

# Haemodialysis Membranes: A Review

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## ABSTRACT

In the hemodialysis process, the blood of patients suffering from severe renal diseases is treated by removal of uraemic products, while at the same time retaining the blood protein molecules with the help of a semipermeable membrane. The membrane is the backbone of separation in hemodialysis. In this review a brief history; in which comparison of different haemodialysers and the membranes used previously is given. The modern synthetic membranes and the modifications that these membranes underwent using different techniques for obtaining better biocompatibility and fluxes have also been reviewed. The current membranes that are used in the process of hemodialysis are hollow fibers. The fabrication of these hollow fiber membrane and the parameters which affect their morphology and performance are discussed. Finally, the future prospects of membranes which can give us acceptable separation and improved hemocompatibility are highlighted.

**Keywords:** Uraemic; Hollow fiber; Biocompatibility; Fabrication

**Abbreviation:** ESKF: End-Stage Kidney Failure; KUF: Coefficient of Ultrafiltration; Mwt: Molecular Weight; K: Mass Transfer Coefficient; UF: Ultrafiltration; TMPs: Transmembrane Pressures; Da: Dalton; BVs: Blood Compartment Volumes; B2M:  $\beta$ 2 Microglobulin; AC: Adsorption Capacity

## INTRODUCTION

Haemodialysis is the purification of blood by using a semipermeable membrane. In hemodialysis, blood is purified by removal of toxic products that generally are uraemic in nature. Haemodialysis treatment is for patients suffering from severe renal diseases and End-Stage Kidney Failure (ESKF). In ESKF the patient suffers from kidney failure for the long term in which the filtration rate in the glomerulus is less than 5 ml/min [1]. The uraemic products are classified into three groups on the basis of their molecular weights (Mwt). Molecules with  $Mwt < 500$  Da are grouped in small water-soluble molecules, between  $500 \ll 15000$  Da are referred to as middle molecules and above that are large molecules (up to 55000 Da). In hemodialysis, the transfer of waste molecules from blood occurs by diffusion or ultrafiltration (UF). The transport of molecules from high concentration to lower concentration is referred to as diffusion [2]. Usually, molecular diffusion depends on Mwt, the concentration gradient of blood-dialysate, flow rates of blood and dialysate, electric charge and nature of membrane [3]. While in UF the transport of molecules across the membrane occurs by the pressure gradient and the rate of UF is dependent on hydrostatic blood pressure and porosity of membrane. The performance of

hemodialysis membrane is determined by UF characteristics and solute clearances. The UF characteristic tells us about the flux through the membrane while solute clearance tells us about its efficiency.

The membrane acts as glomerulus of the dialyzer, every good membrane like real glomerulus should have the ability to remove urea molecules of about 55000 Da but should also stop protein molecules like albumin with Mwt of 66000 Da. For achieving this property, the mean pore size of the membrane should be considered. On the basis of pore size, the dialysis membrane is classified two types which are low flux (with small average pore size) and high flux (with large average pore size). The movement of solute molecules out of the blood is termed as convective clearance which is indicated by KUF (coefficient of ultrafiltration). KUF refers to the permeability of the membrane to water (hydraulic permeability) or 'leakiness' of a membrane. A dialyzer having  $KUF < 10$  mL/h/mmHg is called a low flux dialyzer and with  $KUF > 20$  mL/h/mmHg is known as high flux dialyzer. KUF is a specific property that characterizes a 'clean' (i.e. unfouled) membrane, its value is influenced by protein-membrane interactions while average pore size and distribution of pore size also affects the KUF and filtration property of a membrane [4]. The pore density determines the hydraulic permeability and the diffusive permeability (represented by the product of mass transfer coefficient and area i.e.  $KoA$ ) of the membrane. The  $KoA$  parameter is dependent on the flow rate of dialysate, the flow rate of the blood and clearance of dialyzer and is measured in zero net ultrafiltration conditions [5]. The

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conceptualization of KoA can be done as the maximum dialyzer clearance through the membrane surface area while considering the flow rates of blood and dialysate as infinite [6]. The higher the KoA the higher is the efficiency of urea clearance. A high-efficiency dialyzer has a KoA > 800-1000 ml/min.

### History of dialyzers

In early times different kind of approaches were utilized for dialysis purpose but they were of small scale. The first dialysis configuration employed for treatment of large numbers of the patient was the rotating drum kidney they have limited very low transmembrane pressures (TMPs i.e. the hydrostatic pressure gradient) and large extracorporeal volumes. The rotating drum kidney was replaced by coil dialyzer though in coil dialyzer high TMPs were achieved, it was limited by the unreliable control of high TMPs and UF volumes. Commercially it was available and was known as "The twin coil" because it was having two coils with a surface area of about 1.8 m<sup>2</sup> [7]. The Kill dialyzer was later employed in which the blood and dialysate flow was parallel. In the blood compartment, cellophane sheets were used which were supported by plastic boards [7]. Due to narrow channels (obtained by compression of boards) and copper-based cellulosic membrane i.e. Cuprophan the diffusive mass transfer efficiency was increased. These configurations were used but all these configurations were limited by high blood compartment volumes (BVs) and inadequate mass transfer (separations). The comparison between different kinds of haemodialysers that have been used in the past with their advantages and disadvantages is shown in Table 1.

Dialyzers do not just dependent on membranes. They depend on the path of blood, the potting compound (for holding membranes usually resins), the geometry of dialyzer, the sterilant and spacers between the hollow fibers which are all important, influencing clearances (i.e. diffusive and convective) and inducing reactions in the patients.

### Membranes used (Ismail)

Generally, the membranes used in hemodialysis are made up of polymer. For the preparation of membrane, dissolution of polymer is done in an organic solvent or relying on membrane solubility an acid can also be used and a solution is made known as a dope solution. This dope solution may be wholly organic or it may

contain an inorganic compound. The dope is used then, cast into a membrane by phase inversion method. Due to the diversity of membranes they can be classified on the basis of two standard i.e.

- 1.) Polymer's chemical nature
- 2.) Modifications in the membranes

**Polymer's chemical nature:** On the basis of chemical nature of the polymer, the early membranes were classified into three categories i.e. Simple cellulosic membranes, cellulosic membranes with some modifications and synthetic membranes.

**Cellulosic membranes:** In the early stages of hemodialyzer development, cellulosic membranes were used. They were made up of cellobiose which is a disaccharide. Due to the symmetry of this membrane over the entire wall thickness, the resistance to mass transfer was uniform side by side they were having low mean pore size, noticeable hydrophilicity and good diffusion clearances [8-11]. High porosity and low wall thickness were achieved due to their hydrogel structure. Due to their dense morphology, they showed impermeability to large molecules like  $\beta_2$  microglobulin (B2M) and were bioincompatible. Biocompatibility is the safety of blood purification without any complications when there is an interaction of blood and membrane [12]. Bio-incompatibility can induce infection, cardiopulmonary diseases, malignancy, and various diseases processes [13].

**Modified cellulosic membrane:** Due to bio-incompatibility modifications were done to the cellulosic membrane and two new membranes were formed i.e. Cellulose acetate (CA) and Hemophan, these modifications were done by replacing hydroxyl groups [14]. These membranes were first used in the 1980s for hemodialysis but are still limited due to their inefficient separation. Comparison between different membranes is shown in Table 2.

**Synthetic membranes:** After cellulosic membranes in the 1970s, various type of man-made polymers like Polyvinylidene fluoride (PVDF), Polysulfone (PSF), Polyethersulfone (PESf), polyacrylonitrile (PAN) and Polymethylmethacrylate (PMMA), etc. have been used in the fabrication of hemodialysis membrane [11]. These membranes were made from thermoplastic polymer synthetically due to which desirable characters are achieved. Advantages and disadvantages of some synthetic membranes are given in Table 3.

Table 1: Comparison between early haemodialysers.

Dialysis configuration	Membrane used	Configuration	Dialysate bath	Advantages	Disadvantages	Ref.
Rotating drum kidney (1945s)	30 m cellophane (Di=35 mm)	Spiral around cylinder	a Stationary	low resistance to blood	1. Low TMPs 2. Large BVs (500-700 mL)	[8,9]
Coil dialyser (1956)	Cellophane Tubing (CT)	Fiber glass screen on CT in a single coil	Recirculating	High TMPs	Unreliable control of UF volumes Large BVs	[7]
The Kill dialyser (1960-1970s)	Cellophane supported by plastic boards	Flat sheet	Recirculating	Improved diffusive mass transfer efficiency due to narrow channels and thin walled Cuprophan membrane	Large BVs	[10]
Hollow fiber artificial kidney (1960s and onwards)	Polysulfone acetate etc.	Cellulose Tubular	Recirculating	1. Improved SA/Vol in blood compartment 2. Decreased boundary layer effects 3. Acceptable TMPs	Not any	

Table 2: Some synthetic membranes with advantages and disadvantages.

Membrane	Cellulosic	Modified Cellulosic membranes (1980s)	Synthetic (1970)
Material	Cellulose (OH group)	1. Cellulose acetate 2. Hemophan	PAN, PES, PVDF, PMMA, PA
Morphology	Symmetric/Hydrogel type	Symmetric	Asymmetric
Wall thickness	Uniform	Low i.e. 6-15 $\mu\text{m}$	-
Mean Pore size	Low	Larger (22 $\mu\text{m}$ )	Larger
Hydrophilicity	Strong	-	Strong
Permeability	-	Good permeabilities compared to cellulosic membrane	High
Transport	Diffusive	-	-
Biocompatibility	Low	Low	High
Molecular weight range (MWTCO)	Impermeable to $\beta$ 2- Microglobulin	Low i.e. 2000 Da	High

Table 3: Some synthetic membranes with their advantages and disadvantages.

Membrane Material	PAN	PVDF	PA	PMMA	PES
Advantages	Good biocompatibility	Thermally stable	Thermally stable	Good permeability	Thermally stable
Disadvantages	Wall thickness	Good mechanical properties	Good mechanical properties	Low production of cytokine	Good mechanical properties
References	Activation of dialyzer reaction	Hydrophobic	Hydrophobic	Low sieving coefficient for B2M	Hydrophobic
	Low CR	Low CR	Low CR	Oxidative stress	
	[15]	[16]	[16,17]	[16,18]	[19]

**Copolymer:** For achieving a better balance of antifouling performance, biocompatibility, and economy, copolymerization is done. Modifications in hemodialysis membranes can be inflicted by copolymerization technique. In, copolymerization there is simultaneous chain polymerization of two or more than two monomers [15-20]. Some materials like ethylene-vinyl alcohol copolymer (EVAL), polylactic acid-block-poly (2-hydroxyethyl methacrylate), etc. have evolved to produce the hemodialysis membranes [21]. Currently, the focus is on the improvement of hemodialysis membrane for increasing removal of B2M.

**Modifications in hemodialysis membranes:** For the enhancement of biocompatibility, the membranes should be modified. Two approaches can be made for this modification i.e. Blending and Surface Coating. The membrane modified by these approaches is referred to as a composite membrane.

**Blending:** Blending is the simplest way for modifications of hemodialysis membrane an organic compound having close resemblance with the chemical properties of the polymer and with the polarity with the solvent is generally considered for blending. While the difficulty arises in the blending of the raw inorganic compound for its blending with polymer modifications should be done in it

**Blending using biomaterial:** For the improvement of biocompatibility, biomaterials are added to polymer working as membrane additives. In comparison to simple polyethersulfone membrane, blending of PES with polyurethane (PU) has resulted in improved antithrombotic and antifouling properties [22]. However, by blending PES with sulfonated polyether ether ketone the biocompatibility is enhanced due to the emergence of forces (repulsive) between negative charges on blood components and surface of the membrane [23]. Anticoagulants like citric acid

and heparin etc can be used for prevention of clotting which occurs during hemodialysis [24]. The newly blended membranes like heparin mimicking Polyurethane are made for effective haemocompatibility.

**Blending using hydrophilic polymer:** The conversion of the hydrophobic membrane into the hydrophilic membrane is done by the addition of hydrophilic additives. These additives which are used are polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) etc. [25-27]. The positive impact of PVPs on the membrane hydrophilicity enables the membrane to prevent fouling and be biocompatible [27]. PES is blended with PVP or copolymers like PVP-co-methyl methacrylate-co-acrylic acid is used which can result in improved cytocompatibility [28].

**Blending using sorbents:** Studies have shown that adsorption, besides, diffusion can be helpful in the separation of toxins from the blood [29]. The addition of sorbents having the greater surface area to the membrane can play a role in even removal of small protein-bound molecules, efficiently. Combination of adsorption and diffusion increases the adsorption capacity (AC) of a membrane which can be helpful in efficient removal of low Molecular weight particles. Keeping in focus on the improvement of AC a mixed matrix membrane (MMMs) were fabricated in which adsorption and diffusion occurred in one step achieving improved creatinine clearances [30,31]. Membranes with sorbents like hydroxyapatite (HAP) and zeolites have also been fabricated with about 67% elimination of creatinine and 29% removal of p-cresol [16].

**Blending using inorganic nanoparticles:** In recent times, the focus is placed on the intercepting fouling of the membrane. The membrane fouling results in the decline of fluxes through the membrane. Modifications are done in the membrane by incorporation of nanoparticles to for the enhancement of the

flux. These nanoparticles range from in size from 1-100 nm. The uniqueness of nanoparticles is due to their possession of the large surface area. The nanoparticle generally used are metal oxides and carbon nanoparticles. Carbon nanoparticles like carbon nanotubes and metal oxides such as an iron oxide or titanium oxides are used in blending. Titanium oxides and silver-based nanoparticles blending have shown improved durability, thermal stability and better performance of polymeric membranes side by side they have antiviral, antibacterial properties which help in reducing membrane biofouling [32-34]. Multi-walled carbon nanotubes (MWCNTS) were first used for enhancing clearances of toxins [35]. Currently, iron oxide nanoparticles have been added to the PSF membrane showing improved quality of hemodialysis [36].

**Surface coating:** Membranes can be modified by coating its surface. The membranes initially made by surface coating technique were not suitable for extended usage but recently novel methods have been developed which can keep the supporting and coating layer intact. The surface coating was done to avoid the long term the complications that were produced in hemodialysis patients. Complications like deficiency of red blood cells which is known as anemia were diagnosed due to which the focused inclined towards surface coating. Vitamin-E coating has been used to over Polysulfone membrane to improve antioxidant position in the patients [37]. Heparin immobilized PLA membrane was also prepared [38]. The adhesion of heparin to the surface of PLA membrane is done by polydopamine, due to the which the hemocompatibility was improved. About 18% lysozyme and 79% of area were removed and retention of more than 90% of bovine serum albumin BSA was obtained. Polymers like PVA swell up when are exposed to water due to which there is loss in the mechanical strength, as well as rejections, are also reduced [29]. The best way to completely utilize this kind of membranes is that a hydrophilic polymer supported by hydrophobic polymer is coated which faces the blood. The composite membrane of nanofibers is also made by a combination of a layer of hydrophilic PVA with Pan as support. Due to the distinctive structure, this membrane showed eminent permeability, good selectivity while better durability and satisfactory blood compatibility. Most considerably, the membrane removed toxin to about 46% having a middle range molecular weight [39].

**Hollow fiber:** Currently, hemodialyzers comprised of thousands of hollow fiber membranes (10,000 hollow fiber membranes) bundled in a unit which is known as module [40]. The module serves as a support for hollow fibers and is the main entity in which enables dialysis between blood and the dialysate [40]. There are two basic geometries in which a hollow fiber module is formed i.e. shell side feed geometry and bore side. In shell side the feed is entered at the shell, the permeate passes through the walls of fiber and exit through the open fiber ends. In bore side, the fibers are open at both end and feed is passed through the inner (hollow) side of the fiber. To keep the pressure, drop low in bore side, the fibers with larger pore dia are used as compared to shell side feed system. The module of hollow fiber is sealed in two steps process. The first step involves the application of a potting compound at one end of the bundle so that the fibers should be encapsulated. This step is done to avoid the obstruction of the lumen. Polyurethane is generally, used as a potting compound. After curing of polyurethane, the bundle is cut using a blade at a specific temperature. The sealing of casting is done and after that, the sterilization is done [5]. The technique of fabricating of membrane, properties, performance,

and clearances of toxins by the membrane are interconnected. The fabrication process used for hollow fibers is known as electrospinning which has produce membranes with high surface area [41]. The identification of parameters, procedure, and structure of the membrane is of major importance [42].

### Preparation of membrane

**Nonsolvent induced phase separation (NIPS):** The technique used in the de-mixing process is known as phase inversion in which transformation of dope solution from liquid to solid state occurs in a controlled environment. This technique is classified into different techniques that may include thermally induced phase, evaporation induced phase and non-solvent induced phase (NIPS) also known as immersion precipitation. For the production of UF membranes (average pore size=0.001-0.1  $\mu\text{m}$ ) NIPS is considered to be a suitable technique [43]. Firstly, the immersion dope solution in a non-solvent coagulation bath is done where first evaporation and after that precipitation occurs due to exchange between solvent and non-solvent. In NIPS spinning process, to efficiently achieve the membrane of desired properties different parameters should be controlled and manipulated before during and after the process.

**Casting solution:** Prior to preparing a casting solution, the pellets of polymer should be dried so that the moisture content is removed. After drying, the dissolution of polymer in a suitable solvent is inflicted. The solvent which is generally used in hollow fiber membranes is N-methyl-2-pyrrolidone (NMP), dimethyl-acetamide (DMA), dimethyl-formamide (DMF) and dimethyl sulfoxide (DMSO). The solution resulted in the dissolution of polymer into a solvent is referred to as a dope solution. The selection of solvent is decided on the basis of Hansen solubility, mutual affinity (miscibility) of solvent and polymer and thermodynamic behavior of the solvent concerning polymer. Generally, with an increase in miscibility between solvent and nonsolvent, causes rapid demixing resulting in an increased porosity of membrane while decreasing the miscibility can most probably result in asymmetry i.e. dense layer at the top and porous at the bottom, of the membrane [17]. Generally, used polymers are PSF and PES polymers because membrane can be easily prepared by immersing of the dope solution in the coagulant bath i.e. water [17].

**Spinning parameters:** During the fabrication process, the principles of the spinning parameter have a significant effect on the morphology of the fabricated membrane. Various essential factors are listed in.

**Polymer solution:** The blending of a polymer, generally with a solvent or occasionally with a non-solvent gives a dope solution. Before, the process of spinning the viscosity of dope is measured so that the structure of fiber should be predicted. If the dope has low the concentration of polymer then it is diluted. This is done so that a membrane with a porous outer layer is obtained due to a rapid inversion phase process. If the viscosity of dope is high due to high polymer concentration then membrane with denser (non-porous) layer is obtained which is because due to obstruction in the movement of solvent during inversion of phase [25].

**Dimensions of spinneret:** The spinneret is a device used for the extrusion of dope resulting in the formation of the hollow fiber. It may contain channels from which a bore fluid and a dope solution are passed and eventually the combination of both decides the morphology of hollow fiber. The spinneret is chosen according to

the required dimensions of the hollow fiber. It is to be ensured that the spinneret dimensions should be such that each hollow fiber made for hemodialysis should have size is less than 200  $\mu\text{m}$  [44].

**Bore fluid:** For deciding the inner morphology or lumen of hollow fiber bore fluid is used. The bore fluid which is usually used is a non-solvent in nature. Generally, water is used as a non-solvent or bore fluid. While some, researches have also shown that by using different percentages of a solvent in bore fluid, the skin layer morphology can also be controlled [2]. The rate with which the bore fluid leaves the spinneret is defined as the bore fluid extrusion rate which is measured in terms of volume (mL) per unit time (min) [45].

**Air gap:** It is the distance between the exit of the nozzle and the coagulation bath. Dry phase inversion is started as the dope exits the spinneret, due to which its solidification occurs. Research has shown that the roundness and dimensions of the pore can be decided by the distance from spinneret to nozzle air gap [46]. The dimensions of membranes are reduced if the air gap is increased because the stresses of elongation are increased. The spinning of the membrane at different air gaps results in alteration of fluxes across the membrane [46,47].

**Coagulation bath:** Due to economic advantage, completely precipitation and stabilization of nascent membrane structure, water is used as the most common coagulation bath. After extrusion, the hollow fiber is dipped in a coagulation bath which decides the outer surface morphology of a fiber.

These above-mentioned factors should be to control to utmost precision if a hollow fiber of desired properties is to be obtained.

## CONCLUSION

The engineering of the membrane is not yet fully developed to excellence regarding hemodialysis despite its performance has exceptionally improved from the past decades. From a critical eye, the biocompatibility, as well as the performance of the membrane, are the pivotal factors in hemodialysis membrane. Therefore, most of the research inclination is focused on developing a membrane that can feature an enhanced removal of urotoxic middle range molecules while at the same time retaining protein molecules. A state of art membrane should overcome the shortcomings of high flux by increasing the pore size while at the same time perfecting the molecular weight cut off ratio. By using different modifications methods and by playing around with the parameters of spinning techniques desirable membrane can be achieved to some extent but in the end, there is always a trade-off in obtaining the 'perfect' membrane. Currently, the goal of achieving a perfect membrane for hemodialysis seems to be distant but the presence of a variety of membrane has given the clinicians a choice of selecting a membrane according to patient's need.

## FUTURE RESEARCH WORK RECOMMENDATION

Fundamentally, in hemodialysis membrane fabrication, the objective of attaining a membrane with efficient removal of uremic toxins and the retention of proteins remains the same. Fabrication of a membrane aided by utilizing the nanotechnology may prove productive in achieving the above-mentioned selectivity. By the combined action of adoption and dialysis can also have a positive impact. In addition, the usage of epithelial cells of kidney in combination with artificial kidneys so that a bioartificial kidney is a device that can revolutionize the process of hemodialysis.

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