since the advent of the technology, many elements of hemodialysis have been improved. Material improved beside the pore size adjustments and different modifications done regarding purification of blood which increase the demand of hemodialysis in hospitals and home. Still the quality of life is major challenge for the hemodialysis patients. Accordingly, major efforts must be put on the incompatibility of the membranes [38].

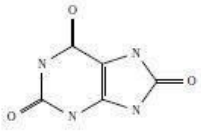
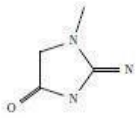
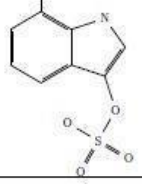
2.5. Uremic Toxins

Toxins that develop in people with severe renal disease are uremic toxins. These toxins have a variety of serum cytotoxic functions, molecular weights, and some are primarily bound to albumin and other proteins. Table 2.6 contrasts their aggregation in healthy individuals and in patients with kidney disease. Table 2.7 give the detailed scale and chemical composition of these toxins. Water soluble toxins, protein bounded toxins, and massive toxins are the three types of toxins that are commonly found.

Table 2. 6 Comparison of concentration of toxins where (CH) Blood measurement in healthy persons and (CK) Chronic kidney disease patients, including maximum (Cmax) [39].

Solute	CH/μM	CK/μM	Cmax/μM	Group
Urea	**<6700**	**38,333 ± 18,333**	**76,667**	**Carbamides free water-soluble solutes**
Urea Acid	**<400**	**496±265**	**873**	**Purines free water-soluble solutes**
Creatinine	**<106**	**1204±407**	**2124**	**Guanidines free water-soluble solutes**
p-Cresol	**5.6±9**	**186±41**	**377**	**Phenol's protein bond solutes**
Indoxyl sulfate	**2.4±22**	**211±365**	**940**	**Indole's protein bond solutes**

Table 2. 7 Toxins of blood its dimension and formation [23].

Solute	Structure	MW $gmol^{-1}$	pK_a at 293K	λ_{max} nm	Size x	Size y	Size z
Urea H_2NCONH_2		60	0.1	200	0.56	0.63	0.30
Urea acid $C_5H_4N_4O_3$		168	5.6	286	0.77	0.10	0.30
Creatinine $C_4H_7N_3O$		113	4.4	235	0.71	0.81	0.30
p-Cresol $CH_3C_6H_4OH$		108	9.6	220	0.66	0.76	0.39
Indoxyl sulfate $C_8H_6KNO_4S$		251	unknown	220	0.79	0.11	0.54

2.5.1. Toxins that are water soluble.

The molecular weight of the molecules smaller than 500 Da are water-soluble toxins. The agents are urea and creatinine [24]. Since they are strongly soluble in water and not protein-bound, hemodialysis will remove them easily. They may not have toxic behavior necessarily [25]. Creatinine is the renal function marker and is selected in this thesis as a reference for water-soluble toxins. The spike in serum creatinine is generally due to uremic accumulation or by breakdown of the muscle. Infection, organ damage and death are positively linked to serum creatinine levels in hemodialysis patients [40].

2.5.2. Protein Bound Toxins.

The toxins that are linked with the albumin are said as protein-bounded uremic toxins. Since the efficacy of hemodialysis is normally measured by urea removal, they are often ignored. Progressively, researches have suggested that Chronic kidney disease are linked with protein-bound toxins development and coronary disease production and aggravation [27]. The two agents are indoxyl sulphate and p-cresol sulphate. Indoxyl sulphate in dietary proteins are the consequent of tryptophan (figure 2.4), whereas p-

cresol sulphate is obtained from tyrosine and phenylalanine. Hence released into the kidney into the urine. Their rise in serum suggests that kidney processes are worsening [41].

2.5.3. Large Toxins.

Large toxins are toxins greater than 500 Da in molecular weight. A prototype is βmicroglobulin. An aggregation of molecules is separately correlated with higher chance of mortality [29]. The size of the pores inside the hemodialysis membrane is larger enough that these types of toxins can easily be removed by size sieving technique.

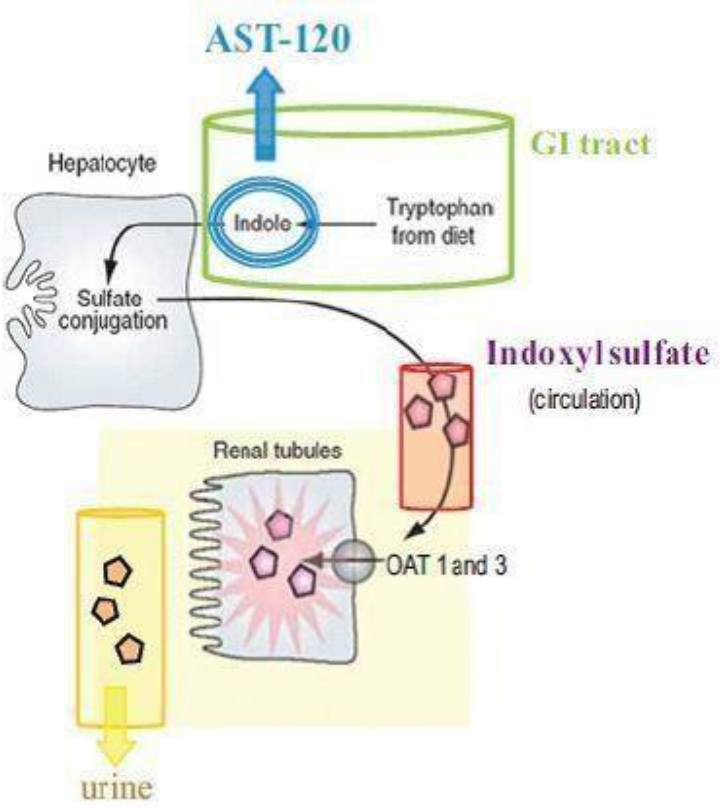


Figure 2. 14 Metabolism of Indoxyl Sulfate. The indoxyl sulfate (IS) protein metabolism production is obtained from dietary tryptophan. [42]**.**

2.6. Adsorbents

The molecules that can be adsorb inside and on the surface are named as adsorbents. The adsorbents are the essential components of the hemoperfusion and wearable kidneys. Most common adsorbents are resin, charcoal and activated carbon, they are essentially used for the removal uremic toxins. The first adsorbent that was reported by Yatzidis was charcoal used for the removal of uremic toxin [73]. The activated

carbon is chiefly used for the treatment of acute poisoning, intoxication and hepatic failure specially in hemoperfusion from 1964 up till now [73] [24] [74]. Activated carbon containing sizeable exterior area as good rapport for both inorganic and organic poison and amphoteric properties is a reasoning choice as an adsorbent [75] [76]. However, the major disadvantage of activated carbon is non-selective adsorption for both uremic toxin and life sustaining molecules from blood.

The further encouraging nominates to adsorb uremic toxins are zeolites. The small molecular sized uremic toxins can be adsorbed by MFI zeolites reported by Wernet and colleagues [77]. Activated carbon contains such adsorbent level for urea which are moderately equal and lower. For to increase the rapport towards specific uremic toxins and for to enhance the adsorption capacity of zeolites the chemical and physical optimization of zeolites via ion exchange or surfactant are helpful. Zeolite can hold better selectivity and affinity for protein-bound toxins as compared to activated carbon. This selective adsorption ability is highly helpful that can resolve certain problems in hemodialysis.

The direct contact of adsorbent such as activated carbon with the blood leads many complications and problems like hemolysis and blood coagulation. However, the blending of adsorbents into the membrane solution can reduce the shortcoming of hemodialysis [77]. For to reduce the blood clotting addition of heparin can be highly useful [73]. However, overdose of heparin can conduct to far complications such as hemorrhage and injury [24].

For to decrease the complications effected by the contact of adsorbent with the blood is to enhance the biocompatibility of the membrane as well as the adsorbents which is a growing and viable trend [78]. Coating and encapsulation of activated carbon and carbon nanotubbed adsorbents was used as part of the set-out strategy for improving biocompatibility. Many different coating hemo-compatible membranes are used to coat the adsorbent particles, such as cellulose nitrate and plyhydroyethly methacrylate [79]. However, for to prevent platelet adhesion and blood coagulation heparin has been used for to coat particles [24]. When the adsorption sites of the adsorbent have been blocked due to coating and encapsulation of the adsorbent the uremic adsorbing efficiency decreased [80].

The functionalization method is considered to be advantageous in enhancing the hemocompatibility of the adsorbent particles as compared to coating and encapsulation technique. A hydrophilic functional group must be introduced into the surface of the adsorbent particle to enhance the hemocompatibility [24]. The zeolite particles are incorporated in my proposed composite membrane. This zeolite particle can be used as a biomedical implant as well as a coating material. It can also can be used as a drug delivery material and it also shows good biocompatibility [81] [82].

The most broadly used industrial adsorbents and catalysts are zeolites that contains micropores and are aluminosilicate minerals [43]. The medium toxins named as creatinine, indoxyl sulfate and p-crecole were removed and adsorbed by zeolites in this study. Their chemical and structural composition are discussed here.

2.6.1. Chemical Compositions of Zeolites.

For many zeolites the general formula is represented as**,**

|Mx(H2O)|[AlxO2tSit−x] − IZA,

Where, in bars, the visitor species are given (||). Within brackets, the provider context is depicted ([ ]). M is the cation, x is the number of Al frame atoms in the unit cell, γ is the number of water molecules adsorbed, t is the cumulative number of tetrahedral frame atoms in the unit cell (Al+Si) and IZA (International Zeolite Association) is the frame form code given by the International Zeolite Association's Structure Committee [24].

2.6.2. Structure of Zeolite

The composition of Zeolite is related on a related SiO4 and AlO4 tetrahedra matrix besides the exchange of oxygen atoms. The fundamental construction and combined construction units of zeolites are presented here.

2.6.3. Basic building unit (BBU): the tetrahedron

By periodically connecting the basic building unit (BBU), the tetrahedron, all zeolite structures can be created [77]. Si4+, Al3+ or P5+ atoms are in the middle of the tetrahedron, while oxygen anions (O2−) are in the corners. The balance could be SiO4, AlO4, PO4, etc.

2.6.4. Composite building unit (CBU)

By connecting groups of simple building units together (BBUs) the zeolite composite building units (CBUs) can be built (BBUs). Rings are the easiest specimen of CBUs.

The ring containing n tetrahedra is commonly referred to as the n-ring. 4, 5, 6, 8, 10 or 12 tetrahedral rings are the most common rings [51, 52]. The pore size and configuration of the 8-ring are shown in Fig. 2.15. Table 2.8 indicates the size of the other rings. As seen in Fig. 2.16, further combination of n rings will guide to bigger CBUs with complex and fascinating formations. Cages will include cations, water molecules, and vice versa. One-dimensional CBUs are called chains that are made of rings (either similar or different) [76].

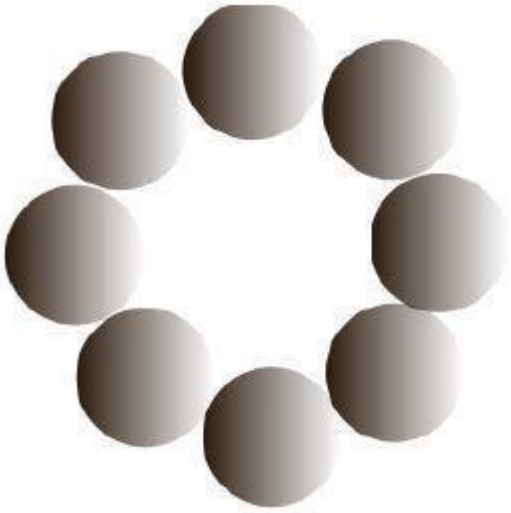


Figure 2. 15 Drawing of 8-ring.

Table 2. 8. The loose T-atoms in 4, 5, 6, 7, 8, 10, 12 ring

T-atoms in ring	Maximum free aperture (nm)	Typical free apertures (nm)
4	0.16	-
5	0.15	-
6	0.25	-
8	**0.43**	**0.30-0.45**
10	0.63	0.45-0.60
12	0.80	0.60-0.80

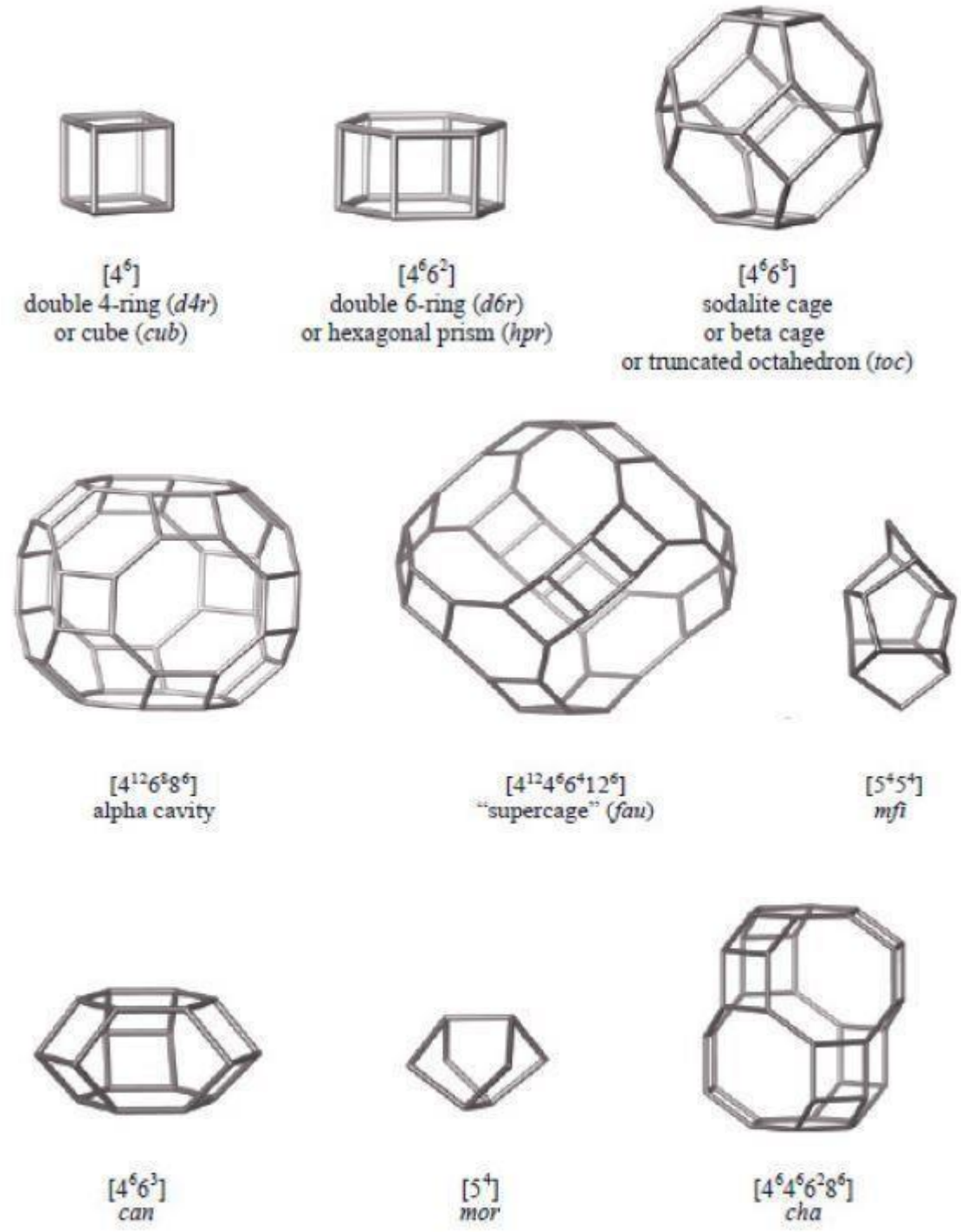


Figure 2. 16 Diagram of the ordinary names and pore symbols with their related polyhedral composite building units (cages). [50].

2.6.5. Pores, cages, cavities and channels.

Windows or pores are the n-rings that define the face of a polyhedral CBU. Since they are too small to pass around molecules larger than H2O, polyhedra with faces no larger than six rings are referred to as cages. Cavities with at least one face greater than six rings are known as polyhedra. In one, two, or three dimensions, the enlarged pores are called channels, and they allow guest species to diffuse (larger than 6rings). The efficient width of the canals is the key feature of zeolites, where along with the drain which is limited by the smallest free aperture. Hence for to get the effective thickness of the channels the composition of zeolites is important [50].

Chapter No. 3

Literature Review

The blended membranes proposed mostly based on adsorbent and pore size to terminate toxins. The membranes that are used for hemodialysis with their advancements also on adsorbents used in renal therapy are presented in this chapter. This gives me acceptable direction in selecting worthy adsorbent and additives that are highly biocompatible.

3.1. History

In Philadelphia, hundred years ago Prof. Abel utilized celloidin tube and performed first process of dialysis [28]. By utilizing these tubes, he examined on mass separation among two fluids [28]. Thirty years ago, in Lund Prof. Alwall on his first artificial kidney conducted an experiment on the cleaning of blood. This experimentation explored the paths to start the treatment of artificial hemodialysis [44]. Willem Kolff in 1942, explored practical artificial kidney having rotating drums which in USA and UK turned out to be the first example of the End-Stage-Renal Disease (ESRD) [45].
But It wasn't commercialized until 1960, when arteriovenous Teflon shunt in Seattle was developed by the Belding Scribner. Afterwards the confirmation of the success of this treatment the artificial kidney center came into existence by James Haviland and Scribner which in 1962 was the first kidney center and also a nonprofit organization [46]. Further, their next challenge was to cure the ESRD patients and also to inaugurate the technique [47].
The efficiency of the process was raised by decreasing the time from 12 hours to 4 hours which lead to the enhancement of blood flow level to 400-500mL/min and cleared away the urea efficiently [48]. In liver the acidosis correction and slow acetate conversion was controlled by the bicarbonates. Then afterwards, home hemodialysis treatment came into existence which turned out to be less expensive and also having capability of reducing the hepatitis risk [48].

The major problem of the 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 [46]. It was effective than previous method but due to complex manufacturing the financial expenses increases which was unaffordable for the dialysis centers. In 1980s flat sheet membranes were fabricated by phase inversion, solution and dip coating method which then considered as the major breakthrough in the dialysis industry [49].

The efficiency of treatment of Hemodialysis depends on the blood clearance. As a kinetics marker for mechanistic analysis, it was utilized by The National Cooperative Dialysis Center. As far as urea is considered the most toxic solute. But apart from its toxicity, the treatment's efficiency and requirement dependable on it. The efficiency of dialyzers is less and is not able to figure out the amount of urea cleared off from the blood due to the middle size molecules accumulation. The various drawbacks of this treatment include anemia, diabetes, hypertension, skeleton abnormalities and carpel tunnel syndrome, [50][51].

3.2. Brief summary of the literature review

In 1994 about 33 patients were studied during the hemodialysis procedure using cellulosic membrane. Important complement activation takes pace with cellulosic membranes. Protein reaction was also determined after both pre- and post-dialysis. [52].

The effect of different molecular weight PEG and different wt percent of the same molecular weight on the structure and permeation properties of the PSf membrane prepared in solvent N-methyl-2-pyrrolidone was studied in 1998. (NMP). The highest pure water flux was obtained from 600 to 6000 g/mole while the solute rejection was decreased. His studies also showed that as the molecular weight of the PEG increases, the membrane's surface morphology and pore size increase, changing the permeation properties from ultrafiltration to microfiltration [53].

In 2000 investigation was done on the polyvinyl Alcohol (PVA) membranes. Acetic acid used as an additive that effects the filtration and structural properties of the membrane. The degree of inundation of the coagulant medium for acid-base equilibrium increases as the volume of acetic acid is increased. Results influenced the relation between the fabricated membrane and the skin structure [54].

In 2004 PS hemodialysis membrane were fabricated by blending with PVP. The aim of this research was to increase biocompatibility. This study showed that using the AC method and the γ- method, high biocompatibility could be accomplished by incorporating significant and small quantities of PVP. Polymer particle swelling investigated by changing the wet/dry ratio of the polymer surface [55].
In 2005, a water soluble amphiphilic 2methacryloyloxyethyl phosphorylcholine (MPC) copolymer was used to produce a CA hollow fiber membrane. This study enhances the biocompatibility of membrane. Less fouling, protein adsorption and excellent permeability had been reported [56].

In 2006 preparation and performance of polysulfone-cellulose acetate blend ultrafiltration membrane it concludes that when the additives were added to make a composite membrane the number and also the size of the pores on the surface of the membranes increased which hence also increased the permeability as well as the flux of the membrane [57].

In 2007 cellulose acetate asymmetric hollow fiber membrane was fabricated to determine the pure water flux (PWF) and protein retention. PEG added as an additive. By increasing the amount of PEG dextran rejection and PWF increases. It also reduces the macro voids and changings in coagulation temperature enhances the permeability performance [58].

Biocompatibility and separation efficiency of antioxidative polysulfone/vitamin E TPGS composite hollow fiber membranes in 2011 is 0.53 percent when PSF/PSFgTPG was used [59].

In 2012 hemodialysis membranes are mostly hydrophobic in nature. As a consequence, it adsorbed protein to the membrane's surface. It could be evaluated by various techniques such as surface Plasmon resonance, mass spectroscopy and X-ray photoelectron spectroscopy. Interactions between the BSA and PSF membrane was investigated by AFM [60].

In 2013, the effect of two different solvents, as well as the effect of PVP of different molecular weights (24.000, 40.000, and 360.000 Da), on the structure and permeation of PSF membranes was investigated, namely Nmethyl-2-pyrrolidone (NMP) and dimethyl acetamide (DMAc). The findings revealed that DMAc was deemed to be

more appropriate than NMP, especially for the removal of BSA. Maximum BSA elimination (at pH 9.3) was achieved when 5 wt% PVP 360,000 Da was blended into the membrane solution. However, as the molecular weight of PVP increases, the membrane becomes denser, with less macrovoids, higher porosity, and a more polished base [61].

In 2013 PAN membranes were prepared by different blending ratios. PEI was carboxylated before being used as a hydrophilic modifier. The biocompatibility of the modified membrane was strong. Protein adsorption, platelet adhesion, and thrombus formation were all minimized [62].

In 2013 to investigate the protein removal during hemodialysis cellulose and polyflux dialyzers used in this research. It was concluded that protein attached more strongly to the synthetic polymer as compared to the cellulose. Various functional group and molecular ranges of plasma protein was examined [63].

In 2014 PVDF membranes with addition of FMWCNT and PEG additives was 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 [64].

In 2014 PES/PVP-f-MWCNT nano-hybrid hemodialysis membrane was synthesized by phase inversion method. This research concluded that PES nano-hybrid hemodialysis membrane in comparison with PES membrane showed better results. The addition of NCs to the PES membranes increases the surface and efficiency. It also speeds up the removal of uremic waste [65].

In 2014 PSF/PVP/PEG membrane and concludes that by the PSF/PVP/PEG. 500 to less than 400 mg/l concentration of urea and creatinine transported by the other membranes [66].

In 2014 the cross-sectional morphology of the PSF membrane was swapped when NMP as a solvent was used and co-polymer was mixed into the PSF and the changings were increased by increasing the concentration of the copolymer. The finger-like structure of the PSF membrane grew shorter as the co-polymer concentration was increased. The settlement of copolymer on the membrane surface often improved

surface roughness. Furthermore, reversible fouling dominated fouling on the modified membrane surface. After bovine serum albumin (BSA) separation, a flux recovery ratio of 90% was reached [67].

In 2014 the preparation and performance of Polysulfone-Cellulose Acetate Blend Ultrafiltration Membrane this methodology can be utilized for the ultra-filtration in the hemodialysis also tests can be performed for the removal of toxins such as BSA, Urea and creatinine.

In 2015 to enhance the biocompatibility and increases the uremic waste disposal PES membrane was blended with anti-coagulant molecules, zwitter-ion, non-ionic and hydrophilic brushes. Purpose of this research was also to review on compatibility, preparation techniques and method of addition of polymer [68].

In 2015, researchers blended comb-like amphiphilic block copolymers to improve the hemocompatibility and ultrafiltration efficiency of surface-functionalized polyethersulfone membranes, for this PSF polymeric family needs very optimized handling for to make optimized pore size [69].

In 2016 Poly citric acid- grafted-MWCNT added as nanofiller to increase the biocompatibility of the PES membrane.it showed the enhancement in morphology, PWF, BSA rejection and antifouling capability of the membrane. 95.2% BSA was retained and hydrophilic in nature [70].

The role of zeolite form and particle size on their capacity to adsorb uremic toxin as powders and fillers in membranes was studied in 2016, and it was discovered that the creatinine adsorption level inside the membrane greatly affected by the size and shape of zeolites. When zeolite powders are embedded within membranes, microparticles have a higher adsorption potential than nanoparticles, despite the fact that size has little effect on zeolite powders [71].

Drywet spinning was used to make PES/poly (MMA-VP-SSNa-SA) hollow fiber (HFMs) in 2016. The biocompatibility of the membranes and the antibacterial properties of the HFMs were improved. BSA solute was also deducted from membranes and results showed that 95% of the BSA rejected by the membrane HFM24-6 in comparison with HFM-PES [72].

In 2017, researchers investigated the adsorption of indoxyl sulfate by zeolites and polyethersulfone–zeolite composite membranes proving that 550 micro grams of indoxyl sulfate can be adsorbed on the adsorbent [2].

In 2018 incorporation of graphene oxide in polyether sulfone mixed matric membranes by phase inversion technique and 78.30% solute creatinine cleared from the solution [73].

This year's study concentrated on the treatment of ketoacidosis in CKD patients on hemodialysis. Acidosis, 1,25 vitamin D deficiency, and secondary hyperparathyroidism both cause insulin secretion to decline in CKD patients. In patients, diabetes and many other abnormalities occurred during hemodialysis [74].

In 2019 this study showed that dialyzers in dialysis process facing problems with the biocompatibility of the membranes. Reactions occurred between them and remained stable for years. While findings of polyvinylpyrrolidone and polysulfone have been published, cellulose triacetate remains the most appropriate therapy [75].

In 2019 blended membrane of citric acid cross-linked with chitosan/PEG-PVA was fabricated. Heparin with an active sulfate group grafted on blended membrane. Citric acid and grafted heparin increase the mechanical strength and membrane swelling. This membrane also improved urea and creatinine permeation [76].

In 2019, researchers immobilized argatroban and mPEG-NH2 on a polyether sulfone membrane surface to create a nonthrombogenic biointerface, demonstrating that the more hydrophilic the membrane, the better the PRT [77].

In 2020 in this study Polysulfone (PSF)/Polymethyl methacrylate (PMMA) dual layer hollow fiber (DLHF) was used with spinning method and rejection of urea estimated up to 81.2% and Creatinine rejection observed up to 98.8% in this work [78].

The additive-free preparation of hemodialysis membranes from block copolymers of polysulfone and polyethylene glycol was investigated in 2021, and it was discovered that PEG would increase the membrane's hydrophilicity [79].

Chapter No. 4

Research Methodology

4.1. Selection of Material

4.1.1. Poly Sulfone (PSF)

Currently, over 18 different types with different sizes of poly sulfone dialyzers are being used in hospitals, as all these membranes are being used for the effective hemodialysis [69]. As they meet all hemodialysis membrane criteria, including the strong physical ability and tolerance to chemicals, bio-compatibility, and fast sterilization [69].

Fresenius Poly Sulfone R, which was the first poly sulfone membrane, was established by Fresenius in 1983. It has a macroreticular and asymmetric structure. Some widely used polyether sulfone membranes are DIAPES R and Polyamix. Hydrophobic polymers include both poly sulfone and polyether sulfone. A familiar approach to make the membranes more hydrophilic is mixing with a hydrophilic copolymer (polyvinylpyrrolidone), which can contribute to better diffusion results [65].

4.1.2. Cellulose Acetate (CA)

Many polymers have been utilized as therapeutic drugs in the medical field. The basic classification of polymers is natural polymers and synthetic polymers, which have also been divided up into biodegradable polymers and non-biodegradable polymers. As a result of low cost, low immunogenicity, biocompatibility, environmentally friendly and antibacterial properties, biopolymers have played an increasingly important role over synthetic polymers [80]. Cellulose has many commercialized variants, such as cellulose esters, hydroxyethyl, hydroxypropyl fatty acids, hydroxyalkyl cellulose among several more. CA which acts as semi-natural biopolymer that has been extensively used in the medicinal and manufacturing industries the element of plant cell walls, it is also known to be a cellulose derivative. [80].

Tissue engineering, antibacterial technologies, hemodialysis membranes, drug delivery mechanisms and wound care are the biomedical applications of the CA. By modifying

the micro configuration, the construction and nature of the CA's properties may be modified to the end-use specification [81].

From different raw materials such as rice husk, cotton, bagasse and sugarcane straw, CA can be produced. It has been synthesised into two stages. The first step is the separation of cellulose from raw materials, and the second step is cellulose acetylation. Cellulose has a composition that is both amorphous and crystalline. Anhydrous glucose molecules linked by ether bonds (β-1, 4 glycoside bonds) are part of the monomer structure of CA. The anhydrous glucose hydroxyl group is substituted by acetyl groups at positions 2, 3 and 6 [53]. The etherification and esterification response carried out on the free hydroxyl groups improved the thermal plasticity of the CA.

4.1.3. Polyethylene Glycol (PEG)

PEG is a synthetic polymer with significant low-cost, biocompatible, pore-generating and water solubility characteristics. In pharmaceuticals and medical applications, it is a commonly used polymer. Strong solubility and low toxicity improve the material's smoothness. Immune reactions, complement activation, platelet adhesion and protein adsorption are also avoided [82].

The key PEG applications are considered by the formation of hydrogels pore, drug delivery but non-cell adhesion and growth. It is common for alteration of the biomaterial surface and as an environmentally friendly polymer [54]. It is highly drawn to molecules of water that have made it biodegradable. Ethylene glycol is synthesised by poly-condensation with an acidic or simple catalyst. Ethylene oxide polymerization of Foe's heavy molecular weight used as a source [83].

Latest researched showed that PEG increases the hydrophilicity and porosity of the membranes. hemodialysis membranes having PEG in composition are highly porous and features in terms of flux, permeability, pore size and protein rejection [84]. These properties are attractive and useful for the hemodialysis membranes.

4.2. Material and Synthesis Process

As a membrane forming basic polymer the PSF with an average molecular weight of 30,000 Da (Sigma Aldrich) is used. The solvent that used was DMAC with analytical purity of 99% CA with an average molecular weight of 30,000 Da (Sigma Aldrich),

PEG 400 (Aladdin) was utilized as a pore generator to alter the membrane by making a blend with PSF. Distilled water, N-hexane & Methanol (Sigma Aldrich) were used as a non-solvent agent. Experiments were accomplished using Urea with molecular weight of 60.02 MW, creatinine 113.54 MW and BSA (pure) obtained from Sigma Aldrich. The anticoagulant sheep whole blood was purchased.

Table 4. 1 Material used for the preparation of membranes.

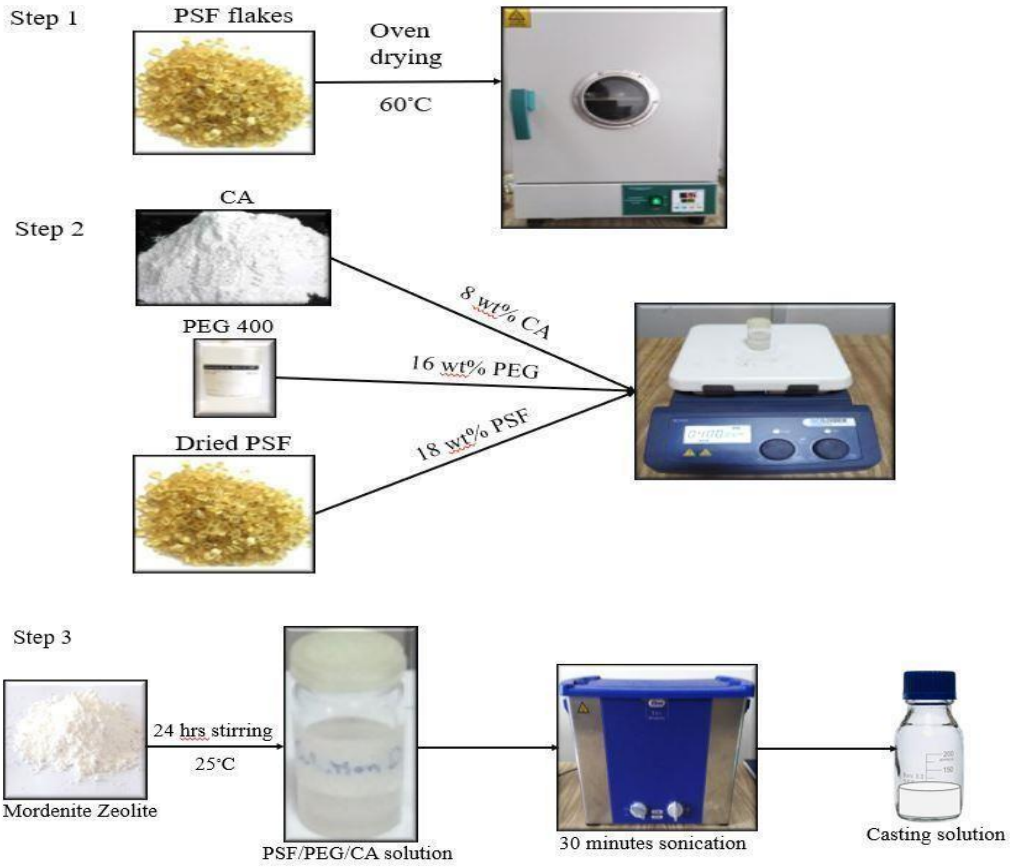
Material	Classification	Characteristics	Supplier
Poly Sulfone	Base Polymer	MW = 35000	Sigma Aldrich
		Chemical Grade	
DMAC	Solvent	99.7% Pure	Sigma Aldrich
Cellulose Acetate	Pore gens	MW = 30000	Sigma Aldrich
Polyethylene Glycol	Pore gens	MW = 200	Sigma Aldrich
Urea	MW = 60.6	-	Sigma Aldrich
Bovin Albumin serum	Purity = 99.7 – 100%	-	Sigma Aldrich
Creatinine	MW = 113.54	-	Sigma Aldrich

4.2.1. Flat Sheet Membrane

To synthesize the membrane, the PSF flakes were firstly dried it in the drying oven at 60 ‘C for 24 hours. Then 18 weight % of solution is prepared from which 7 ml of solution is utilized as base solution. The additive like PEG were prepared as 16 % weight into the solvent and from which 4 ml of solution is mixed with the base solution for pore generation. The CA solution were prepared in 8 weight % into the solvent and from which 2 ml is added into the base solution and at the end the mordenite zeolite were added in different concentrations while rest is DMAC as solvent. The solution is

stirred for 24 hours at 25 ‘C to make the solution homogenous. The solutions were then sonicated for 30 minutes to remove any kind of trapped air bubbles as these bubbles can deform the membrane surface after casting.

The polymeric solution was then casted on the glass slab by using doctors’ blade with the thickness of 200 µm. It is then submerged in the purified water coagulation bath for 24 hours after evaporating for 30 to 45 seconds to complete the phase inversion operation. The distilled water removes the solvent and also helps in solidifying the membrane. It is then left for 24 hours in the distilled water to remove any solvent content before further post treatment, after 24 hours the membrane is then immersed in the methanol for 2 hours and then in n-hexane for 2 hours to eliminate any trapped solvent in the pores of the membrane then the membrane is placed on a clean surface with controlled environment for drying for 24 hours before any further testing. Fig. 4.1 illustrates the complete synthesis process in steps.



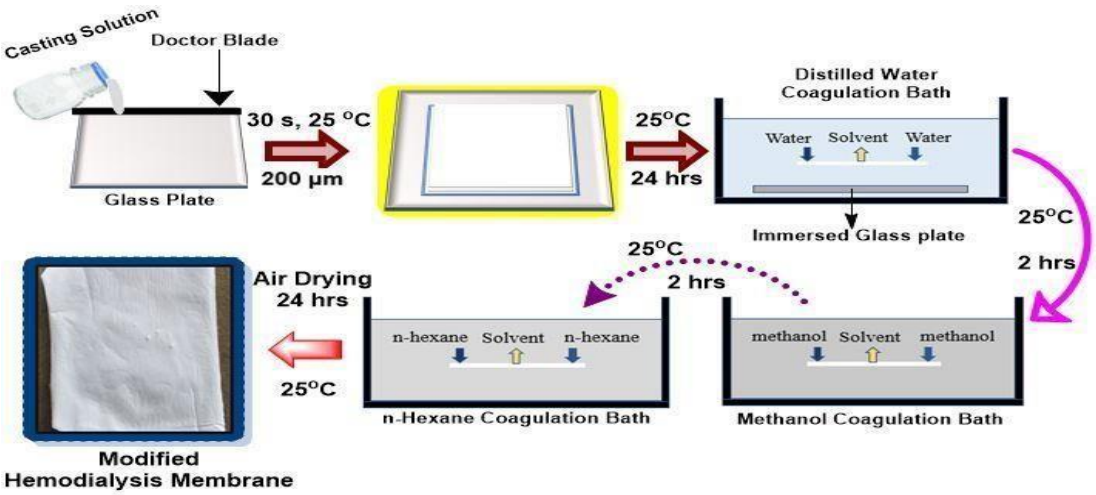


Figure 4. 1 Preparation of solutions and fabrication of the membrane by phase inversion technique

Table 4. 2 Recipe of pure PSF and modified membranes with phase inversion technique

Membrane	PSF wt%	Sol (ml)	PEG wt%	Sol (ml)	CA wt%	Sol (ml)	Mordenite Zeolite
PSF	18	-	-	-	-	-	-
PEG/CA-1	18	7	16	4	8	2	0.18
PEG/CA-3	18	7	16	4	8	2	0.48
PEG/CA-5	18	7	16	4	8	2	0.98
PEG-1	18	7	16	4	-	-	0.18
PEG-3	18	7	16	4	-	-	0.48
PEG-5	18	7	16	4	-	-	0.98

4.3. Methods

4.3.1. Characterization of Membranes

4.3.1.1. Scanning Electron Microscopy

The SEM is the method that elaborates the morphology of the material it is considered as the most important technique for the characterization of the membrane. SEM also

helps in finding the layer adhesion & density, elemental composition, pore size and thickness of the membrane [85].

In SEM model JSM 6490A, JEOL, Japan analysis the dried samples react with the electron beams and produces morphology of the membranes and its relative composition. The secondary electrons are converted from that beam when the sample come in contact. An image is displayed on the screen after the beam detected on the receptor detector by the backscattered electrons on X-rays [86]. The surface morphology and cross section of the samples were taken at the various magnification whereas, the voltage is kept at the 10KV. The analysis was recorded at the various magnifications of X250, X500, X1000, X2000, X5000, X10,000, X15,000 after breaking the membrane sample in liquid nitrogen and mounting it in a lateral position on brass plates with double-sided adhesive tapes Using the SEM model JSM 6409A, JOEL, Japan, the surface and cross-sectional morphology of the membrane was observed for each sample.

Figure 4. 2 SEM model JSM 6409A, JOEL, Japan.

4.3.1.2. Atomic Force Microscopy

In AFM JSPM-5200 Japan, three dimensional topographies are obtained when the image down to the sub nano meter range, with the proper environment and equipment. Vacuum is no required for processing the samples; hence it can be observed at ambient and operating conditions. The main advantage is the high-resolution techniques by assessing the roughness and height of the membranes in the air at nanoscale. The roughness of a membrane is calculated in terms of its mean surface roughness (Rs). It

is the average surface value at the mid of the sample enclosing by equal number of images at angles and sides.

Figure 4. 3 AFM JSPM-5200 Japan.

4.3.1.3. Fourier Transform Infrared Spectroscopy (FTIR)

It is widely used technique in the characterization of applied sciences. It is used to know the functional groups and elemental chains of polymers and give detailed information on the covalent bonding. 100 PerkinElmer, MID-IR instrument used for the FTIR measurements of the membrane samples. Range is kept at the resolution of the $4cm^{-1}$ and spectrometer range 400-4000 cm^{-1}. Flat sheet membranes were cut and placed into pallet holder. They were then seen under infra-red radiations to study various functional organic groups. FTIR Spectrum 100 PerkinElmer, MID-IR instrument used for the FTIR measurements of the membrane samples.

Figure 4. 4 FTIR Spectrum 100 PerkinElmer, MID-IR instrument.

4.3.2. Testing of membrane

4.3.2.1. Membrane porosity

The wet and dry weight procedure was used to calculate the membrane's porosity [87]. The membrane sample was cut into 1×1 cm^2. They were weighted again after being baked and then soaked in distilled water for 24 hours. The following equation can be used to measure the data: W is the weight of the wet and dry membranes (grams), $\boldsymbol{\rho}$w is the density of pure water (g/cm3), and $\boldsymbol{\rho}$p is the density of polymer [88].
The membrane porosity can be obtained by using Eq. 1.

$$\text{porosity } € = \frac{\frac{W_{wet} - W_{dry}}{\rho_w}}{\frac{W_{wet} - W_{dry}}{\rho_W} + \frac{W_{dry}}{\rho_p}} \quad (1)$$

4.3.2.2. Degree of Swelling

Slow swelling phenomenon appears by the diffusion of solvents in the polymeric chains that leads to swelling of the membranes [106]. This test is important to avoid the dissolution of the membrane by replacing polymer-polymer interactions to polymer-solvent. It can be difficult to remove the moisture from the membrane matrix completely so this can be reversible and irreversible [107]. Cross-linking, intermolecular interactions, and crystallinity are the ways to achieve the degree of swelling. It can be seen at macroscopic level and polymer or solvent can also change its properties [108].

To perform this experiment, 1×1 cm^2 of the membrane sample was used. They were pre oven dried at temperature of 60°C for almost 12 hours to remove the moisture and weighted (W_{dry}). The samples were then submerged in the distilled water for 24 hours. The soaked membranes were removed from the water and weighted again (W_{wet})[89]. Digital screw gauge was used to quantity membrane thickness. The measurement was made at 5 different positions and average was taken [89]. The water uptake % then calculated by Eq. 2.

$$\text{Water uptake } (\%) = \frac{\mathrm{W_{wet}} - \mathrm{W_{dry}}}{\mathrm{W_{dry}}} \times 100 \quad (2)$$

4.3.2.3. Contact Angle Measurement

The angle created between a rigid surface and a liquid droplet is known as the contact angle. When solid, liquid and gas molecules come in interaction with each other, then liquid molecule formed 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 [109]. 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 for this experimentation. For this testing, the samples were cut into the stripes and static contact angle was measured using the sessile drop method [90]. Distilled water was poured on the sample at the dosing rate of 0.1µL/s, with the constant dosing rate of 0.2µL, with the help of the micro syringe. The water drop angle measured on the surface. Three times on average the angle was measured.

4.3.2.4. Mechanical Properties of the Membranes

The ultimate tensile strength was done by using Shimadzu, AGS-X series ultimate tensile strength of 20KN. ASTM standard was at a strain rate of 0.5mm/min. the stress strain behavior was observed for the all the samples. The rate applied on the sample until it breaks[91]. This behavior was then studied for every membrane.

Figure 4. 5 Shimadzu, AGS-X series.

4.3.2.5. Water Flux and Permeability

Water flux and permeability experiment was performed in dead end filtration cell. The cell consists of the feed tank on which the nitrogen pressure is applied. The permeate collected after the filtration through the membrane[92]. For the performance distilled water is fed into the tank. To stabilize the system with respect to flow and pressure distilled water runs through for 10 minutes until constant water can be obtained in the permeate. The membrane sample was cut according to the membrane perforated disk size. The pressure of 2.5 bar was applied. The permeate was collected after every 10 minutes which is then measured and calculated. V is the volume of the permeated water in Liters. T is the time in hours. A represent the total area of the membrane in cm^2. The pure water flux was calculated by using Eq. 3. [88].

$$J = \frac{V}{A \times T} \tag{3}$$

Where J is the flux, L/m^2h. The permeability calculated by the following Eq. (4).

$$\text{Permeability} = \frac{\text{Flux}}{\text{pressure}} \tag{4}$$

4.3.2.6. BSA Rejection % Experiment

For the performance testing 1mg/ml BSA solution was prepared and fed into the feed tank. The effective membrane area was $7.085cm^2$ equals to the filtration disk was cut and inserted in the cell. The pressure of 2.5 bar is applied. After the permeate obtained, both retentate and permeate was observed under the spectrophotometer at 278nm wavelength. The BSA Rejection % was then calculated by Eq. 5.

$$\text{BSA \%Rejection} = 1 - \frac{C_p}{C_r} \times 100 \tag{5}$$

Here Cp and Cr are concentrations of permeate and retentate, respectively [92].

4.3.2.7. Urea Clearance and Creatinine Adsorption Capacity

For the urea performance testing. The solution of 1mg/ml was prepared as the mimic of the human kidney in 130 ml solution was poured in the cell and the system runs for 3 Time. After that the permeate and retentate differences was measured under spectrophotometer at wavelength 190nm. The urea clearance was calculated by the Eq.

6 in which Ci is the initial concentration and Cf is final concentration at time t [92].

$$\text{Solute Clearance } \% = \frac{C_i - C_f}{C_i} \times 100 \quad (6)$$

Non-identical composite membranes were tested in a flow state for to observe the creatinine adsorption capacity in a flow state according to the adherent plan. Firstly, the membrane was cut to the size of syringe filter cartridge (EMD Millipore, CA) with a diameter of 10 mm and then placed accordingly. Then 400 mmol h21 creatinine solution was added inside the cartridge and when the pressure is applied the solution exit through the membrane towards the outlet small pipe with a flowrate of 1 mL for minimum 3 hours. Three samples or each variety of membrane were examined and in the end the UV adsorption spectra was calculated for the solution collected from the outlet.

4.3.2.8. Platelet Adhesion

For the biocompatibility of the membrane's platelet adhesion is the most significant experiment. Whenever the blood in contact with the membrane it causes severe biological reactions. Clot formation activated as the blood comes in the air due to platelets. The main purpose of this research to lessen the amount of platelet on the membrane surface.

For the testing, 10 ml anti-coagulant whole blood was taken and centrifuge at the 1000 rpm for ten minutes. With the help of the tubularis the supernatant was separated, and plasma rich plasma (PRP) was attained. 1×1 cm^2 membrane samples was cut and washed with the phosphate buffer solution (PBS). Then the samples were immersed in the 24-well culture plate for the further experiment. With the help of the pipette 100µl PRP is inserted on the samples. Then the samples were incubated for two hours at the temperature of 37°C. After the incubation, the samples were washed thrice to remove the unstable platelets. 2.5wt% glutaraldehyde solution used to fasten the absorbed protein on the membrane surface for 24 hours. Further drying was done the graded ethanol of compositions 50%. 75%, 85%, 95% and 100%. SEM technique is used to detect the platelet attachment on the membrane surface [93].

4.3.2.9. Hemolysis Ratio

Due to biocompatibility, the serum starts degrading itself and color starts to change to transparent golden to reddish brown. This is due to erythrocytes content in the blood and as termed as hemolysis.

1×1 cm^2 membrane sample was washed thrice with the 0.9 wt% of the NaCl solution for ten minutes in sequence. At the temperature of 37°C in the water bath the samples were kept immersed in the NaCl solution. After that whole blood of 200µl was added on the membrane samples and kept at the same conditions for one hour. After one hour the blood with solution of NaCl in it was centrifuge for 10 minutes at 1500 rpm and top layer absorbance was measured using 545nm by UV spectrophotometer. 0.9wt% NaCl solution was taken as negative reference and pure water was taken as positive reference. Eq. 7 was used to quantify the ratio, in which HP and HN reflect the absorption value of the positive reference and negative reference, respectively. HS represent the absorption value of membrane samples [94].

$$\mathrm{HR} = \frac{\mathrm{HS} - \mathrm{HN}}{\mathrm{HP} - \mathrm{HN}} \tag{7}$$

4.3.2.10. Thrombus Formation

The formation of thrombus appears whenever the fistula attached to the vein or artery of the human body. It is function of the body tissues that if the blood vessels are damaged platelets helps in formation of thrombus and fibrin; coagulation of blood[95]. During hemodialysis, the process of hemostasis was done to control the vascular damage and became a seal on the vein or artery of the human body

Membrane samples of 1×1 cm^2 were immersed in the 1.5 ml whole blood and incubated in 5% of CO_2 for 2 hours at 37°C. PBS used after the incubation to wash the samples. The in vitro thrombus formation on the membrane surface was measured by the graded ethanol and critical point drying [96]. The Eq. 8 is used to calculate the degree of formation of thrombus in which DT is degree of thrombus, W_t and W_d represent the weight of blood coagulated membrane and weight of dry membrane.

$$DT = \frac{W_t - W_d}{W_d} \quad (8)$$

4.3.2.11. Plasma clotting time

When the blood exposed to environment, it starts to coagulate. 20 to 45 minutes is considered as normal blood clotting time but if the anticoagulant is added in the blood this time increases [97]. During hemodialysis when blood touch the surface of membrane starts to coagulate and effect the biocompatibility. For this behavior, test was done by adding anticoagulant agent in sample to increase the clotting time and enhance the biocompatibility of the membrane.

Anticoagulant 10ml blood was centrifuged at 3000rpm for 15 minutes. Supernatant contains Plasma poor plasma (PPP). 24 well-culture plate was taken with sample of $1\times1cm^2$ membrane area. 200µL drop of PPP inserted on the samples for further process. After that incubation of the sample done at the temperature of 37°C in the water bath for 10 minutes. 100 µL of the 0.025 mol/L $CaCl_2$ solution was added on the samples. As a thread emerged in the mixture, the time consumed was registered as plasma recalcification time [98].

Chapter No. 5

Results and Discussion

5.1. Membrane Characterization

5.1.1. Surface and Cross-sectional Morphology.

SEM is the analytical technique that explains the surface and cross-sectional morphology of the membrane. It explains the effect on the PSF membrane by adding CA and PEG. All the blended membranes SEM comparison images are shown in Fig. 5. 1 and 5. 2. The Surface morphology revealed that when the CA and PEG were added the surface contains more pores and clearer finger-like structure are formed in the cross-section [9]. With the addition of mordenite, the surface and cross-sectional morphology changed as the zeolite nanoparticles can be seen properly dispersed inside the cross-section but also on the surface of the membrane. Uniform pores were formed as due to the addition of PEG along with the CA. it can also be seen that as the amount of mordenite increased from 0.18 to 0.98 g the pores become smaller hence increase the protein rejection capacity.

The surface image of pure PSF membrane showed that the pores of the skin layer were too small to be represented by SEM, whilst the PEG/CA and PEG membranes showed pores and gap structure on the membrane surface. When PEG and CA were added in the membrane, the surface showed more pores with large size as shown in Fig. 5. 1 (b, c) in comparison to the pristine PSF but at the bottom the pores were of smaller or of same size of pristine PSF when inspected at the cross-sectional image Fig. 5. 2 (b, c). With the addition of only PEG, the membrane surface pores were of smaller and equal size up till the bottom of the membrane as shown in Fig. 5. 1 (d, e, f).

With the addition of PEG the fingers length increased in the cross-section of the membrane as shown in Fig 5. 2 (d, e, f). However, with the addition of PEG along with CA the width of the fingers also increased as shown in Fig. 5. 2. The integral membrane surface roughness became very rough, even though there were some small spherical structures on the membrane surface after the addition of additives. Low surface roughness can also prevent the adsorption of significant quantities of protein [36].

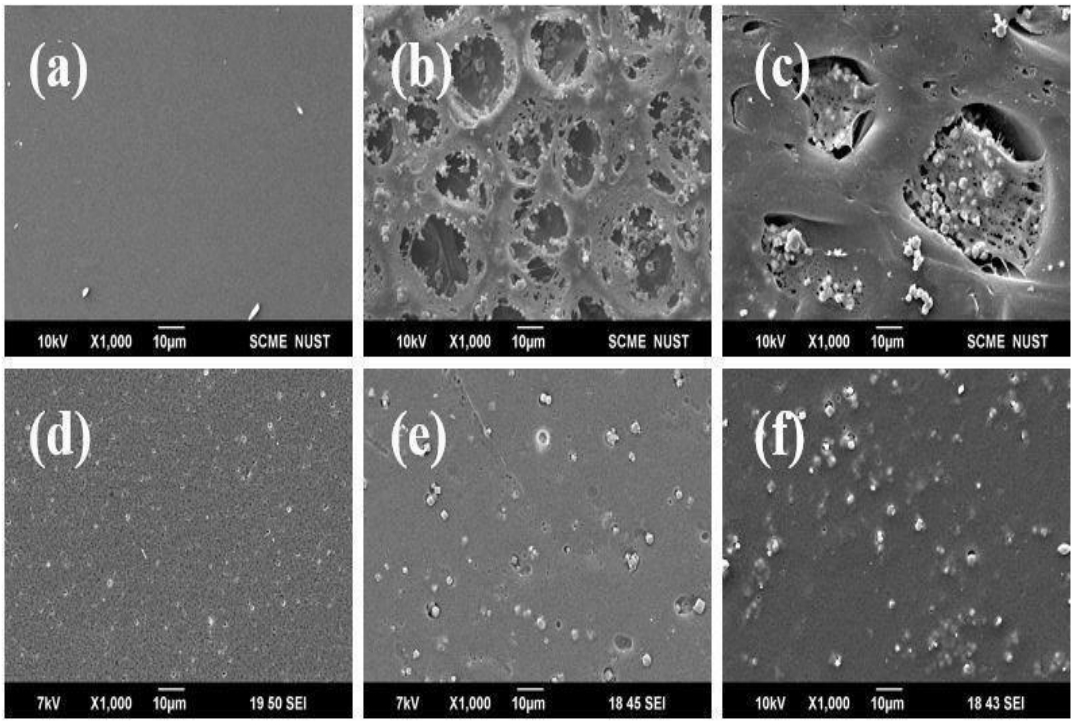


Figure 5. 1 The SEM image of surface morphology of the pristine and modified membranes at magnification of 1000 × (a) PSF, (b) PEG/CA-1, (c) PEG/CA-3, (d) PEG-1, (e) PEG-3, (f) PEG-5.

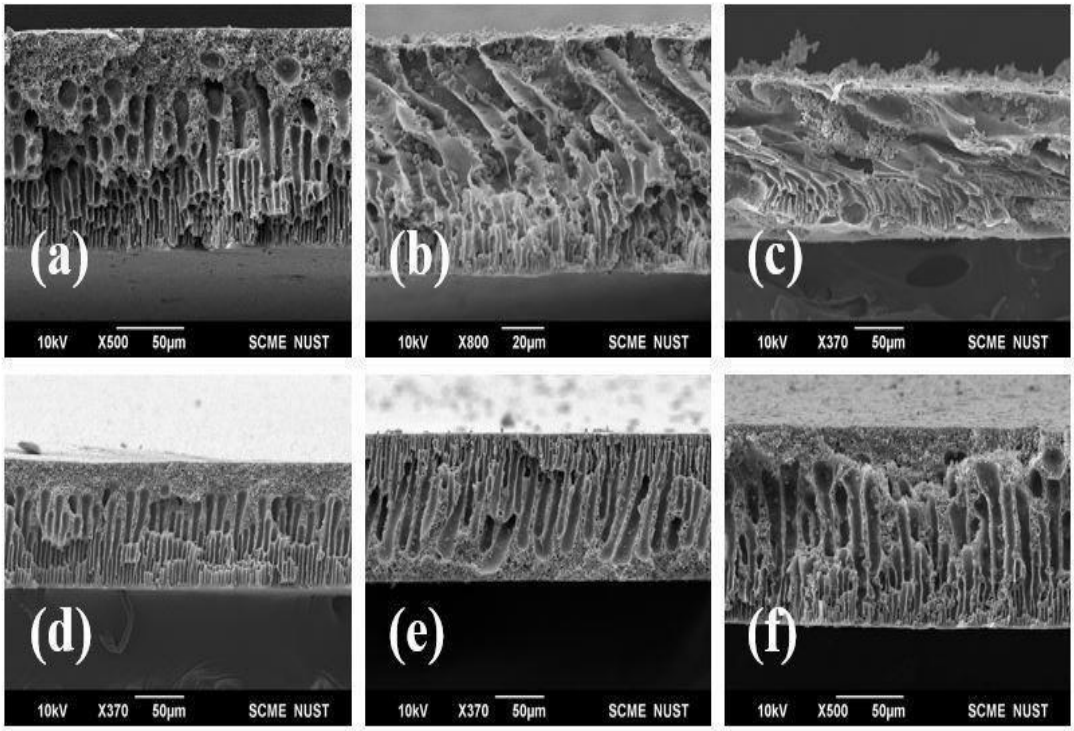


Figure 5. 2 The SEM image of cross-sectional morphology of pristine and modified membranes magnification is represented in 370× (a) PSF, (b) PEG/CA-1, (c) PEG/CA-3, (d) PEG-1, (e) PEG-3, (f) PEG-5.

5.1.2. Membrane Surface Roughness

The AFM explains the surface topography of the membrane surface as shown in Fig. 5. 3. All the samples were examined under AFM in tapping mode. 3D AFM images of the top surface of all the membranes with a scanning area of (10×10 µm) were taken. The dark regions showed depths and the light regions defined the heights on the surface topography [38]. The pristine PSF membrane surface was smooth enough but when the PEG, CA and mordenite zeolite were added the membrane became highly rough because of the pore and the macro void formation and as the amount of mordenite zeolite was increased the membrane roughness started decreasing because of the presences of mordenite zeolite because the void spaces between the pores started decreasing hence making the membrane less smooth.

Fig. 5. 3 (a) revealed the pristine PSF was highly smooth but when CA along with PEG were added as an additive, the membrane became highly rough Fig. 5. 3 (b, c). When only PEG acted as pore-gen the membrane showed less roughness in comparison to PEG/CA membranes as shown in Fig. 5. 3 (d, e, f). The lesser the roughness, the better be the biocompatibility results because of low adsorption of protein on its surface. It would also give good fluxes and most importantly low fouling rates [39]. From the Fig. 5. 3 the AFM images justify the statement that PEG membranes are smoother than PEG/CA membranes.

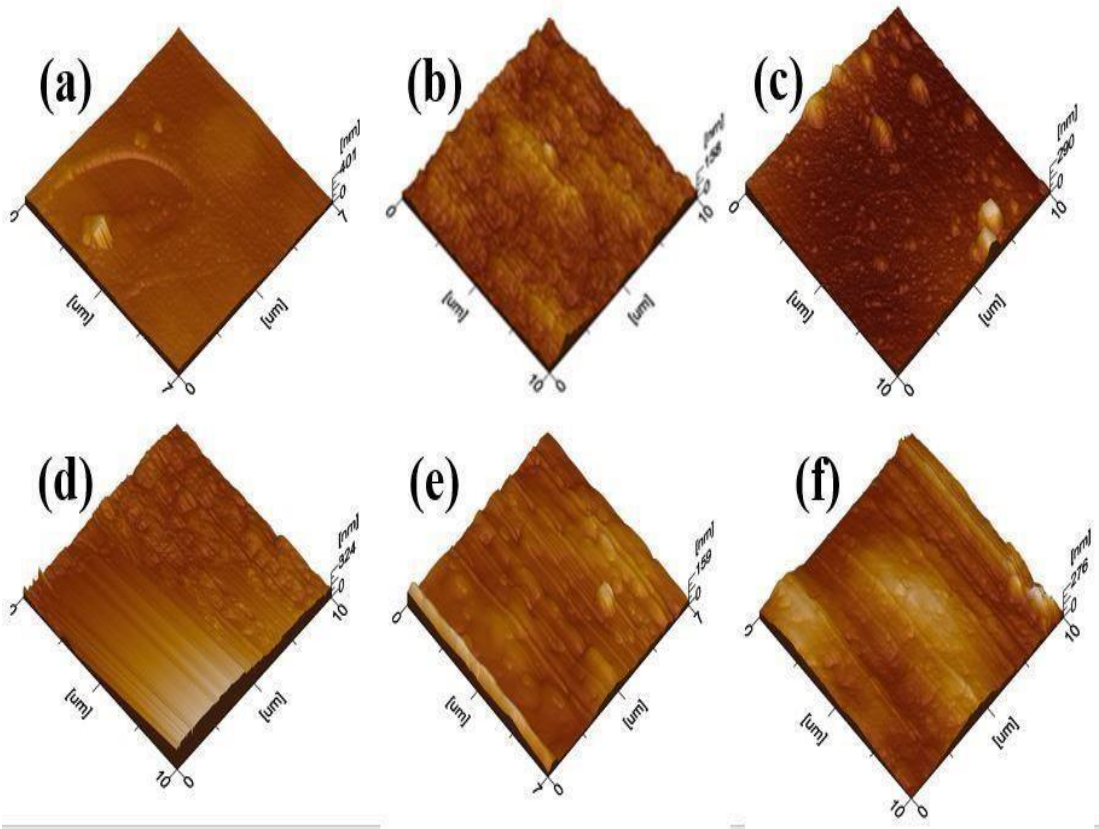


Figure 5. 3 The AFM imaging to determine the surface roughness of pristine PSF and modified membranes. (a) PSF, (b) PEG/CA-1, (c) PEG/CA-3, (d) PEG-1, (e) PEG-3, (f) PEG-5.

5.1.3. Chemical composition of Pristine PSF and modified membranes

The surface chemical composition of modified membranes was determined by FT-IR spectroscopy and are shown in Fig. 5. 4. The PSF characteristic peaks were around 1149 and 1168 cm^{-1} (SO2 symmetrical stretching), 1244 cm^{-1} (aryl-O-aryl C–O stretching), 1582 cm^{-1} (SO2 asymmetric stretching), 1677 cm^{-1} (asymmetric–CH3), and 2151 cm^{-1} (C=C) [37]. In cases of PEG-1, PEG-3, PEG-5 membranes, the peaks at 1244 cm^{-1} were due to the C-O-C bond of PEG additive. At near 3023 cm^{-1} the slight increase in the peak was due to the C-H bond because of PEG. Meanwhile, when PEG along with CA act as a pore-generator for PEG/CA-1, PEG/CA-3, PEG/CA-5 membranes at 1500 cm^{-1} the increase in the peak was due to the C-O bond this is because of the presence of CA. However, the peak at 1244 cm^{-1} was due to the C-O-C bond of PEG additive.

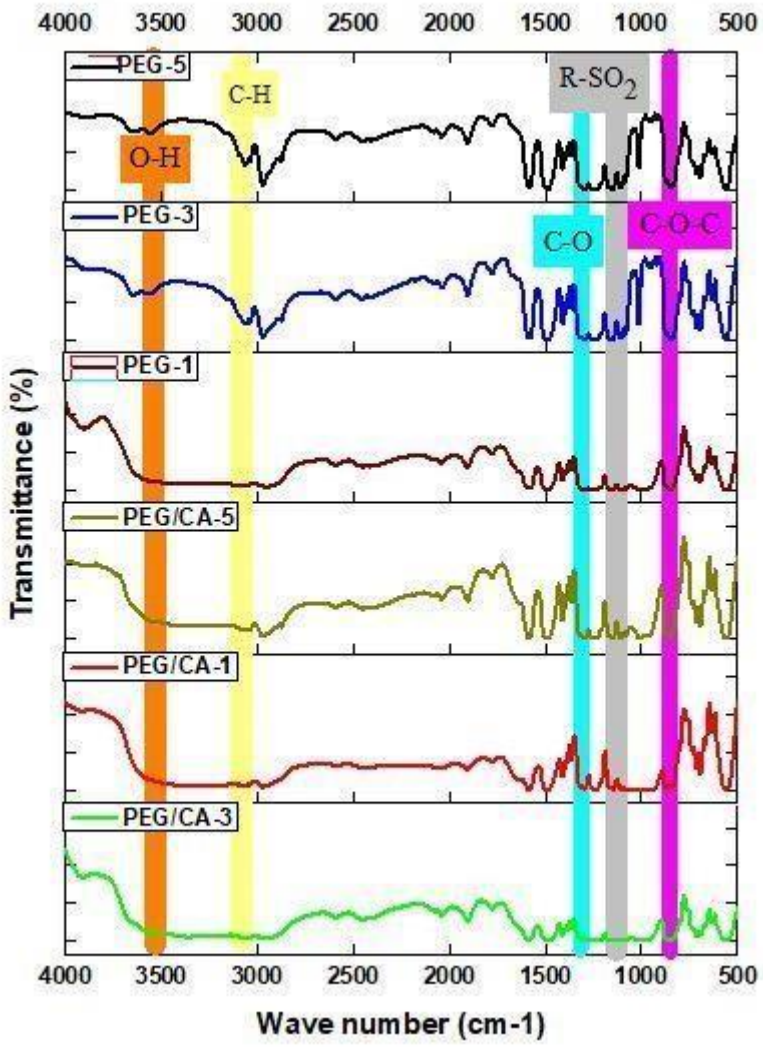


Figure 5. 4 FT-IR spectrum of modified m.comembranes when PEG and CA, when PEG alone act as an additive**.**

5.2. Performance Test of pure PSF and modified membranes

5.2.1. Hydrophilic and Hydrophobic nature

Contact angle less than 90˚ is considered as hydrophilic and more than 90˚ is considered as hydrophobic in nature [40]. The increment in the contact angle is due to the higher densities and compaction of the synthesized membranes. As shown in Fig. 5. 5 that pristine PSF is highly hydrophobic in nature because of the presence of dense surface giving the angle of 87˚. However, when PEG, CA and mordenite zeolite added in the solution, the minimum angle reached to 48.1˚ this is just because of the formation of the pore on the surface of the membrane but also sub pores were also increased in the finger-like structure of the membrane. However, when only PEG acted as a poregen, the minimum angle obtained was 57.6˚. The Fig. 5. 5 justifies that the modified

membranes are hydrophilic in nature that is the main requirement for the optimum hemodialysis process. The PEG/CA membranes are more hydrophilic in nature than pristine PSF and PEG membranes.

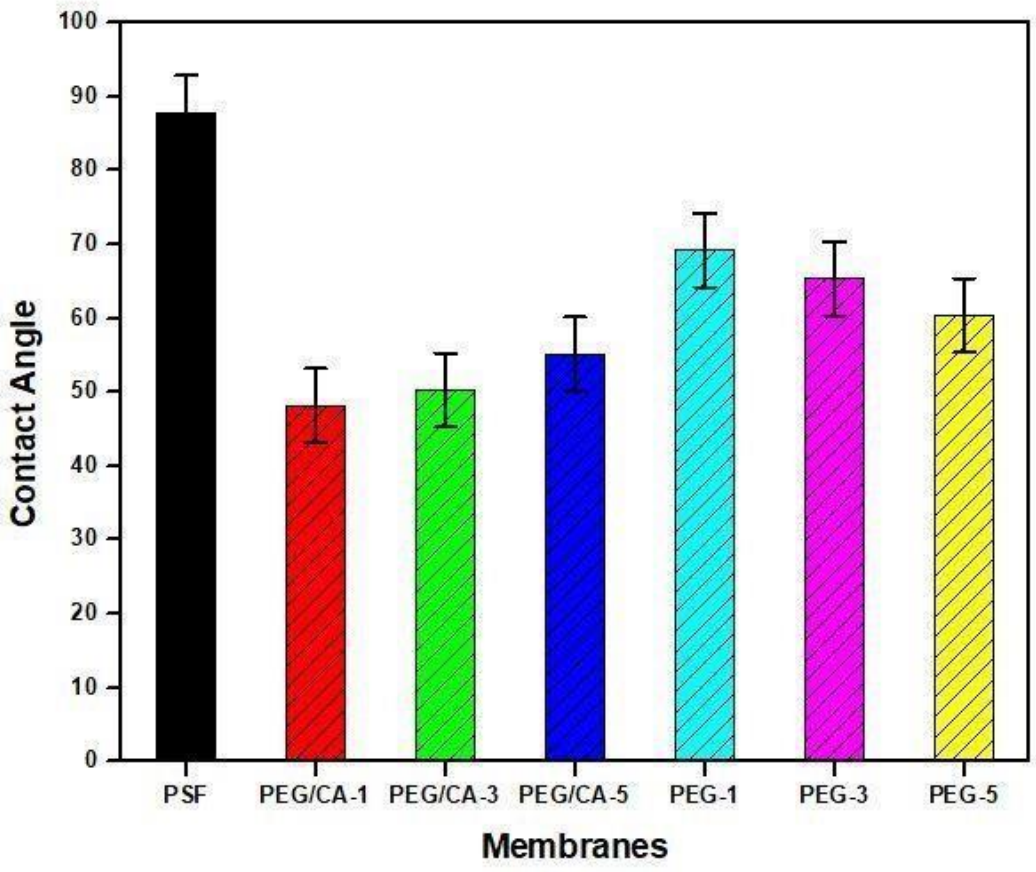


Figure 5. 5 Hydrophilicity and hydrophobicity of pristine PSF and modified membranes with the help of water contact angle.

5.2.2. Porosity of the modified membranes shows increased hydrophilicity

When the porosity and the pore size is changed it cause a major effect on the permeability of water and uremic toxin clearance and also on the protein adsorption and rejection clearance. Hence, the permeability and flux of the membranes are highly dependent on the porosity of the membrane [103]..

When PEG/CA and mordenite zeolite were added in the PSF solution, the flux increased abruptly this was due to the increase in pores on the surface of the membrane. Hence, the porosity was also very high as compared to the pristine PSF. The Fig. 5. 6 showed that as with the addition of additives the porosity was increased up to 90 to

93%. However, when the concentration of zeolite increased it blocked and captured the void spaces between the pores resulting in decreasing of the porosity. However, when only PEG as an additive was added the porosity trend increased as with the increase in the concentration of mordenite zeolite as shown in Fig. 5. 6. This trend showed that as the concentration of mordenite zeolite increased, the surface area of the membrane morphology also increased hence resulting in increased membrane porosity.

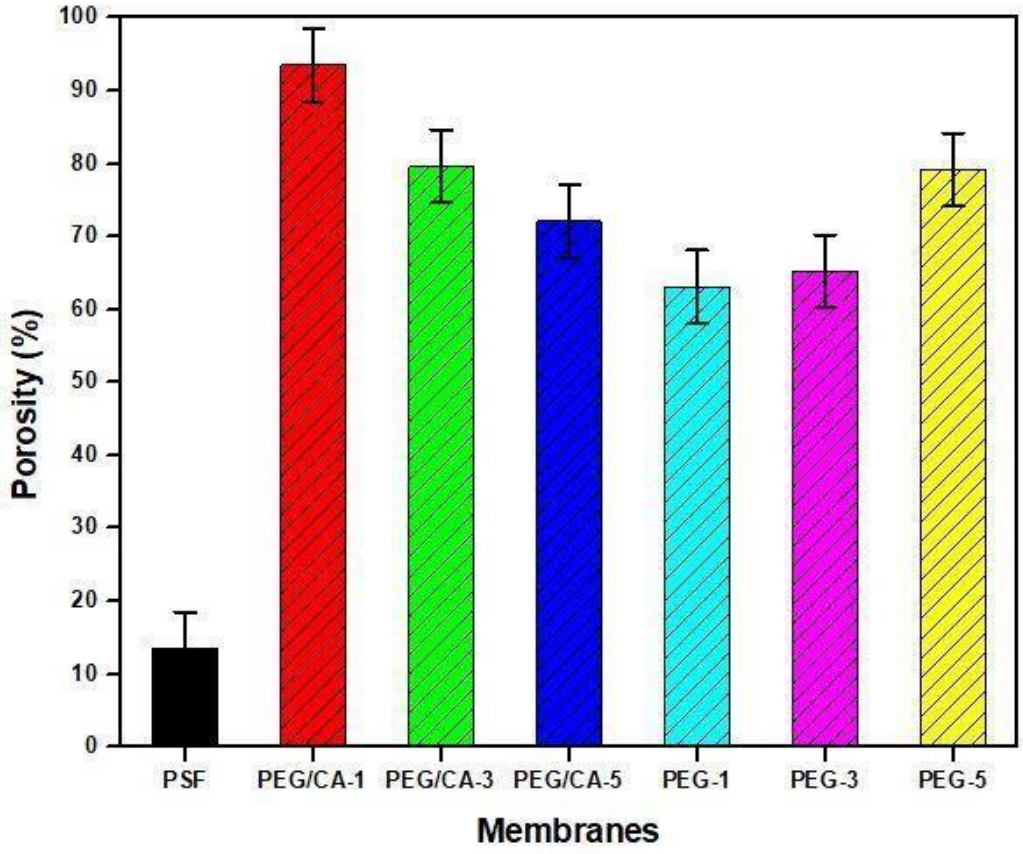


Figure 5. 6 The porosity and of the pristine PSF and modified porous membranes after addition of additives and mordenite zeolite.

5.2.3. Swelling (%) showed modified membranes are hydrophilic in nature

This test basically determines the hydrophilicity and hydrophobicity of the membrane. High water absorption means that the membrane is hydrophilic [79]. Fig. 5. 7 elaborates the trend in the results.

Fig. 5. 7 elaborates the trend in the results. The pristine PSF membrane has extremely less value for the water absorption as the surface of the membrane was very dense containing very less and no pores. But when the PEG along with CA and mordenite

zeolite as an additive were added the water content value increased to a very high extent as shown in Fig. 5. 7. The maximum percentage was obtained for PEG/CA-1 membrane that was 1189% ± 0.03% this was just because of an increase in the number and size of the pores on the surface but also in the cross-section of the membrane. Hence, PEG/CA-1 membrane is highly hydrophilic that can absorb maximum water. On the other hand, when only PEG act as a pore-gen the trend started increasing with the increase in the concentration of the mordenite zeolite this happened because zeolite provides more surface area when incorporated in the membrane. Here PEG-5 membrane was highly hydrophilic in nature giving the percentage of 666% ± 0.03% as shown in Fig. 5. 7.

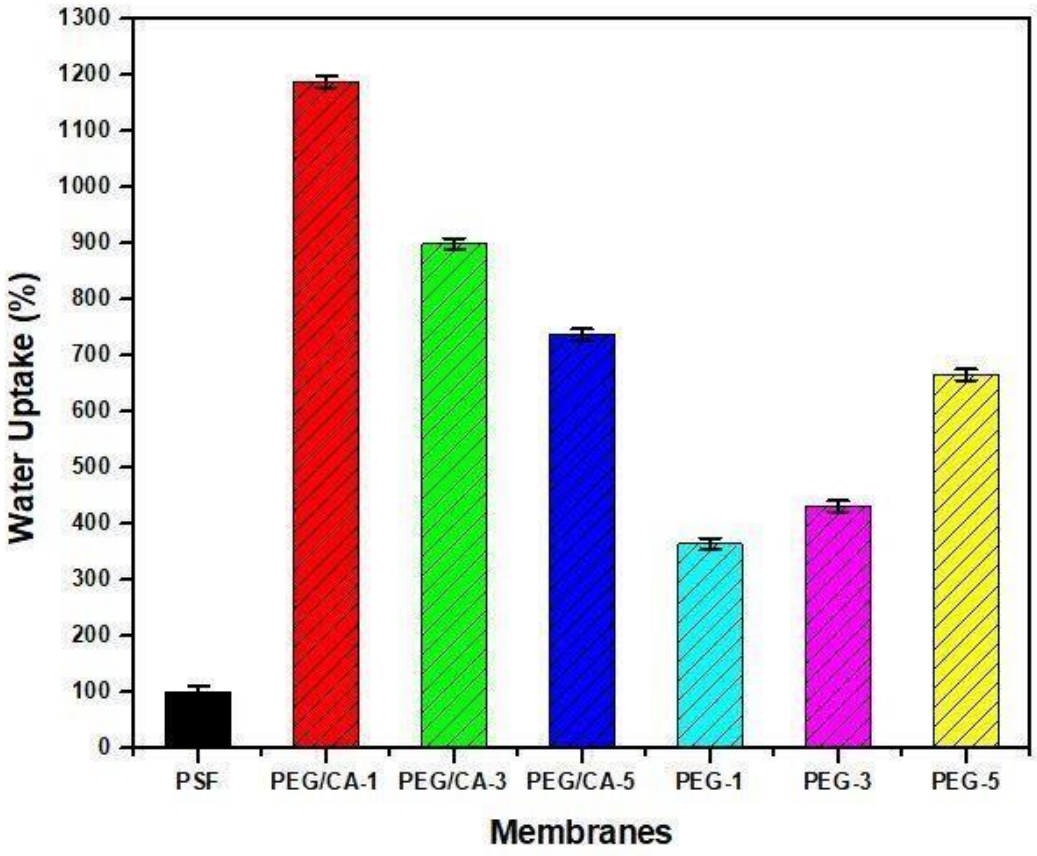


Figure 5. 7 The swelling (%) of the pristine PSF and modified porous membranes after addition of additives and mordenite zeolite.

5.2.4. Mechanical Strength of pristine PSF and modified membranes

The addition of hydrophilic elements like PEG and CA can also affect the mechanical properties of the membranes that can also be compared by its morphology. Fig. 5. 8

represents that pristine PSF membrane showed highest tensile stress of 30.76 MPa. Because the pristine PSF membrane contains dense surface, the high tensile stress and strain curve justify that it was very dense and contained less pores on the surface as well as short sized fingers in the cross-section of the membrane were present. However, when the additives like PEG along with CA were added in the membrane the tensile stress decreased abruptly to 9.98 MPa of PEG/CA-3 membrane, due to the less density and polymer packing. However, with the addition of PEG the tensile stress was 25.8 MPa for PEG-1 membrane which was still lesser than pristine PSF. Further, when mordenite zeolite concentration increased it increased the stress/strain curve than the previous compositions showing that the void spaces between the pores now start blocking hence making the membrane denser again. Similarly, because of the addition of the pore-generators the elongation rate also increased as cross-sectional morphology also influenced on mechanical properties justifying that membrane contained more pores and sub pores were also produced in the fingers in the crosssection of the membrane as shown in stress strain curve in Fig. 5. 8.

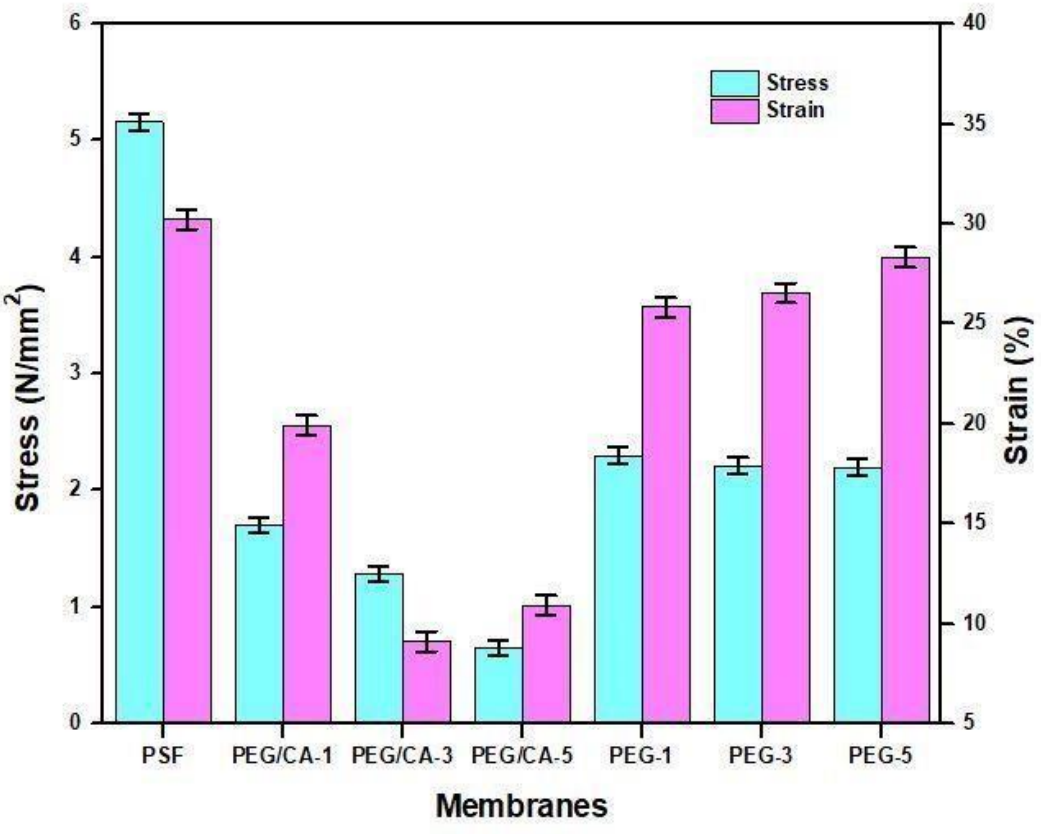


Figure 5. 8 Stress-strain curve of pristine PSF and modified membranes.

5.2.5. Modified membranes give higher water Flux & permeability compared to pristine PSF membrane

To determine the efficiency of the modified and pure PSF membrane Pure water permeability test was performed. The Distilled water as a solvent is used to determine the behavior of the membranes. The flux is then calculated and then the graph was plotted. From the graph with comparison to the contact angle & porosity that when the additives were added because of the increase in the pore sizes and sub pores the permeability & flux of the modified membrane increased [42].

In the permeability test, the dead-end filtration cell was utilized. The flux and permeance were measured after every 10 minutes, the final measurements were obtained after 80 minutes where all the membranes gave constant fluxes. The pure water flux that was obtained for pristine PSF was very low 18.91± 0.010 L/m^2h which was extremely less than the modified membrane. This behaviour occurs because of the less bonding interaction and also due to the dense surface morphology (less and small surface pores) of the membrane.

The PEG/CA-1 membrane showed maximum flux and permeability because of its less contact angle and high porosity. As shown in Fig. 5. 9 that as the concentration of the mordenite zeolite increased it decreased the flux because the void spaces between the pores start blocking the membrane and making the membrane denser. The
Hemodialysis requires the moderate water flux so that less water will be lost from the blood during the dialysis process so PEG/CA-3 membrane showed the moderate flux and permeability [9]. Similarly, when only PEG as a porogen was added, the trend increased gradually as shown in Fig. 5. 9 so PEG-3 can be considered as the best membrane.

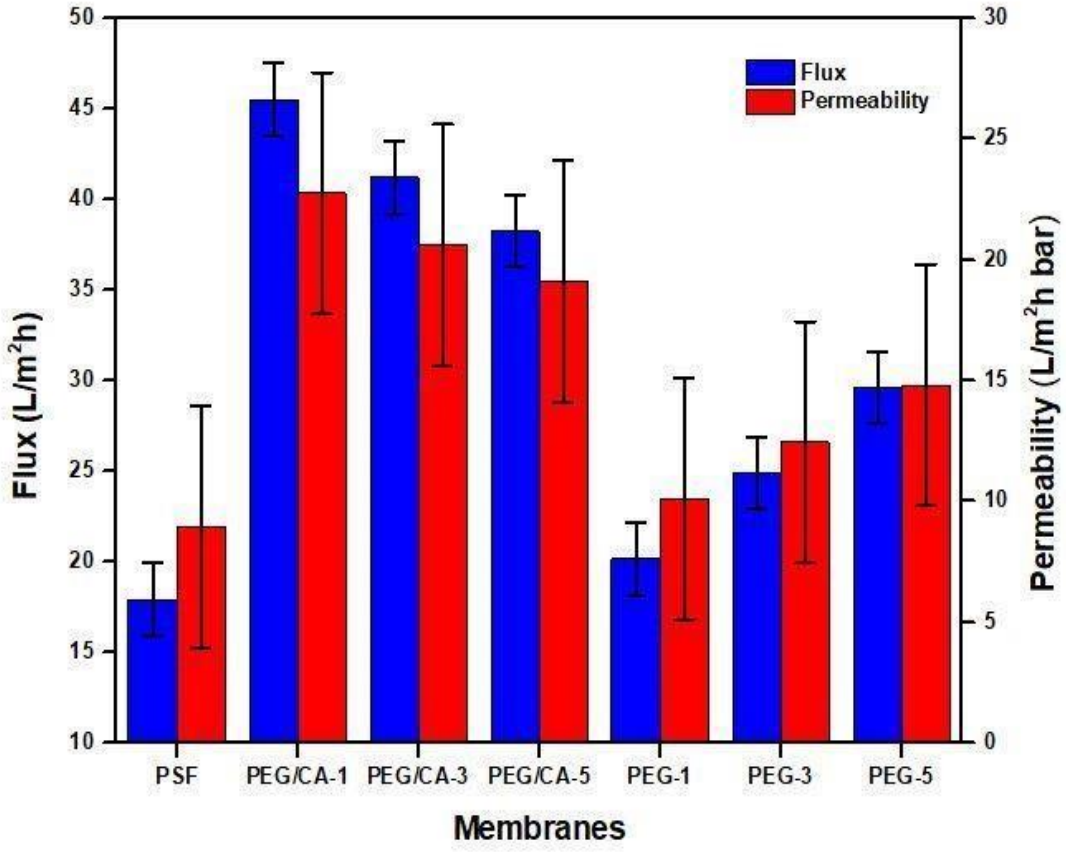


Figure 5. 9 Water flux and permeability after 80 minutes (when constant water was obtained in the permeate in the dead-end filtration cell) in comparison with the contact angle.

5.2.6. PEG membranes give higher BSA rejection % than PEG/CA membranes

During the hemodialysis process the albumin is lost which can be the biggest drawback for the patient health. The albumin loss can be controlled by the membrane morphology & composition for to justify this BSA with molecular weight of 67 kDa was used to determine the solute rejection %. Some membranes can have poor water flux but BSA retention should be higher than 75% for dialysis treatment [79].

The albumin loss can be controlled by the membrane morphology and composition to justify this BSA with a molecular weight of 67 kDa was used to determine the solute rejection % [9]. The Fig. 5. 10 showed that pristine PSF cannot reject BSA because of the dense surface of the membrane. Meanwhile, the maximum rejection of the BSA was obtained in PEG/CA-1 membrane that was 83.21 % because of the porous surface and also the sub pores in the fingers of the membrane. However, when only PEG as a porogen was added, the BSA rejection increased to 93.5% in PEG-5 membrane as

shown in Fig. 5. 10. This difference in the membranes for BSA rejection justifies that optimization is required in the pore size of the PEG/CA membranes to increase the BSA rejections to a maximum percentage. As all PSF family polymers needs very optimized handling to make optimized pore size [43].

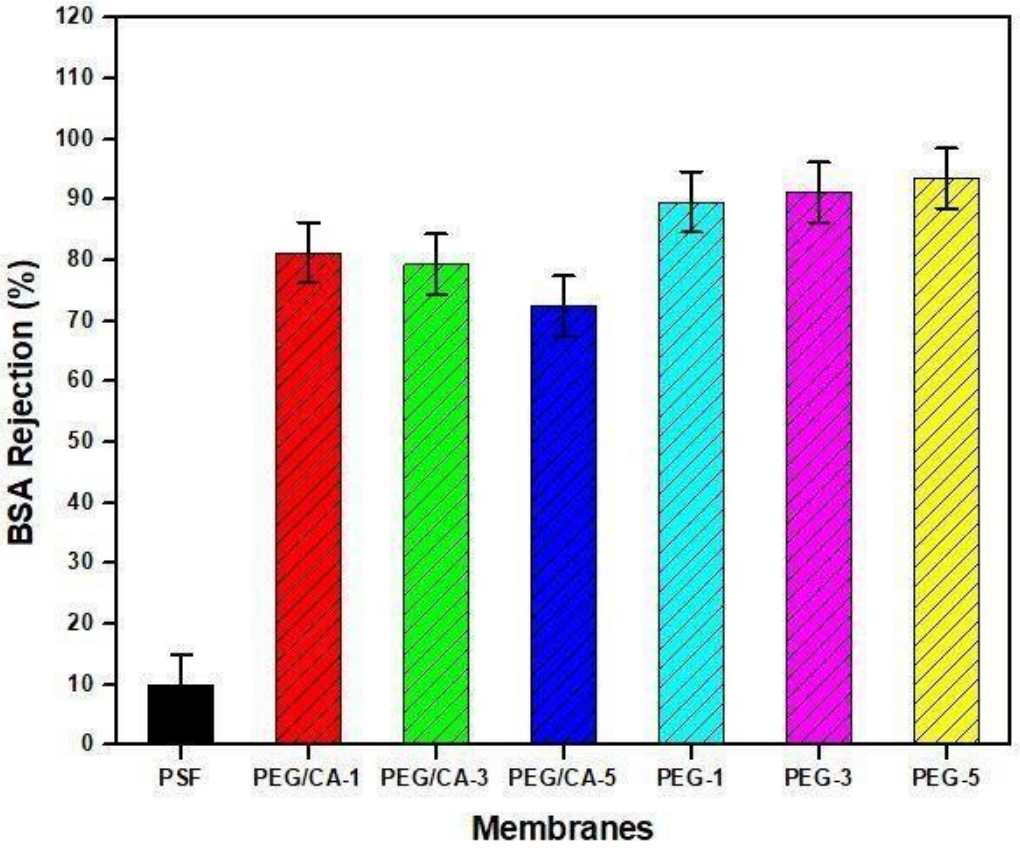


Figure 5. 10 BSA clearance of the modified membranes after 4 hours simulating dead-end filtration cell.

5.2.7. PEG membranes give high Urea clearance % than PEG/CA membranes.

As the uremic toxins also contain urea which is important to remove from the blood during the dialysis process. Minimum 60 % of the urea clearance must be obtained after the blood passes through the hemodialysis membrane [44]. As in the literature, when using CA as a base polymer the maximum clearance for the urea was 80.39 % [45]. Fig. 5. 11 shows that PEG/CA-1 membrane gave clearance of 72±0.001%, which was more than the pristine PSF membrane with the increase in water flux. The urea clearance then decreased after that due to denser membranes because of the presence of high concentrations of mordenite zeolite and blockage of the pores with urea

molecules coming from different directions. From Fig. 5. 11 when only PEG act as an additive, the urea clearance reached to 93±0.01%. As with the addition of only PEG as a pore-gen the pores were uniformly scattered throughout the membrane, hence it gives maximum urea clearance this statement can also be justified by the SEM morphology Fig. 5. 1 (d, e, f). But here with the increase in the concentration of mordenite zeolite the urea clearance also increases because the mordenite zeolite provides more surface area.

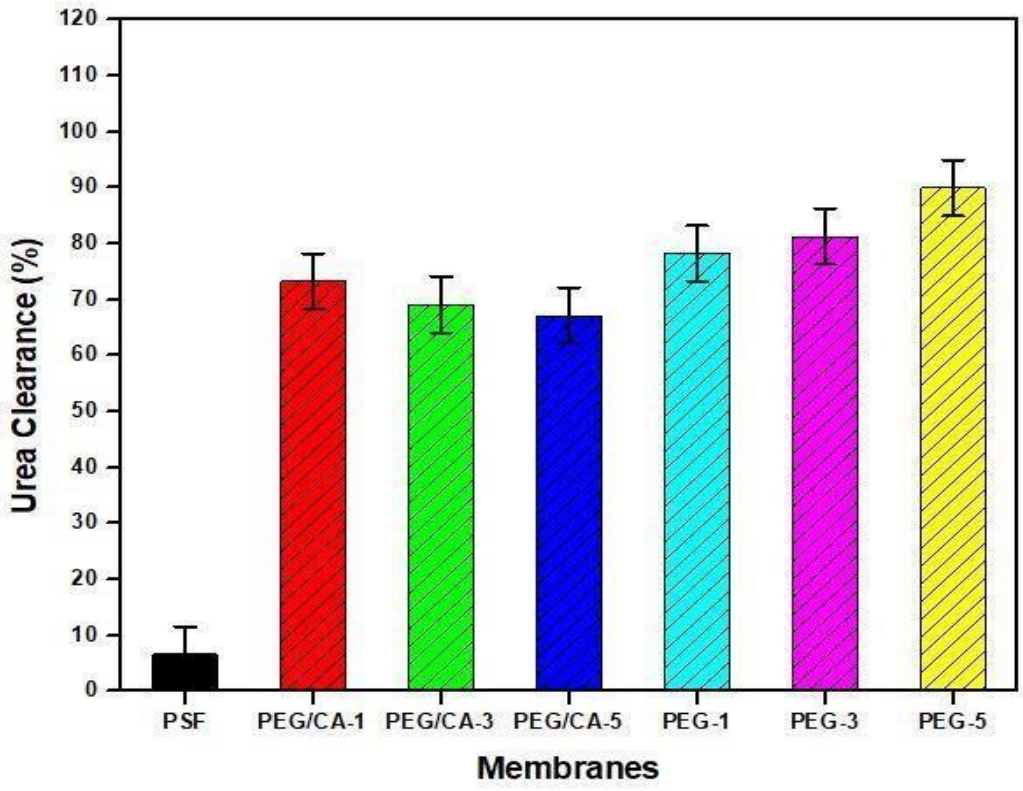


Figure 5. 11 Urea clearance of the pure and modified membranes after 4 hours simulating dead-end filtration cell.

5.3. Biocompatibility evaluation of pure PSF and modified membranes

5.3.1. Creatinine Adsorption capacity by composite membranes

Creatinine is a uremic toxin formed in the muscles by the degradation of creatine phosphate. In relation to the degree of creatinine absorption, the size and shape of zeolite particles can theoretically affect the efficiency of the membranes. From the literature the spherical-shaped particles work better inside the membranes than rodshaped zeolite [46]. The effect of the concentration of mordenite zeolite inside the membrane on the creatinine uptake level was observed. As the shape and size of the

nanoparticle integrated inside the membrane had a great effect on the creatinine adsorption as in literature while using PAN as a polymer along with the rod-shaped zeolite particle the creatinine adsorption was 7000 ug/g [47]. That is why the mordenite zeolite was selected as it has a spherical shape and the size of the particle is 48nm in diameter that will provide more surface area for the adsorption of creatinine. As the powdered zeolite can adsorb more creatinine rather when it was incorporated inside the membrane this is just because of 1/3 surface of the nanoparticle was blocked when particles were incorporated on the surface but also inside the fingers of the membranes [47]. From Fig. 5. 12, the trend explains that as the concentration of the mordenite zeolite increases in the composition of the membranes the adsorption capacity of the creatinine also increased hence making the membrane more suitable for the removal of protein-bound toxins. Hence the PEG/CA-5 membrane can adsorb maximum creatinine compared to the PEG-5 membrane. This is because the pore size is small and are less in number so when the nano-particles were incorporated the reactive sites are masked in the membrane.

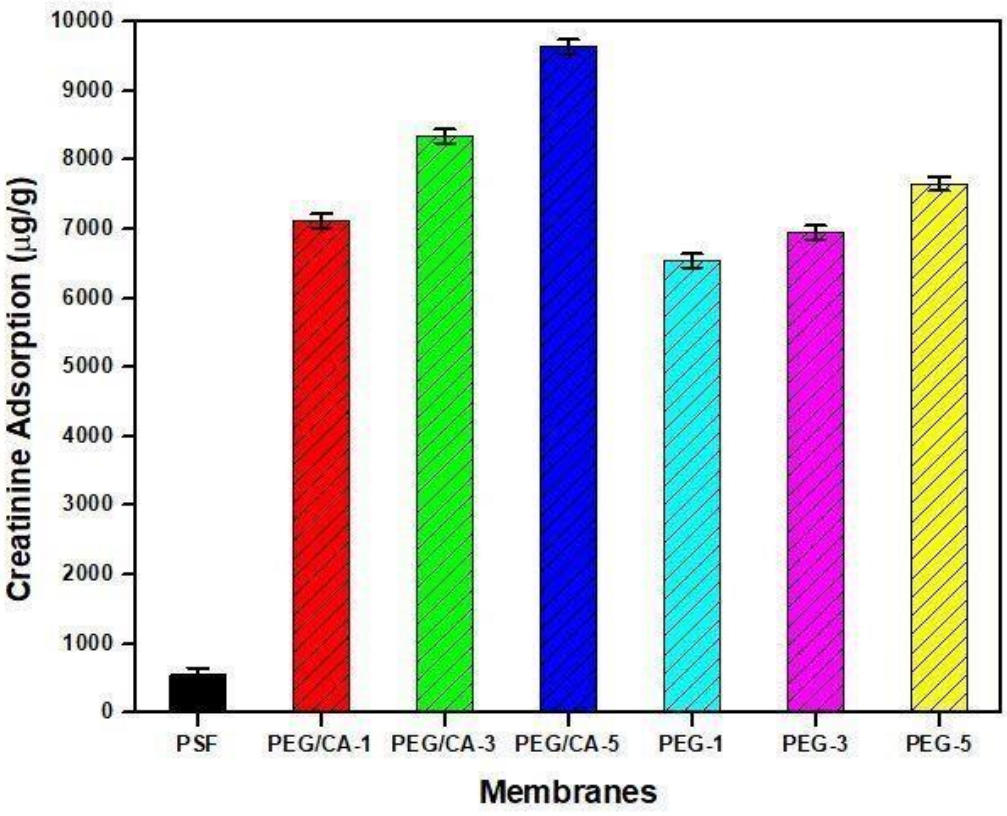


Figure 5. 12 Creatinine adsorption capacity in membranes (by membrane mass and by zeolite mass).

5.3.2. Platelet Adhesion via protein adsorption

The key objectives of this research are to reduce the number of platelets on the surface of the membrane. SEM photographs have been used to observe the platelet adhesion behavior on the membrane surface. From the literature large number of platelets aggregated on the hydrophobic membrane surfaces such as pristine PSF or PLA membranes [44] As shown in Fig. 5. 13, the overall surface of the pristine PSF membrane had evident platelet adsorption. In addition, all reticulate pseudopodia structures displayed adhesion of platelets, suggesting activation of platelets. But the involvement of ether bond in PEG by hydrogen bonding can be closely coupled with water molecules that form a hydration layer (physical and energetic barrier) near the surface with the addition of PEG/CA and mordenite zeolite to keep the bio components from adsorbing the polymer surface [45]. Therefore, the PEG/CA-1 layer, expressed on the membrane surface by PEG chains, enables best anti-protein surface that effectively inhibits platelet accumulation. Since PEG and PSF are covalently bonded, we can assume that this strong performance of anti-adsorption can be sustained for a long time rather than steadily decreasing over time. Although the platelet cannot adequately aggregate on membrane surface due to the larger pore sizes, hence less platelet adhesion can be observed in Fig. 5. 13 (b) as compare to Fig. 5. 13 (c, d).

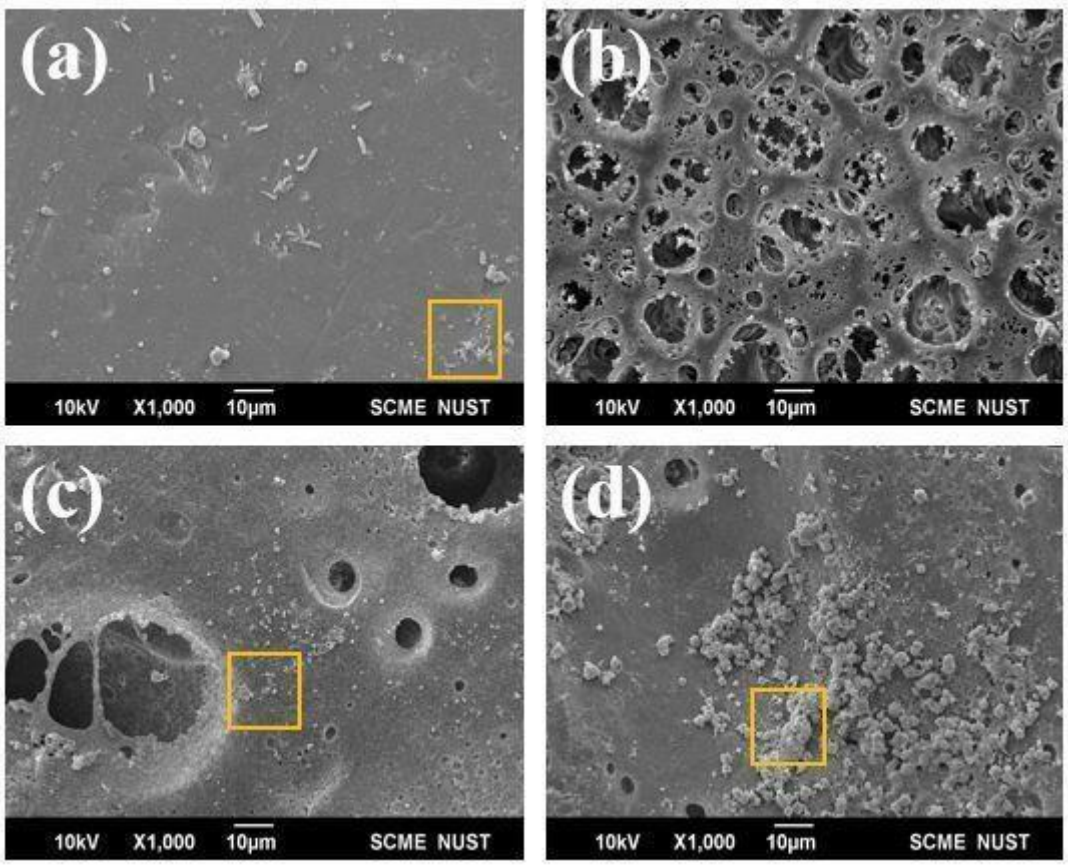


Figure 5. 13 SEM images of surface morphology showed the amount of platelet adhesion on pristine and modified membranes. (a) PSF, (b) PEG/CA-1, (c) PEG-1, (d) PEG-3

5.3.3. Thrombus formation and hydrophilicity.

Whenever the fistula is attached to the human body in the vein or artery, it causes thrombus formation as when the accumulation of the platelets on the membrane exterior occurs the thrombus formation also occurred as because of this phenomenon the blood when it interacts with the outside materials, blood protein adsorptions take place initially. In formulation of the blood contacting membrane the main obstacle is the self-induced thrombosis[109]. So, the thrombus formation is being examined by using the whole blood.

As the pristine PSF membrane was highly hydrophobic, hence it contained highest thrombus formation value which was 9% ± 0.05% as the platelets were highly aggregated on the surface of the membrane. However, with the addition of additives, the thrombus formation decreases. When PEG along with CA act as a pore-gen the minimum value was obtained for PEG/CA-1 membrane which was 5% ± 0.05%. When

only PEG act as a pore-gen the minimum value of thrombus formation was 5.06% ± 0.05% for PEG-1 membrane. However, from Fig. 5. 14 the trend explains that with the increase in the concentration of the mordenite zeolite the thrombus formation also increased slightly. So, the more accumulation of the platelets on the surface of the membrane occurs the more thrombus formation value is obtained.

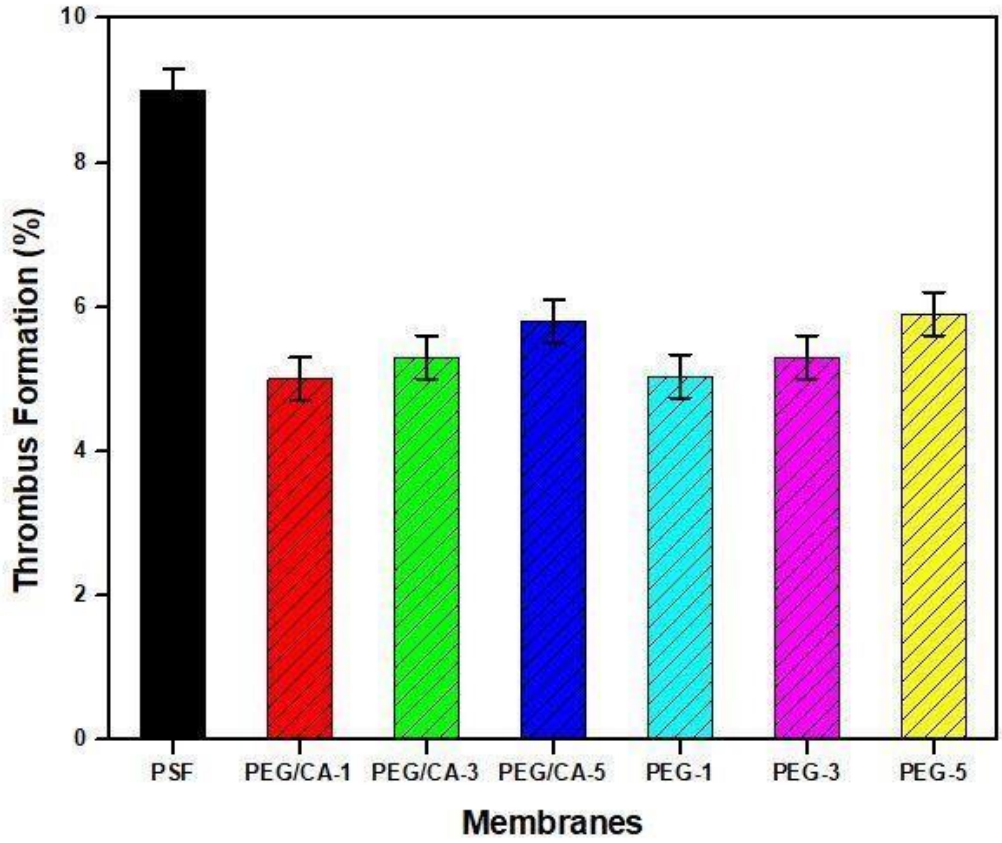


Figure 5. 14 Thrombus formation of pristine PSF and modified membranes

5.3.4. Hemocompatibility of pure PSF and modified membrane

Due to biocompatibility, the serum started degrading itself and color starts to change to transparent golden to reddish-brown. This is due to erythrocytes content in the blood and as termed as hemolysis. Blood continues circulating through the dialysis membranes during hemodialysis. In this continuous cycle, because of the association of erythrocytes with the membranes, erythrocytes can burst and release haemoglobin (known as hemolysis). To assess the degree of damage to the erythrocytes caused by the dialysis membranes, HR is then used. The ASTMF-756-08 finds that HR below 5 percent is considered to be harmless. Certain polymers give certain hemolysis ratios

like when PSF/PSF-*g*-TPG is used the HR was 0.53% [11]. In comparison to all of the polymers the pristine PSF membrane gave 0.55% ± 0.03% however with the addition of PEG along with CA the value decreased to 0.37% ± 0.05% for PEG/CA-1 membrane which was extremely lesser than 5% hence proving that the membranes have excellent hydrophilicity, electronegativity and anti hemolytic activity justified by the contact angle. Similarly, from the Fig. 5. 15, when only PEG act as a pore generator the values were 0.46%± 0.03% for PEG-1 membrane which was still lesser than 5% but also lesser than the literature. The slight increase in the trend can be seen due to the decreased porosity [43].

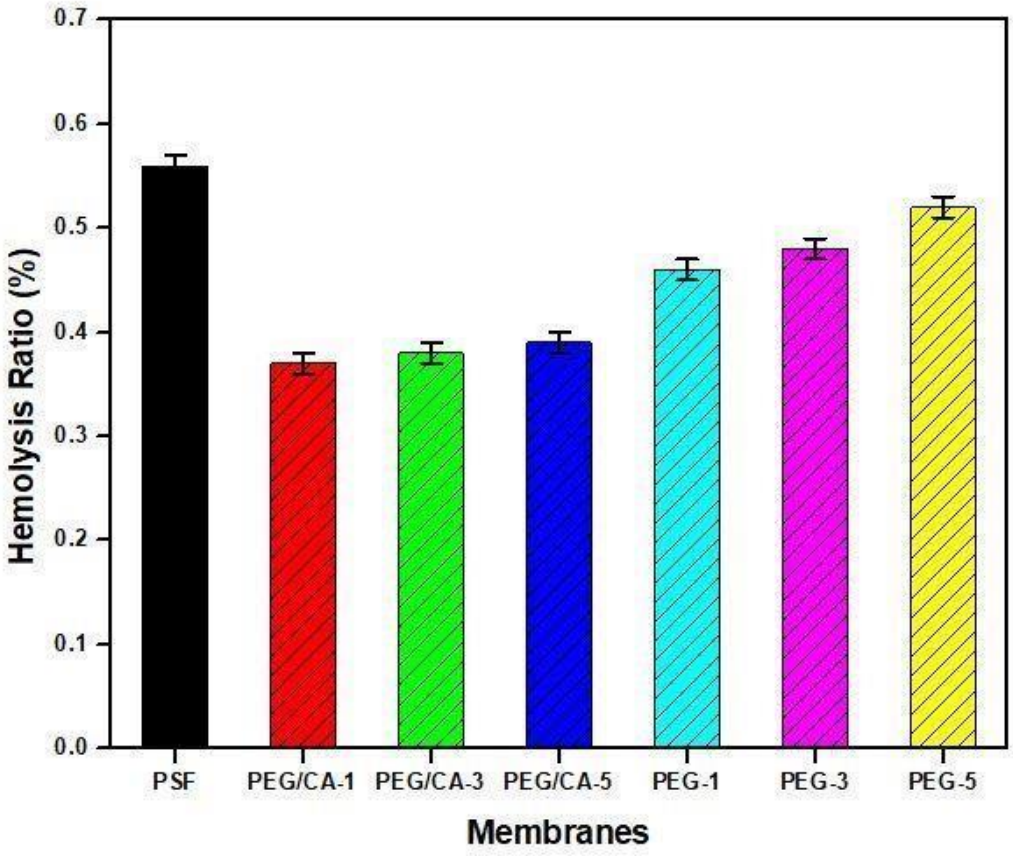


Figure 5. 15 Hemolysis ratio of pristine PSF and modified membranes

5.3.5. Improved Clotting time with the addition of additives

When the blood comes in contact with external surfaces, it clots in very less time. For the biocompatibility relations of the membrane with the blood, it should require more time to clot as interact with the outer surface. The clotting time and the presence and absence of clotting factor can be determined by PRT [108]. The clotting factor VIII is

triggered with the assistance of stepped-activity and the thrombin is produced from the coagulation progenitor. After that, thrombin facilitates the transfer of fibrinogen, which is the source of thrombus production, from plasma to fibrous protein. Fibrous protein cross-links with one another and becomes insoluble and stable due to the addition of calcium ions and the activation of factors VIII. The clotting time and the presence and absence of clotting factor can be determined by PRT [49]. The PRT of the pristine PSF membrane was 321 ± 5 s as shown in Fig. 5. 16. As the thrombus formation is greatly reliant on the hydrophilicity of the membrane. So with the addition of the additive (PEG) the PRT increased to 392± 5 and when (CA along with PEG) was added the PRT increased to 490 ± 5 s which proved that the activation of fibrinogen on PEG-1 and PEG/CA-1 membranes was repressed, due to the improvement of membrane hydrophilicity [50]. But due to the increase in the concentration of the mordenite zeolite the PRT starts decreasing as the membrane surface starts becoming hydrophobic in nature Fig. 5. 16 justifies the statement.

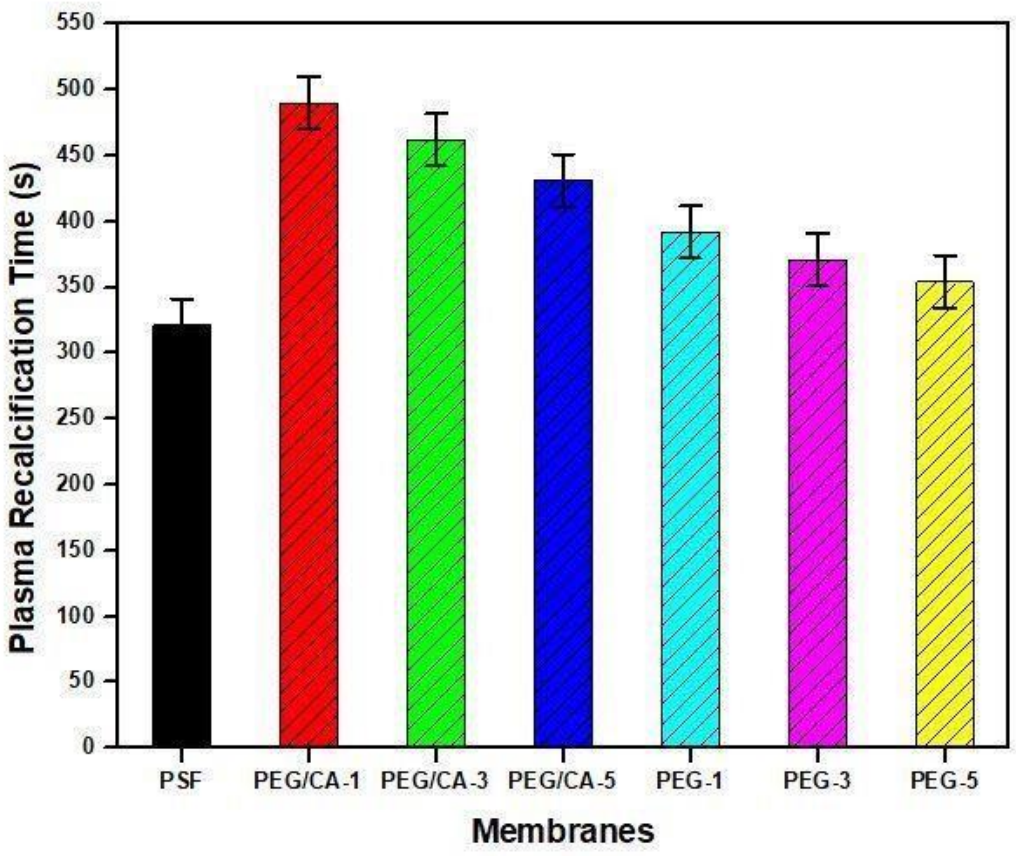


Figure 5. 16 PRT of the pristine PSF and modified membranes.

The table 5.1 elaborates clearly that when only PEG as an additive was used it gives good performance or solute rejection % results. However, the biocompatibility results were less in comparison to those membranes when PEG/CA were used as an additive. While the performance test and solute rejection % was not the appreciable.

Table 5. 1 Comparison of results of Pure PSF and PSF (with additives)

Membrane materials	BSA rejection (%)	Urea toxins Clearance (%)	Creatinine Adsorption (µg/g)	Thrombus formation (%)	Hemolysis ratio (%)	Recalcification Time (s)
PSF	N/A	N/A	N/A	9.00	0.55	311
PEG/CA	83	74	9643 ug/g	4.9	0.37	490
PEG	93	89	7654 ug/g	5.04	0.46	392

Conclusion and Future outlook

The main achievement of this thesis was to make a hemodialysis membrane containing optimized pore radius, pore distribution, density, and pore size that can speedily remove both water-soluble and protein-bond toxin (creatinine). Although for the less inflammatory and complement activation on the membrane surface the membrane morphology is also biocompatible.

This work started with the fabrication of hemo-compatible and biocompatible PSFbased hemodialysis membranes using hydrophilic compounds like PEG and CA. The addition of the additive PEG/CA improved membrane hydrophilicity and resulted in better water flux efficiency, but the BSA rejection percentage and Urea clearance were drastically reduced. In comparison to a pure PSF membrane, however, there was less platelet adhesion, a longer PRT, and a lower HR. Meanwhile when only PEG as an additive is used it provides better BSA rejection % and urea clearance but with high platelet adhesion, lower Plasma recalcification time and high value of Hemolysis ratio was obtained. When PEG/CA were added 9643 ug/g of creatinine were adsorbed along with PRT of 490 s but solute rejection was only 83%. When only PEG was added the creatinine, adsorption was 7654 ug/g with less PRT 392 s but the maximum solute rejection % were 93%. The spherical and uniform sized zeolite can adsorb more middle toxins such as creatinine when its particle size is very small 48 nm hence providing the maximum surface area while it is incorporated in the membrane. The membranes show excellent stability in water.

Future Outlook

Certain modification in the membrane composition and fabrications are required so that maximum BSA and urea can be cleared along with the highest biocompatibility while using only PEG or using PEG/CA as an additive. The spherical nanoparticle shape gives better surface area than rod shaped nano particles while it is merged in the polymer fiber produced through electrospinning. So, the membrane can be fabricated by electrospinning technique rather than phase inversion technique. Meanwhile specific protein bound medium toxin such as

indoxyl sulfate and p-cercrole adsorption test can also be performed with these membranes and effect on ph and salts tests can be performed to justify that with the smaller sized zeolite particle more amount of medium toxins may be adsorbed in the membrane.

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