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10-Year Historical Development of Dual Layer Hollow Fiber Hemodialysis Membranes

Sumarni Mansur[a] & Muhammad Nidzhom Zainol Abidin[b]*

[a]Fuel Cell Institute, Universiti Kebangsaan Malaysia, 43600 Bangi, Selangor, Malaysia
[b]Department of Chemistry, Faculty of Science, Universiti Malaya, 50603 Kuala Lumpur, Malaysia

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ABSTRACT

Hollow fiber membranes have been employed to purify blood from within the heart of hemodialysis process, namely dialyzer. In the past 10 years, the interest on the utilization of dual layer hollow fiber (DLHF) membranes has arisen due to the innovative idea of combining adsorption and diffusion processes into one step. This short review outlines the historical development of DLHF hemodialysis membranes that spans from year 2012 to year 2022. The motivation and the outcome from the first and the second generation DLHF hemodialysis membranes are discussed. In addition, the use of DLHF membranes in other hemodialysis-related application is presented. This short review would provide a perspective for membranologists to recognize the issues in DLHF hemodialysis membranes and to work their way to finding the real solutions.

Keywords: Dual layer hollow fiber, hemodialysis, mixed matrix membrane, adsorption process, diffusion process

1.0 INTRODUCTION

Over the last six decades, hemodialysis treatment has evolved to improve the life of kidney failure patients, i.e., not just to remove uremic toxins, e.g., urea and creatinine from blood but also to keep them healthy doing daily activities. The major developments of this technology include biocompatible and high-performance dialyzers, sophisticated monitoring systems that provide online clearance, volumetric and temperature controls, and convective modalities such as hemofiltration and hemodiafiltration [1–3]. Yet, the core design of the hemodialysis components especially the dialyzer remains relatively unchanged ever since their invention by William J. Kolff. In current dialyzers, thousands of semi-permeable hollow fiber membranes are gathered inside a hard-plastic casing, a jacket. Both ends of the jacket are then capped. Each beginning and near end of the jacket has a small, spaced header so that blood can flow into, before entering the hollow fiber membranes and then out of the dialyzer.

In hemodialysis, the mechanism of solute clearance is either by simple diffusion, where the solute dissolved in blood moves across the semi-permeable membrane into the dialysate via concentration difference or by convection, where the solute dissolved in blood is permeated into the dialysate together with water via pressure difference, with blood and dialysate flowing in opposite directions.

The type of hollow fiber membrane contained inside a dialyzer is the one that majorly determines the degree of

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* Corresponding to: M. N. Z. Abidin (email: nidzhom@um.edu.my)
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the removal and restoration processes during hemodialysis. The dialyzer's capacity to perform the necessary separation is pre-determined by the permeability and the selectivity of the hollow fiber membrane which are based on the porosity and the sieving coefficient, respectively.

The design and the configuration of membrane are among the talking points in determining the efficiency of a hemodialysis membrane in terms of their permeability and clearance efficiency. In addition, some major issues including bio-incompatibility that induces long-term side effects and the poor removal of protein-bound uremic toxins are still unresolved. Thus, in the past few years, there have been a few numbers of work attempting to solve these problems through the development of dual layer hollow fiber (DLHF) membranes. The DLHF membrane design and configuration were believed to be the viable solution to the listed issues. In this short review, we try to include the historical development of DLHF hemodialysis membranes in the past 10 years. In general, the DLHF hemodialysis membranes can be divided into two generations. In each generation, the motivation and the outcome of the research are different to each other.

2.0 ADVANTAGES OF DLHF HEMODIALYSIS MEMBRANES

DLHF membranes consist of two asymmetric membrane layers laminated layer by layer (Figure 1b and 1c), as compared to single layer hollow fiber (SLHF) membrane (Figure 1a) and they are typically fabricated via a single step co-extrusion technique. DLHF membrane has been introduced and utilized in various filtration technologies such as ultrafiltration, reverse osmosis, forward osmosis, electrodialysis and membrane distillation.

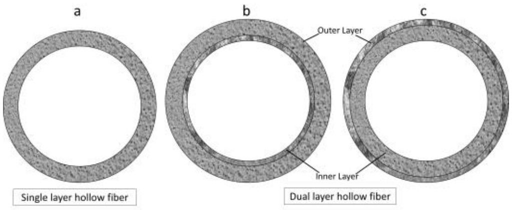

Figure 1 Cross-sectional image of (a) SLHF and (b, c) DLHF membranes

One advantage of DLHF membrane is the feasibility to design the membrane morphology according to the need and objectives of the studies. Research has shown that the incorporation of inorganic particles can increase the removal of uremic toxins from blood component [4]. Hence, DLHF membrane has been designed to ensure the safe loading of these particles in the membrane. The thicker, particle-free layer of DLHF membrane will be facing the blood side to thicken the blood boundary layer while the thinner, particle-loaded layer of DLHF membrane will be facing the dialysate to prevent the release of the particles into blood. Typically, in-to-out filtration system is commonly used for hemodialysis and thus the morphology of the DLHF membrane is designed as shown in Figure 1c. However, there was also attempt to use an out-to-in filtration system as in Figure 1b [5]. The purpose is to provide a higher effective membrane surface area for increased removal of uremic toxins.

The motivation to fabricate DLHF membrane is also due to the limitation of SLHF membrane which requires additional process. For instance, an adsorptive cartridge is sometimes coupled with a SLHF dialyzer to adsorb protein-bound uremic toxins in a process called hemoperfusion. Protein-bound uremic toxins such as p-cresol and indoxyl sulfate are difficult to be removed using conventional hemodialysis treatment, even when using high-flux membrane. In a study by Yamamoto *et al.* [7], the reduction rates of indoxyl sulfate and p-cresylsulfate by conventional hemodialysis are only 31.8 and 29.1%, respectively. Among the widely used adsorbents for hemoperfusion include activated carbon (AC), zeolites, mesoporous silica, graphene oxide, and minerals monolith. However, some absorbents are bio-incompatible. Coated AC was used in hemoperfusion to minimize the contact between blood and AC, though it was reported that the clearance of protein-bound molecules reduced by 50% [7]. Instead of having two separated processes, DLHF membrane can be employed to combine adsorption and ultrafiltration in a single process.

On the other hand, biocompatibility aspect of the material used for the development of hemodialysis membrane is very important because bio-incompatibility of the material can cause adverse effects on health. The contact between blood and membrane can induce undesirable bio-response that could trigger the anaphylatoid or allergic reaction. Complement activation may occur when the localised inflammatory mediator is generated due to the reaction caused by the body defence mechanism. This mechanism initiates and amplifies inflammation that could lead to the allergic reaction. For example, the presence of hydroxyl groups on the surface of unsubstituted cellulose membrane has been linked to the activation of complement system. This complement system activation induces the cleavage of several anaphylatoxins such as, C3a, C5a and the membrane attack complex, C5b-9 [8]. On the other side, membrane fouling can happen on synthetic polymer-based membranes due to the adsorption of non-polar solutes and hydrophobic bacteria. This fouling problem will reduce the lifetime expectancy of the membrane and subsequently increase the cost.

3.0 FIRST GENERATION DLHF HEMODIALYSIS MEMBRANES (2012-2016)

The idea of using dual layer membrane for hemodialysis application started in 2012, where a group of researchers from University of Twente, The Netherlands [9] wanted to combine hemoperfusion and hemodialysis processes into a single step by developing a dual layer mixed matrix membrane (MMM) and they started off with the flat sheet membrane configuration. The main purpose was to compensate for the intrinsic disadvantage of both techniques and simultaneously enhance the diffusion and adsorption performance of the fabricated dual layer MMM. AC was immobilized into the outer layer facing the dialysate while the particle free inner layer is facing the blood. The dual layer MMM membrane was able to remove more than 80% of creatinine and para-aminohippuric acid, which is a protein-bound uremic toxin. However, the dual layer MMM produced a much lower water permeability (~350 $Lm^{-2}h^{-1}bar^{-1}$) than the single layer MMM (1800 $Lm^{-2}h^{-1}bar^{-1}$).

In the following year, the similar group of researchers employed the dual layer concept on the hollow fiber membrane configuration to remove creatinine and protein-bound uremic toxins, i.e., hippuric acid, indoxyl sulfate and p-cresylsulfate [10]. Although the DLHF MMM produced a higher adsorption capacity of creatinine (100 mg/g AC at the equilibrium concentration of 0.05 mg/mL), the water permeability of the DLHF MMM was much lower (58.4 L/m^2·h·bar) when compared to the flat sheet dual layer MMM reported in their previous work. With high maximum adsorption capacity towards those molecules, the DLHF MMM maintained 83% removal of creatinine and it adsorbed 60% p-cresylsulfate, 90% indoxyl sulfate and 95% hippuric acid after 4 hours of incubation in human blood plasma. Despite the great performance, albumin which is an essential protein in blood was partially removed from the blood via convection.

Inspired by the two previous works, Pavlenko *et al*. [11] later developed a smaller dimension DLHF membrane with an internal diameter of 450 μm using a smaller triple orifice spinneret. The outer layer of the DLHF MMM was embedded with mesoporous Norit A Supra, a commercial carbon-based adsorbent.

This study achieved a promising creatinine adsorption capacity of 2579 mg/m^2 with a higher removal of indoxyl sulfate and p-cresylsulfate, in comparison to the first DLHF MMM developed in 2013. It was stated that the low UF coefficient of the MMM (3.35 mL/m^2/h/mmHg) and a molecular weight-cut off of around 12,000 g/mol had prevented albumin leakage while achieving excellent removal of protein-bound uremic toxins.

These first generation DLHF hemodialysis membranes have successfully achieved what has always been their main focus which was to introduce this concept and apply it on hemodialysis.

4.0 SECOND GENERATION DLHF HEMODIALYSIS MEMBRANES (2017-2022)

The second generation DLHF membranes expanded the horizon by either studying the biocompatibility aspect of the membrane, exploring the different membrane forming materials or solving the problems faced by the first generation DLHF membranes. The focus is to prove the viability of DLHF membranes for hemodialysis.

An attempt to incorporate AC into macroporous cellulose acetate dual layer flat sheet MMM was done by Saiful *et al*. in 2018 [12]. This study produced a high water flux of 800 L/m^2·h·bar and resulted in creatinine removal of up to 83%, which was on par with the first generation DLHF hemodialysis membranes. The high convective effect promoted by the improved flux did not provide a positive impact on the creatinine removal which highly depends on diffusion and adsorption. In addition, this study did not provide information on protein rejection which is paramount to ensure no albumin leakage.

In a study by Geremia *et al.* [13], DLHF MMM was developed with the aim to achieve endotoxin free dialysate and high removal of uremic toxins via the combined effects of diffusion and adsorption. This study highlighted the risk of bacterial contamination from the dialysate. Hence, the idea was to create a safe barrier to reduce the inflammatory response caused by the bacteria in the dialysate system. Norit A Supra was incorporated in the outer layer of the DLHF membrane to adsorb lipopolysaccharides from *E. coli* in the dialysate compartment, indoxyl sulfate and hippuric acid in the blood compartment. Based on the dynamic adsorption results, the fabricated membrane successfully removed 54.1 ± 1.8 x 10^6 EU/m^2 lipopolysaccharides, 420 mg/m^2 indoxyl sulfate, and 2573 mg/m^2 hippuric acid with 11.4 L/m^2·h·bar of water permeability.

In the subsequent year, Geremia *et al.* [14] proceeded with the evaluation of the hemocompatibility of the previously developed DLHF MMM.

The inner layer was kept free from particles to achieve optimum hemocompatibility. They investigated the hemocompatibility of the low flux MMM and the high flux MMM, focusing on the inner blood contacting selective layer. Since the inner layer was composed of biocompatible materials and was not in contact with the carbon particles contained in the outer layer, the MMM showed good hemocompatibility that is on par with the commercial hemodialysis membranes. The low flux MMM, although showing high diffusive removal of uremic toxins, had a low convective effect which is not preferable for the removal of middle molecules. Similar observation was reported by Kim and Stamatialis on their first attempt of producing DLHF MMM for hemodialysis that had a low flux (2.5 L/m^2·h·bar) [15]. On a contrary, the high flux MMM is commonly associated with poor protein rejection.

The effort to enhance the separation performance of DLHF MMM was attempted by Kim and Stamatialis to turn the low flux DLHF MMM into the high flux DLHF MMM [15]. They fabricated a small diameter DLHF MMM that produced a much higher flux (132 L/m^2·h·bar). On top of that, the MMM displayed low protein adhesion and low protein leakage (99% rejection) in comparison to the commercial hemodialysis membranes.

In the most recent year, a study by Mansur *et al.* [16] aimed to solve the three main problems of DLHF hemodialysis membranes encountered in previous studies including theirs in 2021 [17]. The problems include the poor removal of uremic toxins, bio-incompatibility of the membrane, and bacterial endotoxin contamination in the dialysate. In their study, the DLHF MMM was incorporated with silica/α-mangostin nanoparticles in the inner layer of the membrane to enhance the biocompatibility of the membrane while maintaining the adsorption capacity towards uremic toxins. Apart from that, AC was incorporated in the outer layer of the membrane to improve the antibacterial property in preventing penetration of bacterial endotoxin from dialysate into the blood compartment. This study was able to remove 60.57% of urea, 75.18% of creatinine with a 3.81 L/m^2·h·bar water permeability. In addition, AC was also proven to enhance the inhibition of bacteria by preventing the bacteria from passing through the membrane in filtration studies, thus producing a membrane with antibacterial property.

Of all the studies developing DLHF membranes for hemodialysis, the study by Beek *et al.* [18] wanted to revolutionize the way hemodialysis works. They performed an outside-to-inside filtration of human blood plasma through the DLHF MMM containing AC. In contrast to other DLHF hemodialysis membranes, the AC was incorporated into the inner layer of the MMM while the particle free outer layer of the MMM became the blood-contacting selective layer. The results were comparable to the existing hollow fiber membrane in the market in terms of flux, hippuric acid and indoxyl sulfate clearances.

Using this new setup, they hypothesized that the hemodialysis session will be prolonged and the removal of toxins from the patient's blood will be improved, thus increasing the overall health of the patient.

To date, the majority of the DLHF hemodialysis membranes incorporate AC as the inorganic particles or fillers into the outer layer for the adsorption of the uremic toxins. In different filtration setup where the outer layer is facing the blood, AC is incorporated into the inner layer of the membrane. The main purpose is to ensure there is no direct contact between inorganic particles and blood to maintain the biocompatibility of the membranes. This is due to the incompatibility of the particles. In some studies, biocompatible adsorbent was used to minimize the blood complication while maintaining its adsorption capacity towards the uremic toxins.

DLHF hemodialysis membranes were able to remove various sizes of uremic toxins including protein-bound uremic toxins, depending on their flux. Apart from that, the difference in membrane flux also carries some drawbacks to the hemodialysis treatment. The reason for having high flux is to promote convection, which applies to the removal of middle molecules. The downside of high flux membrane is the high tendency for albumin leakage and hypertension. In a hemodialysis treatment that aims for small-molecular uremic toxin removal, low flux membranes are favorable for improved diffusion process. However, the accumulation of middle molecules may happen when using low flux membrane which would later cause amyloidosis. Therefore, further and deeper studies are needed to overcome the problems and to improve the hemodialysis treatment.

4.0 DLHF MEMBRANES FOR HEMODIALYSIS-RELATED APPLICATION

In between those years where DLHF membranes were designed and tested for the synergistic removal of uremic toxins by adsorption and diffusion, portable or home dialysis was introduced and has become of a great interest among nephrologists. The implementation of home dialysis demands a system to regenerate dialysate, where ions such as phosphate and potassium, small molecular uremic toxins such as creatinine and urea, and middle molecules such as β_2-microglobulin need to be removed from the spent dialysate. Ion-exchangers can be used for the removal of phosphate and potassium, while AC can efficiently remove most small molecular weight uremic toxins via adsorption. On the other hand, middle molecules can be rejected via sieving effect. Therefore, the idea of DLHF membranes can be used to remove a wide range of uremic toxins from dialysate.

Abidin *et al.* [19] took the liberty to develop an attractive approach to collectively remove uremic toxins by combining membrane filtration and adsorption process [19,20]. In their work, DLHF membrane consisting of polysulfone (PSf)/AC inner layer well attached to PSf/amino-silanized poly(methyl methacrylate) outer layer was prepared. Under dynamic filtration condition, the membrane removed creatinine and urea with a combined average percent removal of 29.3% and showed desired sieving characteristics for other solutes including middle molecules. Moreover, the membrane exhibited creatinine and urea uptake recoveries of 98.8 and 81.2%, respectively. The combined action of PMMA and AC in the PSf DLHF membrane has made the removal of multiple uremic toxins possible during dialysate regeneration.

Following the success of combining adsorption and membrane filtration for dialysate regeneration, there were other researchers started to investigate the potential of MMM in removing a wide range of uremic toxins from dialysate. Geremia *et al.* [21] and De Pascale *et al.* [22] practised the similar concept but using the SLHF MMM, and they achieved the improved urea removal and the massive water permeability compared to the pristine polymeric membrane.

5.0 CONCLUSION

In a nutshell, DLHF membranes do bring some improvements to hemodialysis treatment in general compared to the SLHF membranes. In specific terms, the synergistic effect of adsorption and diffusion can clearly be observed on the removal of small molecular uremic toxins and the removal of protein-bound uremic toxins. Nevertheless, effort should be also made to promote the convective removal of middle molecules by increasing the flux of DLHF membranes. Based on the research outcomes and the trends, it is expected that the number of works and publications on DLHF membranes will become higher not only for hemodialysis but also for hemodialysis-related applications such as dialysate regeneration.

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