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REVIEW ARTICLE

Comprehensive Study of Cellulosic and Synthetic Membranes for Dialyzer

Divya Patil[1], Santosh Balivada[1], Satyam Gorde[2]

[1]*Centre of Excellence-Additive Manufacturing, Andhra Pradesh MedTech Zone (AMTZ), Visakhapatnam, Andhra Pradesh, India.*
[2]*MIT School Of Bioengineering Research And Science, Pune, India*

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ABSTRACT

The kidney is the primary osmoregulatory organ in the mammalian body, removing harmful wastes such as ammonia and excess fluid from the blood and maintaining the ionic concentrations of the blood by retaining electrolytes, calcium, and phosphorus. In kidney failure, the kidneys are unable to filter the blood effectively. Dialysis is a survival treatment for patients with kidney failure. Dialysis involves the exchange of blood and dialysate across a semipermeable membrane. Concentration gradients drive diffusion, and hydrostatic pressure gradients drive convection. There are two different types of dialysis: peritoneal and hemodialysis. During hemodialysis, the blood is filtered by an external device called a dialyzer. Since the 1950s, dialyzers have been used commercially for hemodialysis; their removal capacity of uremic substances, biocompatibility, and combination of glomerular and renal tubular function have all been the subject of ongoing development. Despite the progress, mortality remains high. Investigating how dialysis membranes affect long-term morbidity and mortality in hemodialysis maintenance patients is essential. Dialyzer membranes play a vital role in dialysis treatment. Important characteristics of membrane material include permeability, hydrophilicity, and biocompatibility. Cellulosic and synthetic polymeric membranes are the two primary types of dialysis membranes. This article comprehensively analyzes the concept of dialysis and the characteristics of dialyzers and their types. This review focuses critically on the membranes of the dialyzer and their classification. We anticipate that this review will aid researchers in selecting the optimal dialyzer and membrane material to improve hemodialysis treatment outcomes for renal disease patients.

Keywords: Kidney failure, Dialysis, Dialyzer Membrane, Synthetic membrane.

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INTRODUCTION

Kidney failure is one of the most significant health issues in the world. More than 900 million individuals worldwide suffer from some form of renal disease, which is roughly double the number of people who live with diabetes (438 million) and 21 times greater than the global rate of cancer (43 million) or the number of people living with AIDS (39 million).[1] The high mortality rate is a result of inadequate treatment. The prevalence of CKD (chronic kidney disease) is 10.9% among men and 12.4% among women worldwide. In the 5th stage of chronic kidney disease, end-stage renal disease (ESRD) or kidney failure is identified. Dialysis and kidney transplantation are both options for patients with kidney failure. Due to the extremely low likelihood of receiving a kidney transplant, patients must undergo dialysis while they wait for a suitable donor. Over 3 million people worldwide depend on dialysis for survival, although this estimate may represent only 13% of those who need treatment to survive.[2] Modern technology can now replace the glomerular and excretory functions of the kidney through hemodialysis (HD) or peritoneal dialysis (PD). HD utilizes blood circuits and biocompatible membranes, whereas PD uses peritoneal and fluid circuits.[3] Hemodialysis is a highly effective treatment for sustaining the lives of individuals with kidney failure. Hemodialysis typically involves multiple cycles of pumping the patient's blood through a dialyzer unit containing hollow polymeric fibers made of hydrophilic/hydrophobic polymer.

Hemodialysis employs an extracorporeal system with a semipermeable polymeric membrane to filter the blood. Essential qualities of membrane materials include permeability,

**Author for Correspondence: divyapatil1802@gmail.com*

Table 1: Stages of chronic kidney disease

Stages	Glomerular Filtration Rate (GFR)	Albuminuria* (acr) mg/g proteinuria mg/24h	Kidney function Severity	Action
1	90 or Above	< 30*	Normal-Mild	Diagnosis and treatment, slowing progression, CVD(cardiovascular disease) risk reduction
2	60 to 89	30* - 300*	Mild	Estimating Progression
3A	45 to 59	> 300* < 1000	Mild to Moderate	Evaluating and treating complications
3B	30 to 44		Moderate to Severe	
4	15 to 29	1000 -3500	Severe	Preparation for kidney replacement therapy
5	Less than 15	> 3500	Kidney Failure	Kidney replacement (if uremia present) or hemodialysis

Flowchart 1: Developments in dialyzer membranes

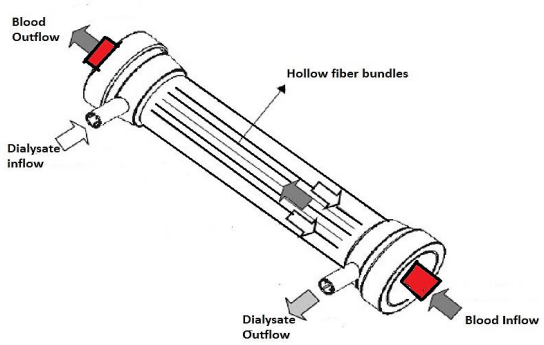


Fig 1: Hollow fiber Dialyzer

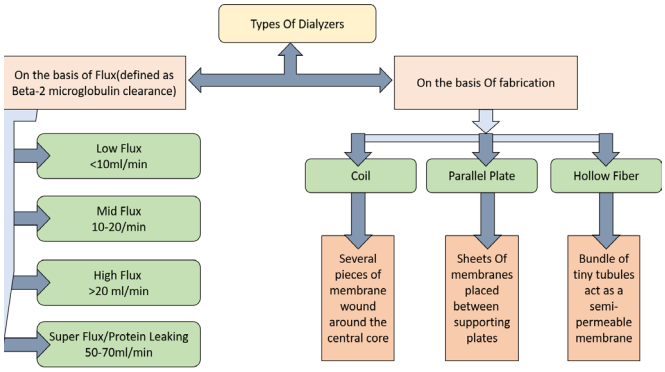
hydrophilicity, and biocompatibility. [4,5] The amount and flow rate of molecules that can flow from one compartment to another, and their size, can be used to measure efficiency. Thomas Graham invented in vitro dialysis in 1861 to separate macromolecules from ions in colloidal solutions. In the early 20th century, John Jacob Abel isolated epinephrine, insulin, and other hormones from living dogs using "vividiffusion" dialysis. In 1944, Kolff pioneered renal failure dialysis. Alwall created a hard-shell dialyzer for pressure-driven ultrafiltration (UF) to regulate extracellular fluid volume and solute clearance.[6] The timeline of developments in dialyzer membranes is shown in flowchart no.1. In this work, the fundamentals of dialyzers, properties, and types of dialyzer (listed in flowchart no.2) and membranes (listed in flowchart no.3) are discussed.

Dialyzer

Dialyzer is also known as the artificial kidney. It is the site of the movement of molecules. It consists of a container that contains a semipermeable membrane that separates the two compartments, one in which flows the patients' blood and the other the dialysate. This membrane has thousands of hollow fibers (shown in fig. no.1) or plate sheets.[10]

The following molecular mechanisms are responsible for the molecular movement in the semipermeable membrane.

1. Diffusion- The movement of solute from the region of a higher concentration to the region of a lower concentration. Diffusion is the movement of solutes along a concentration



Flowchart 2: Types of dialyzer

gradient. The transport of any solute or solvent molecule depends on the size of the molecule relative to the size of the pores in the membrane.

2. **Ultrafiltration-** Ultrafiltration is the fluid removal across a semipermeable membrane caused by a pressure gradient from higher to lower pressure.

3. **Osmosis** - Osmosis is the diffusion of a solvent from a higher concentration to a lower concentration across a semipermeable membrane.

4. **Convection**- Molecular movement through a semipermeable membrane associated with the fluid removed during ultrafiltration is called convection.

5. **Adsorption**-It is the method for removing molecules from blood or plasma by attaching them to a surface of a dialysis membrane.[11]

Specifications of Ideal dialyzer

1. Flux

During hemodialysis, accumulated toxins(listed in Table 3) and excess fluid pass through the dialyzer membrane due to its permeability. Initially, dialyzer "flux" was characterized by the ultrafiltration coefficient (Kuf), with a high flux dialyzer having a Kuf >15 mL/h/mmHg. [12] In response to improved results from middle molecular weight uremic toxin removal, dialyzer flux was redefined based on beta-2 microglobulin clearance instead of hydraulic permeability. Low flux, medium flux, and high flux are currently defined as β2 microglobulin clearances of 10, 10-20, and >20 mL/min. High-flux dialyzers with a beta-2 microglobulin sieving coefficient >0.6 can remove solutes between 10 and 50 kDa. [13] The sieving coefficient is defined as the ratio of solute filtrate concentration to the solute plasma concentration. [14]New high flux dialyzers are described by molecular weight cut-off [MWCO] and molecular weight retention onset [MWRO]. MWRO and MWCO are the molecular weight/radius values at which the sieving coefficient value is 0.90 and 0.10, respectively. Cytokines, free light chains, and myoglobin are cleared faster by these super-flux dialyzers with an MWCO of 65 kDa. Compared to low-flux membranes, high-flux membranes have larger pores and permit greater diffusion of uremic toxins and middle molecules; therefore, they may reduce the risk of dialysis-related amyloidosis(abnormal protein saturation). Low flux dialyzers are an option for acute and chronic dialysis when a lower fluid removal rate (e.g., ultrafiltration coefficient) is desired. [15,16]

2. KOA

The KoA is the maximum clearance efficiency of the dialyzer for infinite blood and dialysate flow rates for a particular solute, expressed in milliliters per minute. Dialyzer membrane surface area is A, and Ko is the mass transfer coefficient. For any given membrane, the coefficient of adsorption (KoA) will be proportional to the membrane's surface area in the dialyzer. However, the gain in KoA will reduce as the membrane's surface area increases. Dialyzers with KoA values below 500 mL/min should only be used for "low efficiency" dialysis. Dialyzers with KoA values between 500 and 700 mL/min are moderately efficient and helpful for routine therapy. Dialyzers with KoA values exceeding 700 mL/min are utilized for "high-efficiency" dialysis. KoA of a dialyzer does not change at

Table 2: Uremic Toxins

	Molecules	Molecular Weight (Da)	Characteristics
Small Molecules	Urea	60	-Molecular weight <500 Da; -Easily removed by dialysis. -Need low flux membranes.
	Uric acid	168	
	Oxalate	90	
	Sorbitol	180	
	Xanthine	152	
Middle Molecules	Beta-2 microglobulin	11800	-Molecular weight >500 Da; -Need high flux membranes. -Many are peptides.
	Leptin	16000	
	Interleukin	24500	
	Hepcidin	2789	
	Peptide-linked AGEs	50-400+	
Protein -Bound Molecules	Indoxyl sulfate	251	-Generally low molecular weight; -Difficult to be removed by dialysis.
	Melatonin	232	
	p-Cresol Sulfate	188	
	Hippuric Acid	179	
	Homocysteine	135	

different blood flow rates; it does increase significantly when the dialysate flow rate increases from 500 to 800 mL/min. The pore density, size distribution, and solute passage resistance of a dialysis membrane determine its KoA.[10,17]

3. KuF

ultrafiltration coefficient (Kuf) or hydraulic permeability measures the water flow rate and volume across the dialyzer membrane. Kuf is the limiting factor for ultrafiltration flow and volume; consequently, it is a crucial consideration when selecting a dialyzer for convective therapies. It is the function of membrane thickness and pore size.[18]

4. Biocompatibility

The dialyzer membranes activate blood cells, complement blood cells, and the complement cascade. Cellulosic membranes are primarily composed of free hydroxyl groups on their surface. The production of cytokines by activated cells results in a variety of clinical consequences and dialytic reactions. New dialyzers with membranes coated with antioxidants such as Vitamin E are being developed to produce antioxidants during dialysis. It has been reported that these dialyzers are associated with reducing oxidant production.[19-21]

5. Solute clearance

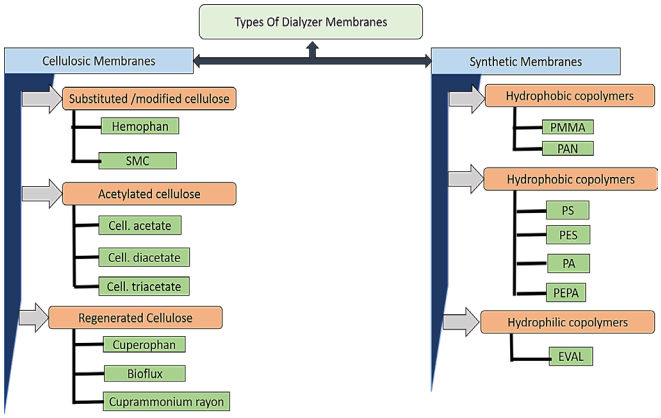
The ability of solute removal measures the performance of the dialyzer. In general, solute clearance coincides with the removal rate of solutes such as urea, uric acid, oxalate, creatine, and beta-2 microglobulin. It is governed by membrane properties such as pore size, thickness, and surface area. The removal rate of urea is the standard for all other solutes, as it is traditionally used in the hemodialysis dose calculation to measure small-molecule clearance. In hemodialysis, solute elimination is achieved through diffusion, convection, and adsorption. The uremic solutes removed by hemodialysis are typically divided into four major categories: (1) small water-soluble compounds with a molecular weight of 500 Da; (2) a middle molecular weight of 500–15,000 Da; (3) large molecules with a molecular weight of >15,000 Da; and (4) protein-bound molecules.[10,22]

Dialyzer membrane material and their classification

The membrane's constituent materials can be divided into 2 broad categories: cellulosic and synthetic membranes.[10]

Cellulosic membranes

Cellulose, a polysaccharide, is a natural, semi-crystalline polymer made up of repeating units of the cellobiose monomer, which is two glucose molecules with three hydroxyl groups that react chemically to form esters (cellulose acetate and nitrate) and ethers (ethyl cellulose). Cellulose is crystalline and hydrophilic but not water-soluble. Acetylation (acetate, diacetate, or triacetate) with copper amino complexes yields water-soluble derivatives of the insoluble natural polymer (cuprammonium). Liquidizing these derivatives allows solvent mixing. Hydrophilic materials are produced. Hydrophilicity creates strong polarity with positive and negative electrical charges. The superficial hydroxyl groups (responsible for



Flowchart 3: Types of dialyzer of membranes

cellulosic membranes' poor biocompatibility) sustain this polarity, increasing hydration capacity and K0A. To maintain K0A, glycerin (up to 40% polymer weight) is added. Glycerin replaces water during rinsing, taking up 40-50 % of the structure. Due to the dialysate fluid and blood-aqueous components, the membrane becomes a hydrogel in clinical use. Cellulosic membranes can now be made with a wall thickness of 5 Å and a mean pore diameter of 50 Å, improving Kuf and K0. A membrane with high porosity optimizes KOA for small molecular weight solutes but penalizes medium molecular weight solute transport. The high hydrophilicity of cellulose-based membranes reduces protein adsorption, allowing constant performance over time. [23-27]

Cuperophan

The "mother of hemodialysis membranes" is cuprophan. The membrane removes small solutes well. Medium/high molecular weight and ultrafiltration capacity solutes perform poorly. Due to its low Kuf and sieving capacity for larger solutes, cuprophan is only suitable for standard hemodialysis, not HDF(hemodiafiltration), or HF(hemofiltration). Due to the polymer's intrinsic properties, cuprophan has lower biocompatibility than other membranes due to the cellobiose structure's high hydroxyl group content. Thus, chemical modification of cellulose structure has produced membrane variants with improved biocompatibility. Cuprophan is a flexible membrane that can be sterilized with all current sterilizing agents and comes in flat sheets, tubular, and capillary forms.

Hemophan

Hemophan is a symmetric, low-flux cellulose membrane like Cuprophan that activates the complement system (bio incompatibility). Positive Charged tertiary amino groups (diethyl-amino-ethyl, DEAE groups) replace 5% of the glucose molecules' hydroxyl groups, improving hemophans' biocompatibility. The DEAE group modification reduces complement activation, but not to the level reached and confirmed for synthetic dialysis membranes. Thus, hemophan has improved biocompatibility and retains many Cuprophan properties, including small molecular solute removal, but it

cannot transport middle molecules and has a low Kuf. Like cuprophane, it can be sterilized with all current methods, but some will affect performance, such as ultrafiltration.[26,28,29]

SMC(Synthetically Modified Cellulose)

SMC, like Hemophan, is a modified cellulose membrane with a small percentage of hydroxyl groups covalently replaced with neutrally charged aromatic benzyl groups to improve biocompatibility. Aromatic benzyl groups make the cellulose surface hydrophobic. SMC (also known as PSN or Polysynthane) has hydrophobic zones (benzyl groups) within a hydrophilic matrix (hydroxyl groups and cellulose), improving biocompatibility and thrombogenicity compared to hemophan. SMC has lower complement activation and leukopenia than other modified cellulose membranes and approaches synthetic membranes. SMC and synthetic low-flux membranes also show no differences in biocompatibility markers like TNF(tumor necrosis factor) and thrombin-antithrombin III complex generation (TAT). Similar to hemophan, SMC is a cellulose derivative. Similarly to cuprophan and hemophan, SMC can be sterilized using all available methods(steam, ETO, gamma irradiation). However, sterilization can alter the membrane properties. Gamma irradiation induces specific chemical and molecular changes that may alter the hydrophilicity and Kuf of a membrane.[30,31]

Bioflux

It is a membrane produced similarly to Hemophan and SMC via the classical cuprammonium process, but it is an unmodified cellulose dialysis membrane, unlike Hemophan and SMC. Bioflux has a similar structure to Cuprophan, but its pores are significantly larger (7.23 Å) than those of conventional cellulosic low-flux membranes. Compared to Cuprophan, Hemophan, and SMC, the membrane has a greater ultrafiltration rate and permeability for small molecular-weight substances. Bioflux is classified as a high-performance membrane due to its higher Kuf and KOA for medium/high molecular weight solutes (including some Beta 2-microglobulin sieving capabilities) (i.e., its properties are somewhat intermediate between those of classical low-flux and high-flux membranes). Recently, beta-irradiation was introduced for the sterilization of Bioflux.[31-32]

Cellulose Acetate

Thalhimer first proposed the CA dialysis membrane in 1937. Pretreatment with pure acetic acid, acetic anhydride, and acetic acid with sulfuric acid as a catalyst acetylates cellulose. These membranes are used for protein adsorption. Biocompatibility is increased by substituting the two (diacetate) and three (triacetate) hydroxyl groups with acetate. After water contact, the membrane remains hydrophobic. Protein adsorption on the internal capillary surface is enabled by hydrophobicity. Cellulose triacetate has all reactive surface groups substituted with acetyl, improving biocompatibility and Kuf. The membrane retains many of cellulose's properties. For blood purification, cellulose triacetate seems to be a good compromise between the benefits of cellulose membranes (high KOA for small molecular weight solutes) and those of many synthetic membranes (high KOA for medium/high molecular weight solutes). HF and HDF are possible with this membrane's high Kuf. It should also be noted that this membrane's producers can adjust the ratios of polymer, solvents, and non-solvents to produce membranes with different KOA and Kuf for various treatment methods. pH sensitivity is one drawback of CA. This membrane is sensitive to high temperatures, making steam sterilization difficult. Alkaline environments cause deacetylation, while acidic environments hydrolyze the polymer.[33-36]

Cuprammonium Rayon

Cuprammonium rayon was created to improve cellulosic membrane biocompatibility and solute removal of higher molecular weight solutes. The first goal was achieved by replacing surface-active hydroxyl groups with hydrogen bonds (Terumo, Toyobo-manufacturer) or polyethylene glycol (PEG) chains. In production, PEG chains prevent skin formation. This allows the membrane's pores to have a funnel shape and a higher surface area for higher molecular weight solutes by having a larger diameter in the internal part than the outer part. High-flux dialysis can be done with a membrane wall thickness of 7 µm. Terumo sterilizes it with ETO, steam, and gamma-irradiation (Asahi). Recently, a multiphase "bioactive" membrane made from cuprammonium rayon (Excebrane, Terumo) was developed. The fiber's external layer (in contact with the dialysate) is high-porosity cuprammonium rayon. In contrast, the internal phase (in connection with the blood) is interfaced with a thin acrylic copolymer coating that hides all the cellulose hydroxyl groups, improving biocompatibility. The copolymer has oleic acid groups to reduce platelet activation, and thrombogenic response reduces platelet activation and thrombogenic response. The copolymer block's upper part contains vitamin E. This neutralizes free radicals produced during dialysis by donating an electron to reactive free radicals. The combination of vitamin E and oleic acid appears to change cell membrane morphology, reducing neutrophil activation and free radical production. The membrane is autoclaved. [37,38]

Synthetic Membranes

Polyacrylonitrile (PAN)

Rhöne Poulenc(French chemical and pharmaceutical company) created the first high-permeability synthetic dialysis membrane in 1970 using poly-acrylonitrile (AN69). Polyacrylonitrile metallyl-Na-sulfonate copolymerization produced a hydrophobic membrane. The membrane has many medium-sized pores and is symmetric and homogeneous. Afterward, many PAN membranes were made. Asahi's asymmetric membrane is a non-sulfonated copolymer made hydrophilic by adding acrylic acid to hydrophobic monomers like acrylonitrile and methacrylate. Rhöne Poulenc continues this production with Hospal by reversible polymer thermic reaction membrane production. Gelification after air contact allows isotropic polymer precipitation. Liquid (unmixable with polymer) controls pore density. Insufflation (blowing gas in the cavity) with nitrogen forms fibers, while sheets are created

by a different method (desiccation rather than gel formation). Thermic finishing makes the membrane rigid, while glycerol prevents phase structure collapse during sheet membrane production. During non-homogeneous precipitation, Asahi's PAN forms an asymmetric structure. The fiber's internal (total) and external (partial) precipitation in a nitric acid bath creates skin layers representing transport barriers to solutes, characterizing transport barriers to solutes and describing the membrane's sieving properties. The median value of the pore dimension of PAN AN 69 is 29Å, allowing diffusion of small molecules and convection of larger solutes. Sulfonic and nitrile groups stabilize water molecule hydrogen bonds, making the membrane polar. Acrylonitrile makes the surface hydrophobic, while metallilsulfonate makes the surface hydrophilic. Biocompatibility and diffusive solute transfer are attributed to the PAN AN69 membrane's hydrophilic portion. Repulsive forces in contact with hydrophobic fields prevent homogeneous diffusion, but the surface's aqueous layer does. PAN membranes adsorb and transmembrane transport beta-2-microglobulin. Due to their high Kuf, membranes are suitable for HDF and HF. The membranes are sold as flat sheets or hollow fibers and can be sterilized by ETO (Asahi, Hospal, Kawasumi, Saxonia) or gamma irradiation (Hospal, Saxonia) without changing their properties. [39-42]

Polysulfone and Polyethersulfone

In the 1970s, PS was established as a dialytic material due to the need for HF membrane improvement. PS membranes, the most widely used synthetic dialysis membrane, were developed simultaneously with the first scientific reports on cellulosic membrane-induced leukopenia and complement activation. In contrast, PS membranes had excellent biocompatibility, diffusivity, and versatility for high-flux dialysis and convective treatments like haemodiafiltration, making the Fresenius PS membrane the gold standard. PS dialysis membranes are available from Asahi, Toray, Terumo, Helbio, and others. An amorphous polymer PS has a sulfone group. PS is the only synthetic polymer used in dialysis that can be sterilized by all primary sterilization methods and has excellent chemical and thermal stability (steam, ETO, gamma-irradiation). Steam sterilization of medical devices is becoming more critical due to ETO's clinically significant hypersensitivity reactions and irradiation's damage to polymer and membrane structures. The Fresenius PS membrane's excellent endotoxin retention is vital when using high-flux membranes for HFD and HF. Back-filtration could allow bacterial endotoxins from contaminated dialysate supplies to pass through. Polyethersulfone (PES) has replaced polysulfone as a dialysis membrane polymer (Membrana, Gambro-Hospal). Both PS and PES (synonymous with polyarylethersulfone, PAES) are steam sterilizable. However, unlike Fresenius PS, all PES-based dialysis membranes do not retain endotoxins, compromising patient safety. PS and PES membranes are asymmetric and hemocompatible with high permeability. PS and PES can be used in HD, HFD, and HF due to their high, middle, and low Kuf. The polymer's repeating phenyl ring groups give it high rigidity, traction, compression, heat, mechanical stability, and pH resistance. The polymer becomes "glass-like" when equilibrated with water at room temperature. The membrane porosity and structure are determined by blending the base polymer with polyvinyl-pyrrolidone (PVP), which makes the two polymers hydrophilic. Because of the different amounts of hydrophilic copolymer PVP used in manufacturing, PS and PES membranes have different hydrophobicity and surface charges. Different types have different protein adsorption capacities. The Kuf, hydrophobic properties, and molecular selectivity depend on adsorbed proteins. Like other membranes, polymer precipitation can form one or more skin layers on a hollow fiber's internal, external, or both surfaces. The membrane's morphology is affected by production technology and manufacturing processes. The KOA of this family of membranes depends on the membrane wall thickness, homogeneous structure, degree of asymmetric design, number of skin layers, and hydrophobicity-hydrophilicity. Due to their high Kuf, membranes are used for HDF and HF. PS 400 and PS 550 Fresenius, Oiapes LF 100 Membrana) have been modified for standard HD to reduce Kuf and create a natural low flux membrane. PS membranes include PEPA (polyester polymer alloy). Polyacrylate and polyether sulfone form this hydrophobic asymmetric membrane. Due to its physical and chemical properties, the membrane resembles PS/PES. Long-term biocompatibility studies are ongoing. HDF uses gamma-irradiated hollow-fiber PEPA membranes. Fresenius medical care developed Helixone, a polysulfone-based membrane. Helixone's inner fiber diameter (185 μm) and its wall thickness (35 μm). Increased internal filtration and decreased diffusion resistance boost convective and diffusive clearances. Helixone also has a unique, cylindrical pore structure and an even pore distribution at the membrane's innermost, separating ('skin') region, which determines its sieving properties. These structural refinements improve the membrane's beta-2 microglobulin removal (beta-2 microglobulin sieving coefficient = 0.8) without losing larger molecules like albumin, as happens with conventional membranes when the mean pore size increases. The bundle's wavy fibers allow dialysate to flow uniformly, improving solute clearance. Helixone is hollow-fiber and steam-sterilized for HDF and HF. Diape's (polyethersulfone, Membrana) is a variation of the PS membrane family, available in low-, middle-, and high-flux. It's hemocompatible. Diapes's performance-enhancing technology (PET®) uses a multifilament spacer yarn to deliver an even-flow dialysate, improving clearances, and the membrane's 30 μm wall thickness increases diffusive permeability. Performance is good due to this membrane's elevated Kuf. Bellco, Baxter, and Kawasumi offer gamma-sterilized hollow fiber for HDF and HF.[43-50]

PMMA (Polymethyl methacrylate)

Asymmetric hydrophobic PMMA is a hydrogel with a substantial amount of water. It is a combination of isotactic polymethyl acrylate and dimethyl sulfoxide. PMMA is produced by the thermally induced phase inversion

Table 3: Specification of dialyzer membranes

	Membrane Type	Base Material	Thickness (µm)	Ultrafiltration coefficient (ml/h/mmHg)
Cellulose	Cuprophan	Regenerated cellulose	From 5–17	2.6–11.2
	Hemophan	Esterified with DEAE	From 5–20	3.1–17.6
	Cuprammonium rayon	Regenerated cellulose	From 9–26	2.5–37
	Cellulose acetate/diacetate	Esterified with 2.0 acetate	From 14–30	1.1–45.0
Synthetic	EVAL	Ethylene vinyl alcohol	From 25–32	4.8–14.5
	PMMA	Polymethylmethacrylate	From 20–40	2.5–41.0
	PAN	Polyacrylonitrile	From 19–55	16.0–65.0
	PS, PES	Polysulfone	From 30–104	1.7–103.0
	PA	Polyamide	From 52–63	8.6–71.0

method. The polymeric paste is made by liquefying the polymer by adding a solvent and plasticizer. Gelification and water substitution produce a capillary fiber from this extruded material. Membranes with different compositions, porosity, and density can be made by changing the relative concentration of isotactic and syndiotactic polymers and water content. Stereochemical crosslinking and thermo-reversible hydrophobic bonds between the isotactic and syndiotactic components of the two polymers allow the mixture to form different spatial structures. HD, high-flux dialysis and HDF can use PMMA. The membrane adsorbs beta-2-microglobulin and is biocompatible. It is a gamma-irradiated hollow fiber (Toray).[10,51-53]

Polyamide

PA membranes have an asymmetrical internal layer (0.1 µm). This layer has many fine pores with an intermediate diameter of 5-10 Å. The membrane's outer part has a macroporous structure of 40-50 Å. that appears as long "fingers" perpendicular to the skin layer. Gambaro's first PA membranes were sheets, then hollow fibers. PA's high Kuf and hydrophobicity make it suitable for HF. High-flux dialysis uses the PA membrane after chemically modifying it with other polymers. The original hydrophobic membrane is still used in ultrapure dialysate filters to adsorb bacterial endotoxin. Aliphatic polymers give the membrane excellent biocompatibility, low complement activation, low protein adsorption, and low thrombogenicity compared to other copolyamides. Mixing the copolymer with hydrophilic water-soluble polyvinylpyrrolidone (PVP) makes PA more hydrophilic. The hydrogen bonds between PVP and PA allow good miscibility across a wide range of concentration ratios and prevent PVP release during clinical use. The hydrophobic to hydrophilic ratio prevents ionic bonds from forming on PA's surface, reducing membrane-plasma protein interaction. ETO sterilizes hollow fiber membranes. [54,55]

EVAL (Ethylene-vinyl alcohol copolymer)

The copolymer EVAL, like Cuprophan and other cellulosic membranes, is symmetric and hydrophilic. Alkaline saponification and extrusion of ethylene and vinyl acetate polymerize it. Manufacturing membranes with different pore densities requires changing chemical and physical conditions. The biocompatible membrane reduces blood contact activation of factors like factor XII, high molecular weight kininogen, and pre-kallikrein, making it suitable for dialysis without heparin. EVAL has a slightly lower KOA than cellulosic membranes for small solutes but a higher KOA for high-molecular-weight solutes. It is a low-flux membrane used only in standard HD. Hollow fibers are sterilized by gamma irradiation (Kuraray). [56,57]

Membrane material characteristics

The removal of solutes that are retained because of renal failure (such as urea) and the restoration of depleted compounds are the objectives of the exchanges that take place through the membranes of the dialyzer (e.g., bicarbonate). The specification of dialyzer membranes are listed in table no.3 and the comparative study of the advantages and disadvantages of membranes is given in table no.4.

1. Biocompatibility towards the immune system

Materials are said to be biocompatible if they produce only negligible effects on the biochemical and biological systems. Leukocyte and complement activation occurs when unmodified cellulosic membranes are used. Inflammation caused by baseline activation of leukocytes is associated with vascular disease. C-reactive protein, an inflammatory marker associated with fatalities, is lower when synthetic, biocompatible, high-flux polysulfone is used compared to unmodified cellulose. [58-60]

2. Adsorption

Synthetic membranes adsorb noxious compounds like interleukin-1, tumor necrosis factor, peptides, interleukin-6, and beta2-microglobulin. Synthetic membrane adsorptive capacity varies. Polyethersulfone, polymethyl methacrylate, and AN69 adsorbent capacities are greater than other membranes. Dialyzers' limited surface area quickly saturates adsorption capacity. Adsorption rates can only be achieved if the surface area is vastly increased by developing devices with high adsorptive areas. These devices should have beads with well-defined adsorptive properties. Contaminants in the dialysate may release lipopolysaccharides, peptidoglycans, DNA, and other pro-inflammatory products when they enter the bloodstream. When back filtration occurs, the risk of inflammation increases. Bacteria penetrate small-pore

Table 4: Membrane material manufacturer, advantages and disadvantages.

Polymers	Abbreviation	Advantages	Disadvantages	Manufacturer	Membrane type
Cellulose triacetate	CTA	-Solute permeability is good. -Symmetric structured membrane -Large pore size	Less Biocompatible	-Nipro	Hollow Fiber
Ethylene vinyl alcohol copolymer	EVAL	-Large pore size -Can reduce inflammation and oxidative stress -Effective for removal of high-molecular weight toxins	Loss of albumin	-Asahi Kasei Kuraray medical	Hollow Fiber
Polysulfone and Polyether- sulfone	PS and PES	-Good thermal and mechanical stability -Highly chemical and pH resistance	Oxidative stress Hydrophobicity	-Asahi Kasei Kuraray medical -Fresenius -Nipro -Membrana	Hollow Fiber
Polyacrylo-nitrile	PAN	-Highly blood compatible -Low anaphylatoxin formed	Dialyzer reaction may get activated due to negatively charged surface	-Gambro	Laminated Hollow Fiber
Polyamide	PA	-High pH tolerance -High thermal and mechanical stability	Dialyzer reaction may get activated due to negatively charged surface	-Gambro	Hollow Fiber

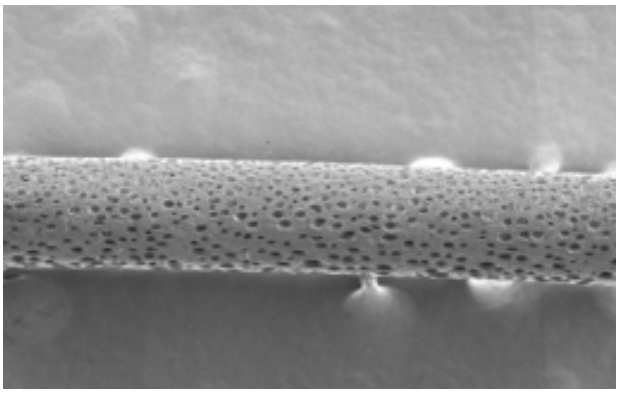


Figure 2: SEM(scanning electron microscopy) image of hollow fiber(longitudinal)

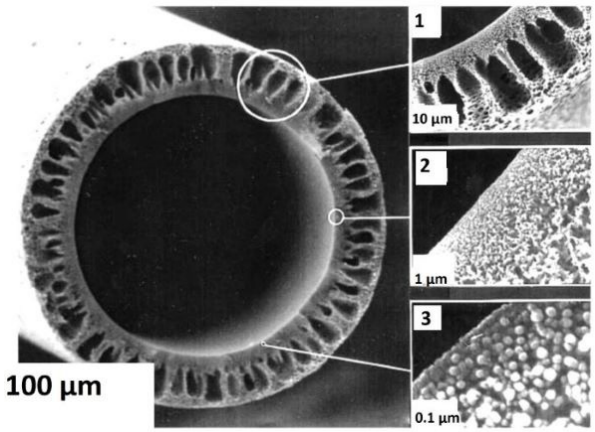


Figure 3: SEM(scanning electron microscopy) image of hollow fiber (cross-section)

cellulosic membranes into the blood compartment more easily than large-pore synthetic membranes, which adsorb them. Bacterial products activate leukocytes. Utilizing synthetic membranes is the better option to prevent contamination. [43.61]

3. Pore size

Increasing numbers of bioactive middle molecules (>500 Da), like leptin (causes malnutrition) and homocysteine (related to vascular damage) may contribute to renal dysfunction. Increasing pore size and flux accelerate solute removal.[10,43]

CONCLUSION

This review highlights the various materials used in hemodialysis membranes and the characteristics of an ideal dialyzer. Improving the range of uremic toxin clearance is most likely to result in patient benefits, as no ideal dialyzer can remove all forms of uremic toxins while retaining vitamins and other necessary elements. Most of the present hemodialysis membranes are composed of polysulfone, with a 25% PES (polyethersulfone) and a 75% PS (polysulfone) distribution. However, PES has a higher protein absorption capacity than PS, and PS retains more endotoxins than PES. PES membranes are more efficient for dialysis than PS membranes. Extreme hydrophobicity linked with membrane fouling caused by the adherence of plasma proteins to the membrane surface is one of the downsides of synthetic polymer membranes. This hydrophobicity may lead to platelet adhesion, aggregation, and coagulation. The biocompatibility of synthetic membranes can be investigated further by culturing glomerular epithelial cells on the membranes, which will help lower the hazard ratio. The advancement of dialyzer membranes has primarily resulted in a reduction in membrane size. Using nanofiber technology, future dialyzers would be wearable, portable, dialysate-free, and continuous-functioning like natural or transplanted kidneys.

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