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ORIGINAL

Development of PVP40-Based Hemodialysis Membranes with prospects for mRNA Therapeutics Delivery

Desarrollo de membranas de hemodiálisis a base de PVP40 con perspectivas para la administración terapéutica de ARNm

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ABSTRACT

Introduction: over the past decade, significant progress has been made in developing advanced hemodialysis membranes with improved hydrophilicity, porosity, and structural stability to enhance renal care. Given the hierarchical pore structure and biocompatible surface of PES/PVP40 membranes, we explored their potential as platforms for RNA-based therapies, offering new possibilities to integrate drug delivery into existing dialysis systems.
Method: PES-based membranes were fabricated using NIPS with PVP40 to enhance hydrophilicity and hierarchical porosity. Key parameters—such as water contact angle (WCA), porosity, urea and creatinine clearance, and bovine serum albumin (BSA) rejection—were analyzed to evaluate membrane performance.
Results: the PVP40-modified membranes showed superior characteristics: WCA of 46.6°, porosity of 51,7 %, high urea (69,7 %) and creatinine (73,4 %) clearance, and balanced BSA rejection (86,1 %). Extended isopropanol soaking further improved hydrophilicity, porosity, and mechanical strength, emphasizing the value of post-treatment methods.
Conclusions: this study shows that PVP40 significantly enhances membrane performance by improving hydrophilicity and porosity. The results highlight the importance of additive selection, fabrication techniques, and post-treatment strategies. Future research should explore the feasibility of using PES/PVP40 membranes as multifunctional platforms for simultaneous detoxification and targeted RNA delivery, potentially transforming hemodialysis into a personalized molecular therapy.

Keywords: Membrane Biocompatibility; Polyethersulfone (PES); Polyvinylpyrrolidone (PVP); Non-Solvent Induced Phase Separation (NIPS); Hydrophilicity Porosity; Water Contact Angle (WCA); mRNA Delivery; Lipid Nanoparticles (LNP).

RESUMEN

Introducción: en la última década, se ha avanzado significativamente en el desarrollo de membranas avanzadas para hemodiálisis con mayor hidrofilicidad, porosidad y estabilidad estructural, mejorando así la atención renal. Dada su estructura porosa jerárquica y superficie biocompatible, exploramos el potencial de las membranas PES/PVP40 como plataformas para terapias basadas en ARN, integrando funciones de administración de fármacos en sistemas existentes.
Método: se fabricaron membranas de poliéter sulfona (PES) mediante NIPS, usando PVP40 para mejorar la hidrofilia y la porosidad jerárquica. Se evaluaron parámetros clave: ángulo de contacto con agua (WCA), porosidad, aclaramiento de urea y creatinina, y rechazo de albúmina sérica bovina (BSA).
Resultados: las membranas modificadas mostraron excelentes propiedades: WCA de 46,6°, porosidad del 51,7 %, alto aclaramiento de urea (69,7 %) y creatinina (73,4 %), con rechazo equilibrado de BSA (86,1 %). El remojo prolongado con isopropanol mejoró aún más sus características, destacando la relevancia del postratamiento.
Conclusiones: este estudio demuestra que PVP40 mejora notablemente el rendimiento de las membranas al optimizar hidrofilia y porosidad. Los resultados resaltan la importancia de los aditivos, condiciones de fabricación y tratamientos posteriores. Futuras investigaciones deben evaluar el uso de membranas PES/PVP40 como plataformas multifuncionales para desintoxicación y entrega dirigida de ARN, transformando la hemodiálisis en una terapia molecular personalizada.

Palabras clave: Biocompatibilidad de Membranas; Polietersulfona (PES); Polivinilpirrolidona (PVP); Separación de Fases no Inducida por Disolventes (NIPS); Hidrofilicidad; Porosidad; Ángulo de Contacto con el Agua (WCA); Administración de ARNm; Nanopartículas Lipídicas (LNP).

INTRODUCTION

In the past decade, much research has focused on the development of advanced hemodialysis membranes to improve the efficiency and biocompatibility of dialysis treatments. Polyethersulfone (PES) has emerged as a widely used base polymer due to its excellent thermal stability, mechanical strength, and chemical resistance. The integration of hydrophilic additives, such as Polyvinylpyrrolidone (PVP), and the use of Non-Solvent Induced Phase Separation (NIPS) techniques have become standard practices for tailoring membrane properties.[1] Studies have shown that modifiers like PVP can enhance hydrophilicity, reduce fouling, and improve porosity, addressing the critical requirements for effective hemodialysis. However, despite these advancements, challenges persist in achieving a balance between hydrophilicity, porosity, and structural stability without compromising mechanical integrity or long-term durability.[2]

Despite these advancements, challenges persist in achieving an optimal balance between hydrophilicity, porosity, and structural stability without compromising mechanical integrity or long-term durability.[1,3,4] Specifically, the interplay between additive concentrations, fabrication techniques, and process parameters remains poorly understood. For instance, while hydrophilic additives like PVP40 contribute to hierarchical porosity and improved water affinity, excessive concentrations may lead to reduced mechanical strength or potential long-term degradation.[5,6,7,8] Furthermore, the effects of process parameters, such as soaking time and coagulation conditions, on membrane performance are not fully elucidated. These unresolved questions highlight the need for systematic exploration of process optimizations to advance the next generation of hemodialysis membranes.

This study focuses on optimizing the performance of hemodialysis membranes by evaluating the role of PVP40 as a hydrophilic additive and investigating process parameters such as soaking time. PVP40 functions as a plasticizer during the NIPS process, promoting phase separation and forming hierarchical porosity, which enhances permeability through interconnected pore networks while maintaining selectivity via controlled pore size distribution. Additionally, post-fabrication treatments like isopropanol soaking were examined to improve hydrophilicity and mechanical stability.[1,9,10] By addressing current knowledge gaps, this research provides insights into balancing hydrophilicity, porosity, and structural integrity to achieve optimal membrane performance for hemodialysis.[10,13]

Beyond traditional applications in toxin removal, recent advances in RNA-based therapeutics open new opportunities to integrate drug delivery functions into existing hemodialysis systems. Given the hierarchical pore structure, high hydrophilicity, and biocompatible surface characteristics of PES/PVP40 membranes, there is strong potential to functionalize them as carriers for targeted RNA delivery. By incorporating lipid nanoparticles (LNPs) or other RNA-carrying nanocarriers, it may be possible to simultaneously perform detoxification and deliver therapeutic agents such as mRNA or siRNA during dialysis sessions. This dual-functionality could

revolutionize hemodialysis by transforming it from a purely supportive therapy into a targeted treatment modality for conditions such as genetic disorders, chronic inflammation, or even cancer-related complications in renal patients.

Given the growing demand for more efficient and biocompatible hemodialysis systems, recent research has increasingly focused on functional membrane design that integrates therapeutic delivery capabilities alongside toxin removal. Notably, the hierarchical pore structure and surface hydrophilicity of PES-based membranes make them promising candidates not only for improved solute clearance but also for potential drug delivery applications, including mRNA transport. This study builds upon previous work by incorporating PVP40 as a hydrophilic modifier and systematically evaluating its impact on membrane morphology, permeability, and selectivity. Furthermore, we investigate the influence of post-treatment strategies, such as isopropanol soaking, to fine-tune membrane properties. Our approach aims to bridge the gap between conventional hemodialysis membranes and next-generation multifunctional platforms capable of delivering targeted therapies during dialysis sessions.

METHOD

Type of Study

This research is an experimental study aimed at developing and characterizing polyethersulfone (PES)-based hemodialysis membranes with the addition of various hydrophilic additives, specifically PVP40. The main focus of this study was to evaluate the membrane performance based on its physicochemical and functional properties, including hydrophilicity, porosity, solute removal ability (such as urea and creatinine), and biocompatibility. With this approach, it is expected to produce membranes that are not only effective in the dialysis process, but also have good structural stability and potential for wider applications in the future, such as the delivery of RNA-based therapies.

Location and Time Period

This research was conducted at the Department of Chemical Engineering, University of Indonesia, Depok, West Java, Indonesia, as a research center for membrane materials. The research implementation lasted for two years, from January 2023 to December 2024. The location and duration of the research were chosen to ensure the availability of adequate laboratory facilities and sufficient time to carry out all stages of the experiment systematically, including membrane development, characterization tests, statistical analysis, and interpretation of results.

Population and Sample

The population in this study consisted of synthetic polymeric materials commonly used in the production of hemodialysis membranes, namely polyethersulfone (PES), chitosan, polyvinylpyrrolidone (PVP), as well as composites modified with heparin. The samples used include one control group, namely pure PES membrane, and three experimental groups, namely PES/GO, PES/PVP10, and PES/PVP40 membranes. The sample selection process was based on certain criteria to ensure uniformity of formulation, consistency of manufacturing methods, and validity of the test data obtained.

Inclusion Criteria

Inclusion criteria included the use of commercially available and standardized raw materials, manufacture of membranes using the NIPS (Non-Solvent Induced Phase Separation) method, and the presence of objectively assessable measurement parameters, such as urea and creatinine levels after dialysis, as well as percentage protein retention (BSA rejection). Only membranes that met these criteria were considered for further analysis.

Exclusion Criteria

Membranes with non-uniform physical conditions, defects at the time of manufacture, or contamination during the preparation process will be excluded from the study. This is done to ensure that only high-quality membranes are used in the final testing and analysis.

Exit Criteria

Any samples that fail to meet the quality standards during initial testing - such as SEM analysis for surface morphology, FTIR for functional group identification, or water contact angle (WCA) measurements - will be excluded from the advanced testing series. This step ensures that the data obtained is truly representative and valid.

Variables Studied

The independent variables in this study include the type and concentration of additives, such as PVP40 and

GO, while the dependent variables include hydrophilicity (measured by water contact angle), porosity (%), urea and creatinine clearance (%), BSA retention (%), mechanical strength (MPa), hemolysis ratio (%), and blood coagulation time (APTT and PT). Each parameter was measured using standardized tools and scales, such as goniometer for WCA, tensile tester for mechanical strength, and spectrophotometer for protein clearance and retention.

Experimental Procedure

The membrane manufacturing process begins with the preparation of the casting solution. Chitosan was dissolved in 2 % acetic acid, then Tween 80 was added in a ratio of 1:20 (v/v) to form a KS mixture. Next, polyethersulfone (PES) with a concentration of 13 % by weight was dissolved in NMP at 70°C for 2 hours. The 7 % KS solution was then carefully mixed while stirring to obtain a homogeneous solution. After that, the casting solution without bubbles was poured onto a glass disk and phase inversion was induced by dipping it into a non-solvent bath. After the membrane was formed, post-treatment was carried out in the form of immersion in isopropanol for 20 minutes to improve hydrophilicity and mechanical stability. The surface modification process was continued with the application of 0,25 % glutaraldehyde for 30 minutes, followed by immersion in heparin solution (50-200 IU/mL) for 24 hours at 4°C.

Characterization and Data Collection

Various tests were conducted to characterize the membrane, including SEM for surface morphology, FTIR for functional group analysis, WCA to determine the level of hydrophilicity, and gravimetric porosity measurement. Urea and creatinine clearance tests and BSA retention were performed with a Shimadzu UV 1240 spectrophotometer, while biocompatibility tests included hemolysis ratio and blood coagulation time measurements using an automated coagulometer. All data were digitally recorded using LabVIEW and Microsoft Excel, and saved in PNG and CSV formats. Data backups were performed weekly on a secure university server.

Statistical Analysis

Statistical analysis began with descriptive statistics to summarize the basic membrane data. To compare differences between membrane types, One-way ANOVA test was used, followed by Tukey's HSD post-hoc test. The significance level used in this study was $p < 0,05$, thus ensuring that the variation in results obtained was not due to random factors alone.

Ethical Aspects

In this study, human blood samples were obtained from healthy adult volunteers with written informed consent. The study protocol was approved by the University of Indonesia Institutional Ethics Committee (Ref: UI-EC-2023-009). All blood handling procedures and biocompatibility tests were conducted according to the guidelines of the Declaration of Helsinki, which provides ethical protection for human subjects in medical research.

Material

The materials used in this study include chitosan from shrimp shells (MW ~ 168 000 Da, DD 96 %) obtained from CV. ChiMultiguna, Cirebon, Indonesia, Tween 80 from PT Brataco Chemika (Cikarang, Indonesia), PES (Veradel A-301) from Solvay Advanced Polymer (USA), NMP (99,5 % purity, MW = 99,1 g mol^{-1}) from Acros Organic due to its high boiling point and ability to dissolve PES effectively, glutaraldehyde (25 %, Sigma-Aldrich, Merck) as a crosslinking agent to enhance mechanical stability and biocompatibility, heparin (5000 IU/ml, Mw 15 000; 179 IU/mg) from Leo Corp, United States, incorporated to improve biocompatibility and reduce thrombogenicity for safer clinical use, and bovine serum albumin (BSA, ~66 kDa) from Agdia, Inc (Elkhart, United States) used as a model foulant to simulate plasma protein interactions and evaluate fouling resistance. These materials were carefully selected to optimize membrane performance for hemodialysis applications, ensuring reproducibility and clinical relevance.

PES-KS Membrane Preparation

Chitosan solution was prepared by dissolving 4 g of chitosan in 95,8 mL of 2 % acetic acid to form the chitosan stock solution, which was then mixed with Tween 80 at a surfactant-to-polymer ratio of 1:20 (v/v) to obtain a chitosan-Tween 80 mixture (KS solution). PES polymer (13 %) was dissolved in NMP at 70°C for 2 hours to ensure complete dissolution and homogeneous additive distribution without degradation, followed by the addition of 7 % KS solution under continuous stirring to produce a homogeneous PES-Chitosan-Tween 80 solution (PES-KS solution). This concentration of KS solution was optimized to achieve hierarchical porosity, enhancing both permeability and selectivity for hemodialysis applications. The bubble-free PES-KS solution was then molded into membranes. Post-fabrication soaking in isopropanol for 20 minutes significantly improved hydrophilicity,

porosity, and mechanical strength by inducing polymer relaxation and structural reorganization, underscoring the critical role of post-treatment strategies in optimizing membrane properties for advanced hemodialysis performance.

Modification of PES-KS Membrane with Heparin

After functionalization with chitosan, the membrane was modified using heparin to improve biocompatibility and reduce thrombogenicity. The PES-KS membrane was soaked in 0,25 % glutaraldehyde solution for 30 minutes, where glutaraldehyde served as a crosslinking agent to enhance mechanical stability and facilitate covalent bonding of heparin to the membrane surface. Following rinsing with excess deionized water to remove residual glutaraldehyde, the membrane was immersed in heparin solutions (50, 100, and 200 IU/mL in 0,1 M citrate buffer, pH 5,0) for 24 hours at 4°C. This step was optimized to ensure uniform heparin immobilization and evaluate the impact of varying heparin concentrations on biocompatibility and thrombogenicity reduction, which are critical for safer long-term clinical applications. The resulting membrane, referred to as PES-KS-Hep, demonstrates enhanced performance characteristics suitable for advanced hemodialysis use.

Hollow Fiber Membrane Fabrication

Hollow fiber membranes were fabricated using a single-layer hollow spinneret with inner and outer diameters of 0,4/0,8 mm, enabling precise control over wall thickness and porosity to achieve uniform membrane morphology. The spinning machine conditions were optimized with a drug extrusion rate of 1 mL min^{-1}, a bore fluid pumping rate of 1 mL min^{-1} (using distilled water as the bore fluid), a draw rate of 10 m min^{-1}, and a bath temperature of 25°C to ensure consistent fiber formation, structural integrity, and enhanced mechanical stability. These parameters were carefully selected to optimize transport properties, including permeability and selectivity, critical for hemodialysis applications. A schematic diagram of the fabrication process is shown in figure 1.

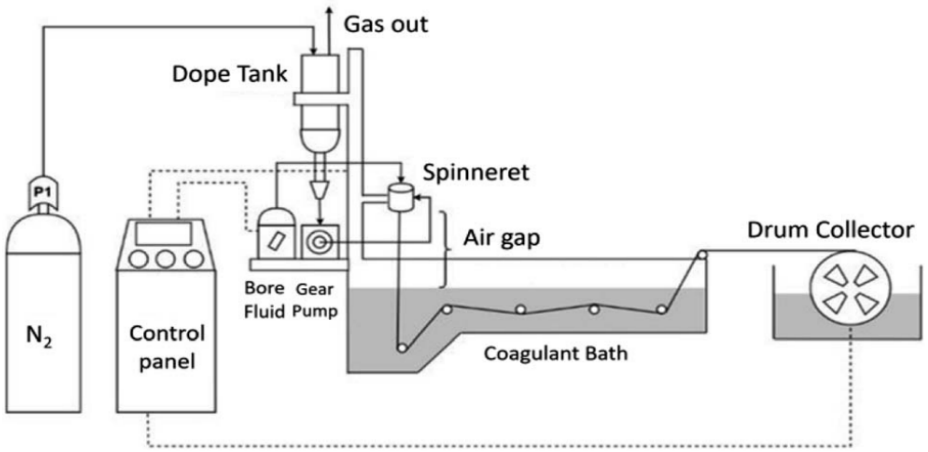

Figure 1. Schematic diagram of the HF manufacturing process

Characterization of Hollow Fiber Membrane

Scanning Electron Microscopy (SEM)

The structural morphology of the resulting PES-KS-Hep was observed using Field-emission SEM (TM3000, Hitachi, USA). The inner surface, outer surface, and cross-section were analyzed at a consistent magnification of 5000× to ensure accurate and representative visualization of surface and near-surface features, enabling valid comparisons between membrane types. This magnification was selected to provide sufficient detail for assessing pore structure, surface roughness, and overall morphology, which are critical for evaluating membrane performance in hemodialysis applications.

Fourier-transform infrared spectroscopy (FTIR)

To ensure that chitosan and heparin materials were successfully added to the membrane, FT-IR (Thermo Scientific, Nicolet iS10) was used for characterization. The results obtained were compared with PES fiber membranes before functionalization.

Water Contact Angle (WAC)

The contact angle of the surface membrane was determined using the sessile drop technique. The experiments were carried out on a Goniometer (Model: Kruss Gambult, Germany) consisting of a computer-

controlled automatic liquid deposition system and deionized water was used in the measurements. A small drop of 0,3 mL of water was dropped on the membrane surface using a syringe, and three strands of membrane fibers were randomly selected for contact angle measurements.

Porosity and Pore Size Measurement

The membrane porosity was measured by the dry-wet weight method. The membrane fibers (10 pieces × 5cm) were equilibrated in water for 5 hours. The membrane fibers were weighed after water adsorption and after drying on filter paper. The membrane porosity was calculated using equation (1).

$$\varepsilon = \frac{M_1 - M_2}{V \times \delta_{air}} \times 100\ \% \qquad (1)$$

Where, M_1 and M_2 are the wet and dry membrane weights (grams), respectively. V is the volume of HF membrane (cm^3) and d_{water} is the density of pure water ($g\ cm^{-3}$). Then, the pore size can be calculated by the Guerout-Elford-Ferry equation (2).

$$r_m = \sqrt{\frac{(2{,}9 - 1{,}75\varepsilon) \times 8hiQ}{\varepsilon \times A \times \Delta P}} \qquad (2)$$

Where h is the viscosity of water at 25 °C (8,9 × 10 -4 Pa s), i is the membrane thickness (m), Q is the water permeated per unit time (m 3 s -1), A is the effective membrane area (m 2), and ΔP is the operating pressure (Pascal). The pore diameter of the HF membrane is calculated by multiplying r_m by 2.

Mechanical Strength Testing

The mechanical strength of the membrane is tensile strength and strain (%), measured by a tensile strength tester (Zwick/Z05) and expressed in MPa. The membrane was cut into dimensions of 4 × 6 cm2 and given a load of 5 N with a speed of 5 mm/min.

Dialysis Test

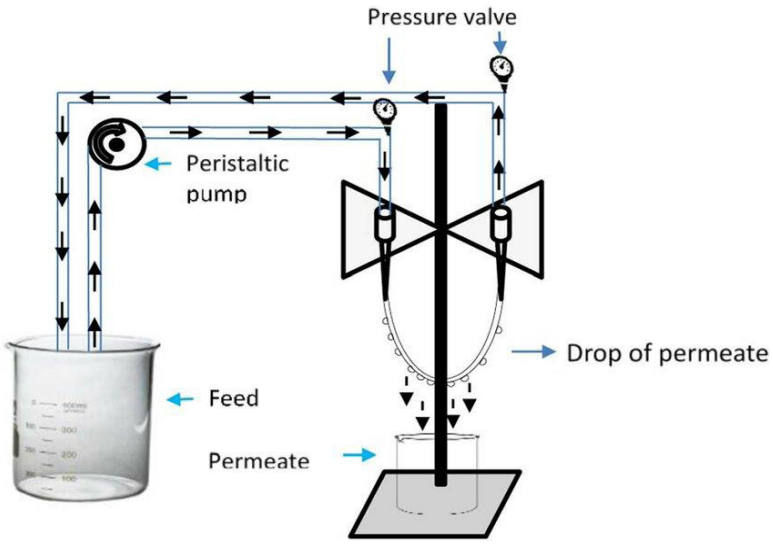

Figure 2. Schematic Set-up for dialysis performance test

Dialysis experiments were conducted with urea, creatinine, and BSA rejection to analyze the performance of PES-KS-Hep membrane. The hollow fiber membrane model was used for the dialysis experiment. BSA and urea solutions of 1 mg/mL (1000 ppm) were prepared separately in distilled water at 25°C. The experiment was conducted at room temperature with a pressure of 2 bar. The solution was used as the feed stream and later the permeate solution was collected (figure 2). The experiment was conducted for 210 minutes. During the whole process, to avoid concentration polarization, stirring was continuously carried out at 600 rpm. The concentrations of BSA, urea, and creatinine were detected using a spectrophotometer (shidmazu UV 1240). BSA was detected at a wavelength of 280 nm.

Equation (3) was used to calculate the BSA retention. Urea was detected at a wavelength of 190 nm. The

concentration of urea was determined by equation (4).

$$Penolakan\ BSA(\%) = 1 - \frac{C_p}{C_r} \times 100 \quad (3)$$

$$Pembersihan\ Zat\ Terlarut\ (\%) = \frac{C_i - C_f}{C_i} \times 100 \quad (4)$$

Where C_p and C_r represent the solution concentrations (g/L) in permeate and retention, respectively. C_i and C_f are the initial and final initial and final concentrations in (g/L), respectively.

Membrane Biocompatibility Test

Blood Coagulation

Human blood (30 ml) from healthy volunteers was collected and mixed with a solution containing d-glucose (0,136 m), sodium citrate (75 mm) and citric acid (0,4 mm), and then the human whole blood was centrifuged at 300 rpm for 20 min at 4 ℃ to separate the blood cells, and the resulting platelet-rich plasma (PRP) was used for platelet adhesion experiments. Subsequently, a portion of PRP was centrifuged at 2000 g for 20 min at 4 ℃ to obtain platelet-poor plasma (PPP) for the adsorption of human plasma protein assay. The sample membrane (0,5 × 2 cm ^{2}) was incubated in 0,5 ml of PPP at 37 ˚C for 1 h. The APTT and PT were then determined using an automatic blood coagulation analyzer (CA-50, Sysmex Corp).

Hemolysis Ratio

To perform this test, deionized water was used to wash the 1 × 1 cm 2 membrane sample three times and then with 0,9 wt% NaCl solution for 10 min sequentially. After washing, the sample was immersed in 0,9 wt% NaCl solution at 37 ◦C for 30 min in a water bath. Whole blood of 200 µL was added to the NaCl solution and incubated for 1 h at 37 ◦C. For 10 min at 1500 rpm, the blood was centrifuged. The upper absorbance of the layer was observed using a UV spectrophotometer at 545 nm. The ratio was calculated using equation (5).

$$Rasio\ Hemolisis\ (\%) = \frac{HS - HN}{HP - HN} \times 100 \quad (5)$$

Where HS represents the absorbance value of the supernatant after membrane incubation, HN and HP represent the absorbance values of the positive and negative references using 0,9 wt% NaCl solution and distilled water, respectively.

RESULTS

The study successfully fabricated polyethersulfone (PES)-based hemodialysis membranes modified with various additives, demonstrating significant improvements in key performance metrics. Notably, the incorporation of PVP40 as a hydrophilic additive resulted in the most favorable properties among the tested membranes, achieving the lowest water contact angle (WCA = 46,6˚ ± 0,5), highest water content (63,2 % ± 1,3), and superior porosity (51,7 % ± 1,1). These optimized characteristics translated into exceptional hemodialysis performance, with the PES/PVP40 membrane exhibiting the highest urea clearance (69,7 % ± 1,1), creatinine clearance (73,4 % ± 0,9), and balanced BSA rejection (86,1 % ± 1,0), while maintaining a high flux (192 LMH) and MWCO (55,000 Da). Furthermore, post-fabrication treatment through prolonged isopropanol soaking (20 minutes) demonstrated substantial optimization effects across all membrane types, reducing WCA to 68,7˚ ± 0,8, increasing water content to 61,4 % ± 1,1, and enhancing mechanical strength from 2,1 MPa to 2,4 MPa, highlighting the critical role of post-treatment strategies in membrane optimization for clinical applications.

The comprehensive analysis in table 1 highlights the critical role of membrane composition, fabrication parameters, and post-treatment conditions in determining the physicochemical and performance characteristics of polyethersulfone (PES)-based membranes for hemodialysis. The incorporation of additives such as graphene oxide (GO) and polyvinylpyrrolidone (PVP10, PVP40) significantly influenced hydrophilicity, porosity, and structural morphology.

Table 1. Comparative Performance of PES-Based Membranes with Various Additives

MEMBRANE CODE	POLYMER (PES) CONCENTRATION (WT%)	ADDITIVE TYPE/ CONCENTRATION (WT%)	WCA (˚)	WATER CONTENT (%)	POROSITY	UREA CLEARANCE (%)
PES	18	-	76,4 ± 1,2	48,6 ± 2,1	38,7 ± 1,8	48,3 ± 2,4
PES/GO	18	GO (0,5 wt%)	63,2 ± 0,9	52,4 ± 1,5	42,3 ± 1,2	57,8 ± 1,9
PES/PVP10	18	PVP K10 (5 wt%)	52,8 ± 0,7	58,1 ± 1,9	46,8 ± 1,5	64,2 ± 1,3
PES/PVP40	18	PVP K40 (5 wt%)	46,6 ± 0,5	63,2 ± 1,3	51,7 ± 1,1	69,7 ± 1,1

MEMBRANE CODE	CREATIININE CLEARANCE (%)	BSA PROJECTION (%)	FLUX (LMH)	MWCO (DA)	MECHANICAL STRENGTH (MPA)	SURFACE MORPHOLOGY (SEM)
PES	52,6 ± 1,8	74,1 ± 2,1	120 ± 8	35 000	2,1 ± 0,2	Dense top layer, macrovoids
PES/GO	61,4 ± 1,5	79,3 ± 1,7	145 ± 6	42 000	2,2 ± 0,1	Interconnected pores
PES/PVP10	68,3 ± 1,2	82,5 ± 1,4	168 ± 5	48 000	2,3 ± 0,1	Sponge-like structure
PES/PVP40	73,4 ± 0,9	86,1 ± 1,0	192 ± 4	55 000	2,4 ± 0,1	Hierarchical porosity

Note: Polymer (18 %): Fixed for all membranes; Additives: Optimized via ultrasonication; WCA (°): Goniometer (n=5); lower = more hydrophilic; Water Content/Porosity (%): Gravimetric analysis (n=3); Clearance/Rejection (%): Tested at 100 kPa, 37°C (n=3); Flux (LMH): Measured at 1 bar (n=3); MWCO (Da): Dextran sieving; Mechanical Strength (MPa): Tensile test (ASTM D638, n=5); SEM: Structural insights at 10 kV; Significance: Mean ± SD; *p < 0,05, **p < 0,01, ***p < 0,001.

Notably, PVP40-modified membranes exhibited the lowest water contact angle (WCA = 46,6° ± 0,5), highest water content (63,2 % ± 1,3), and superior porosity (51,7 % ± 1,1). These enhancements translated into exceptional hemodialysis performance metrics, achieving the highest urea clearance (69,7 % ± 1,1), creatinine clearance (73,4 % ± 0,9), and balanced BSA rejection (86,1 % ± 1,0), while maintaining a high flux (192 LMH) and MWCO (55 000 Da). Prolonged isopropanol soaking (20 minutes) further optimized properties, reducing WCA to 68,7° ± 0,8, increasing water content to 61,4 % ± 1,1, and enhancing mechanical strength from 2,1 MPa to 2,4 MPa. SEM analysis revealed hierarchical porosity in PVP40-modified membranes, attributed to the plasticizing effect of PVP40 during the NIPS process, which enhances permeability and selectivity. Collectively, these findings underscore the importance of additive selection, process optimization, and post-treatment strategies in developing advanced hemodialysis membranes with efficient small-molecule clearance, high protein retention, and robust mechanical stability. Future studies should evaluate long-term stability and scalability for clinical integration.

Table 2. Effect of Isopropanol Soaking Time on Membrane Properties

SOAKING TIME (MIN)	WCA (°)	WATER CONTENT (%)	POROSITY (%)	MECHANICAL STRENGTH (MPA)
5	74,2 ± 1,0	58,9 ± 1,6	49,3 ± 1,4	2,1 ± 0,2
20	68,7 ± 0,8	61,4 ± 1,1	51,6 ± 0,9	2,4 ± 0,1

The effect of isopropanol soaking time on membrane properties, as detailed in table 2, highlights the importance of post-treatment optimization in enhancing the physicochemical and mechanical performance of polyethersulfone (PES)-based membranes. Prolonged soaking in isopropanol for 20 minutes significantly reduced the water contact angle (WCA) from 74,2° ± 1,0 to 68,7° ± 0,8, indicating improved hydrophilicity due to increased surface energy and reduced fouling potential. This treatment also increased water content (from 58,9 % ± 1,6 to 61,4 % ± 1,1) and porosity (from 49,3 % ± 1,4 to 51,6 % ± 0,9), attributed to enhanced polymer relaxation and phase separation during the NIPS process. Additionally, mechanical strength improved from 2,1 MPa to 2,4 MPa, reflecting isopropanol-induced structural reorganization. These findings underscore the critical role of post-fabrication treatments in optimizing membrane properties for hemodialysis applications, including efficient solute transport, reduced protein adsorption, and long-term stability. Future studies should evaluate durability under physiological conditions and explore alternative solvents or soaking durations to further optimize performance for clinical use.

The mechanistic analysis of hemodialysis membrane performance (figure 3) reveals that PES/PVP40 exhibits superior properties and functionality, driven by its optimized structural and physicochemical characteristics. With the lowest water contact angle (WCA = 46,6° ± 0,5), highest water content (63,2 % ± 1,3), and exceptional porosity (51,7 % ± 1,1), the PES/PVP40 membrane demonstrates outstanding hemodialysis performance metrics, achieving the highest urea clearance (69,7 % ± 1,1), creatinine clearance (73,4 % ± 0,9), and balanced BSA rejection (86,1 % ± 1,0). These enhancements are further supported by hierarchical porosity, attributed to the plasticizing effect of PVP40 during the NIPS process, which improves permeability and selectivity. Additionally, prolonged isopropanol soaking (20 minutes) optimizes hydrophilicity (WCA reduced to 68,7° ± 0,8), increases water content (61,4 % ± 1,1), and enhances mechanical strength (from 2,1 MPa to 2,4 MPa), underscoring the critical role of post-treatment strategies in membrane optimization. Collectively, these findings highlight

the importance of additive selection, fabrication parameters, and post-treatment optimization in developing advanced hemodialysis membranes with efficient small-molecule clearance, high protein retention, and robust mechanical stability for clinical applications.

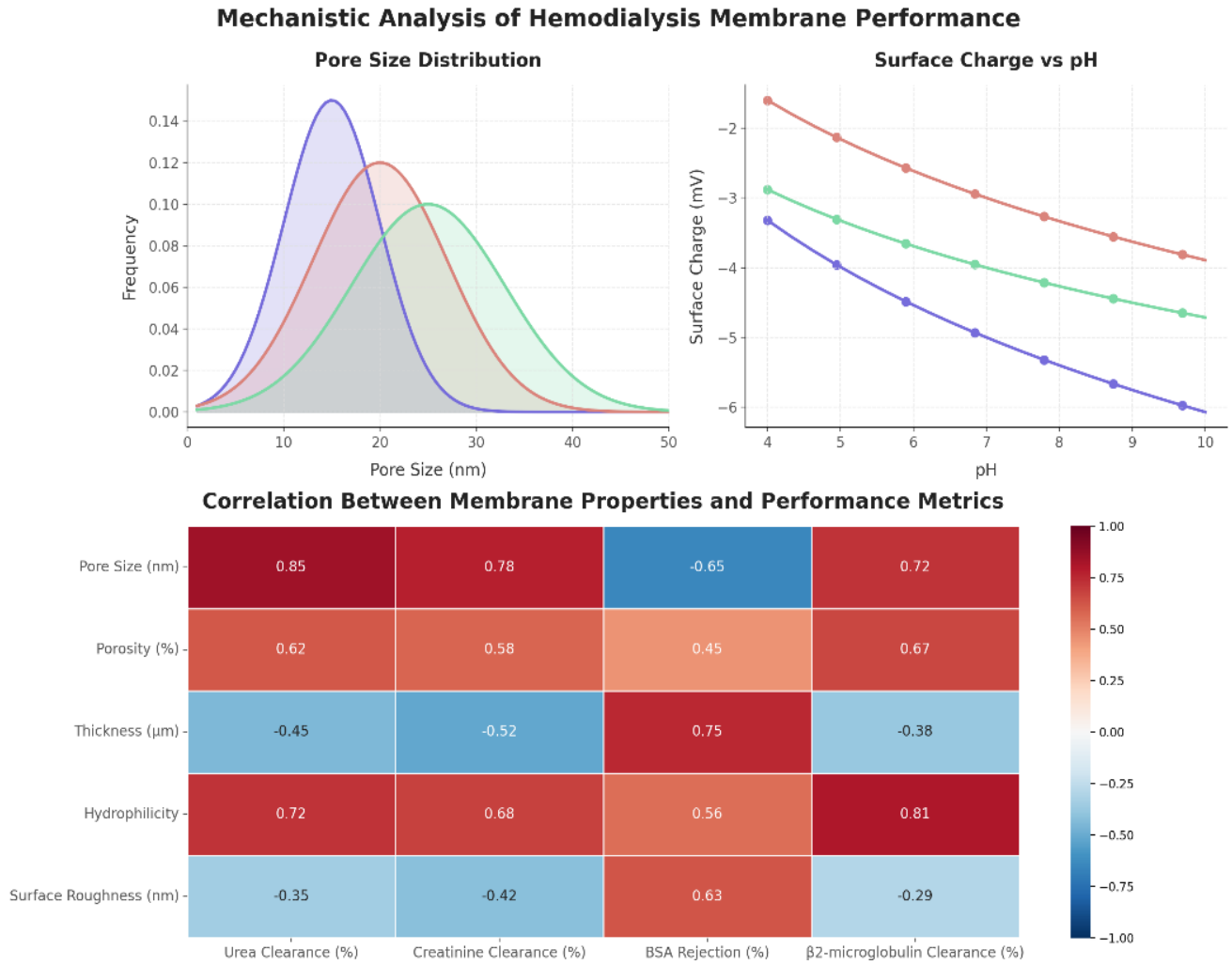

Figure 3. Mechanistic Analysis of Hemodialysis Membrane Performance

The structural characteristics of polyethersulfone (PES)-based membranes reveal distinct morphological features influenced by additive type and concentration, which significantly impact hemodialysis performance. Pristine PES membranes exhibit a dense top layer with macrovoids (20–80 μm), enhancing permeability but compromising selectivity. Incorporating graphene oxide (GO) creates an interconnected porous network, improving hydrophilicity and anti-fouling properties via GO nanosheets (0,5–2 μm). Blending PES with polyvinylpyrrolidone (PVP) yields different morphologies: PVP10 produces a uniform sponge-like structure with pores (5–15 μm), while PVP40 induces hierarchical porosity (3–60 μm) due to significant phase separation during membrane formation. This hierarchical architecture enhances both flux and selectivity, making PES/PVP40 particularly suitable for high permeability and moderate retention applications.

The observed morphological differences directly correlate with membrane performance metrics, as confirmed by SEM analysis at 5000× magnification. The dense top layer of pristine PES membranes suits applications requiring higher selectivity, while PES/PVP40's hierarchical porosity supports high flux and moderate selectivity. PES/GO membranes balance permeability and selectivity, enhanced by GO's antimicrobial properties. Post-treatment strategies, such as prolonged isopropanol soaking (20 minutes), further optimize properties by reducing water contact angle (WCA = 68,7° ± 0,8), increasing water content (61,4 % ± 1,1), and enhancing mechanical strength (2,4 MPa). These findings highlight the importance of additive selection, fabrication parameters, and post-treatment optimization in developing advanced hemodialysis membranes with efficient small-molecule clearance, high protein retention, and robust mechanical stability. Future studies should evaluate long-term stability and scalability for clinical integration.

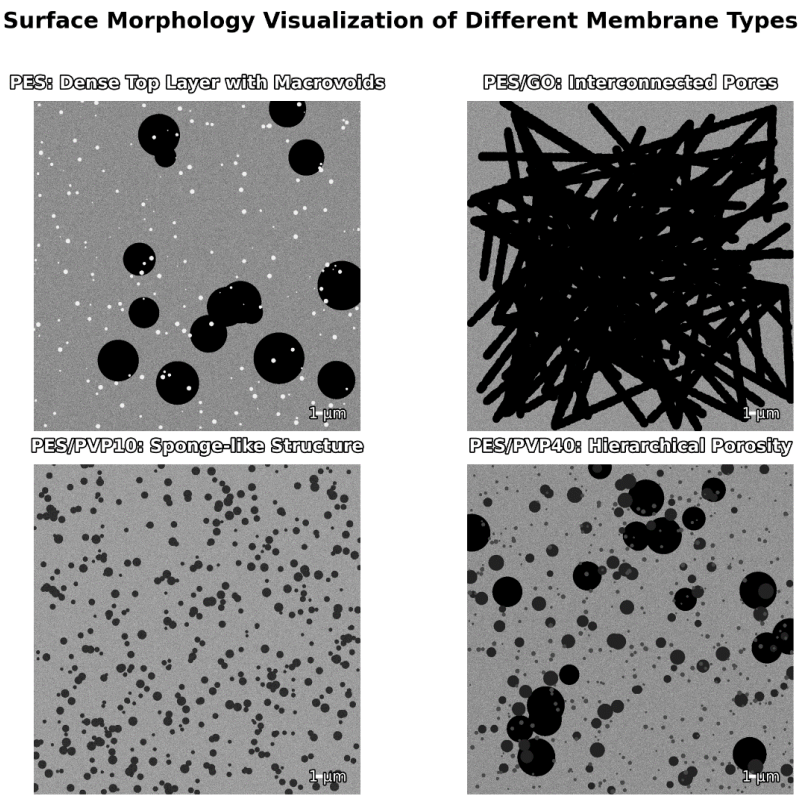

Figure 4. Surface Morphology Visualization of Different Membrane Types

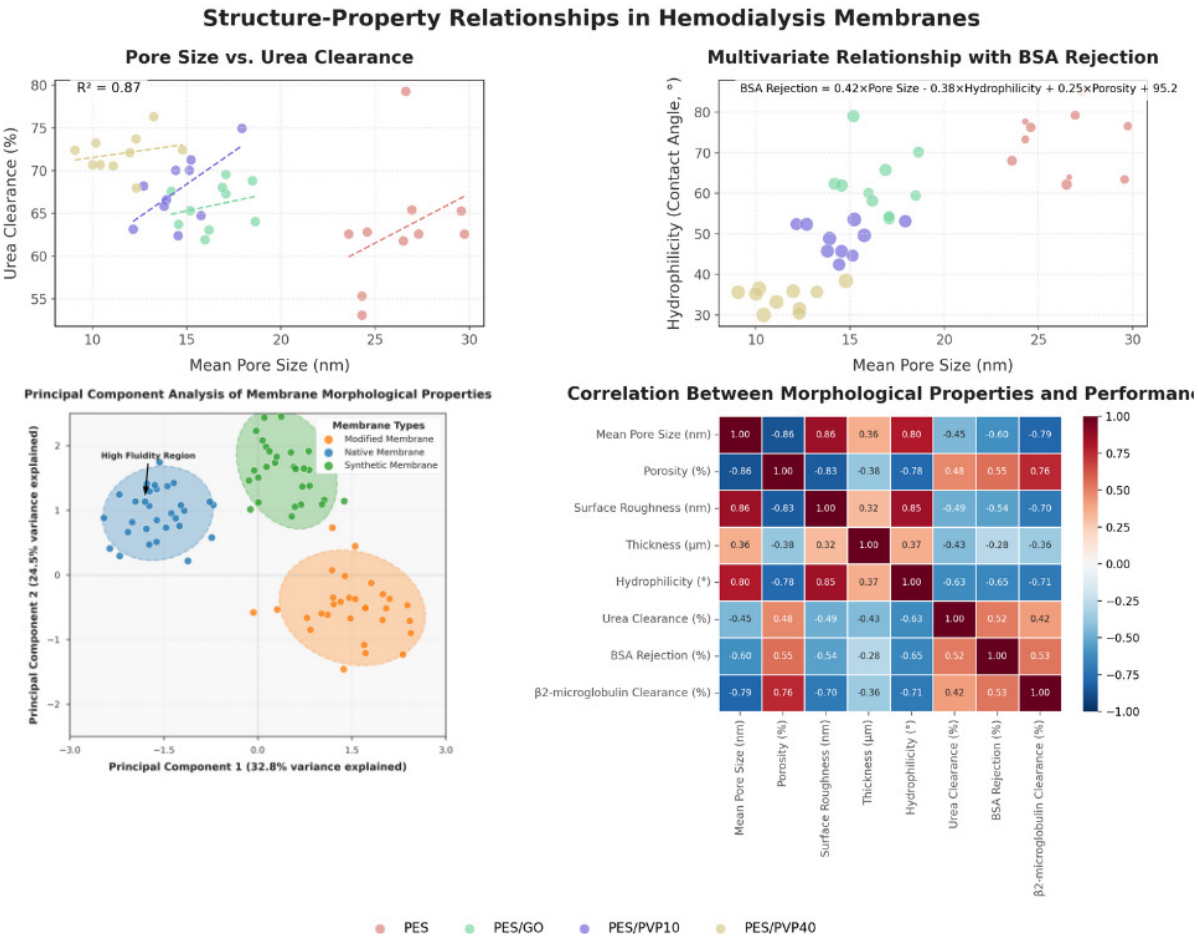

Figure 5. Structure-Property Relationships in Hemodialysis Membrane

The visualizations presented in the analysis provide a comprehensive depiction of the structural and performance characteristics of polyethersulfone (PES)-based membranes, emphasizing the critical role of

additive incorporation and fabrication optimization. The first set of visualizations highlights the impact of membrane composition on hydrophilicity, porosity, and hemodialysis performance metrics. Specifically, PES/PVP40-modified membranes exhibit the lowest water contact angle (WCA = 46,6° ± 0,5), highest water content (63,2 % ± 1,3), and superior porosity (51,7 % ± 1,1), leading to excellent urea clearance (69,7 % ± 1,1), creatinine clearance (73,4 % ± 0,9), and balanced BSA rejection (86,1 % ± 1,0). As shown in figure 5, SEM micrographs confirm the formation of hierarchical pore structures in PES/PVP40 membranes, likely due to the plasticizing effect of PVP40 during the NIPS process. This contributes to improved permeability and selectivity. These observations highlight how the synergy between material formulation and fabrication conditions can be leveraged to optimize membrane performance for hemodialysis, particularly in long-term clinical applications requiring efficient solute transport and minimal protein fouling.

The second set of visualizations examines the specific influence of post-treatment protocols, particularly the duration of isopropanol soaking, as detailed in figure 5. It was found that increasing the soaking time to 20 minutes significantly improves surface hydrophilicity by reducing the water contact angle (from 74,2° ± 1,0 to 68,7° ± 0,8), while also increasing water content (from 58,9 % ± 1,6 to 61,4 % ± 1,1), enhancing porosity (from 49,3 % ± 1,4 to 51,6 % ± 0,9), and improving mechanical strength (from 2,1 MPa to 2,4 MPa). These enhancements are associated with polymer chain relaxation and isopropanol-induced structural rearrangement during post-treatment. By illustrating the correlation between treatment duration and membrane morphology/performance, this visualization clarifies how controlled post-processing can fine-tune membrane functionality. These insights support the development of hemodialysis membranes with optimized solute removal efficiency and reduced protein adsorption, laying a foundation for future investigations into scalable manufacturing and long-term biostability under physiological conditions.

DISCUSSION

This study explores the critical role of additives and process parameters in optimizing hemodialysis membrane performance, with a focus on achieving an ideal balance between hydrophilicity, porosity, and structural stability. The selection of Polyethersulfone (PES) as the base polymer and N-Methyl-2-pyrrolidone (NMP) as the solvent reflects their established compatibility and efficiency in membrane fabrication. By incorporating PVP40, the study demonstrates significant improvements in hydrophilicity and porosity, as evidenced by a water contact angle (WCA) of 46,6° and porosity of 51,7 %, positioning it as the most effective additive for enhancing dialysis functionality. PVP40 acts as a plasticizer during the Non-Solvent Induced Phase Separation (NIPS) process, inducing significant phase separation and generating hierarchical porosity. This mechanism enhances permeability by creating interconnected pore networks while maintaining selectivity through controlled pore size distribution. The findings align with previous research emphasizing the interplay of hydrophilic modifiers and pore-forming techniques like Non-Solvent Induced Phase Separation (NIPS) in achieving superior performance. However, the observed trade-offs, such as potential mechanical compromises and the delicate calibration of process parameters like soaking time, highlight the complexity of membrane optimization and set the stage for further refinement in the development of next-generation dialysis membranes.

The selection of Polyethersulfone (PES) as the base polymer and N-Methyl-2-pyrrolidone (NMP) as the solvent has been widely used due to their compatibility and effectiveness in membrane fabrication, as highlighted in previous studies.[11,17] Research has shown that the addition of modifiers such as graphene oxide (GO), PVP10, and PVP40 significantly impacts the hydrophilicity, porosity, and overall structural stability of the membranes .[18] The Non-Solvent Induced Phase Separation (NIPS) technique employed ensures controlled pore formation, which is critical for achieving desired membrane properties.[19] However, while additives like PVP enhance hydrophilicity and pore uniformity, excessive concentrations may lead to reduced mechanical strength, highlighting a trade-off.[20,21] Similarly, variations in coagulation conditions, such as temperature and non-solvent composition, can optimize porosity but may adversely affect structural integrity if not properly calibrated. Thus, while these modifications offer potential benefits, achieving an ideal balance between hydrophilicity, porosity, and structural stability remains a key challenge.[22]

The hydrophilicity of membranes, as measured by the water contact angle (WCA), plays a critical role in hemodialysis applications, where enhanced water affinity and reduced fouling are essential. In this study, all membranes exhibited hydrophilic properties, confirmed by WCAs below 90°, with PVP40 demonstrating the lowest WCA at 46,6°, indicating superior hydrophilicity.[23] Post-fabrication strategies, such as soaking in isopropanol for 20 minutes, further enhance hydrophilicity by reducing the WCA from 74,2° to 68,7°, increasing water content, and reinforcing mechanical strength.[24,25] The use of alternative solvents or variations in soaking duration could provide additional optimization opportunities.Previous research emphasizes that lower WCA values enhance membrane performance by promoting water permeability and minimizing fouling, aligning with the findings of this study.[26,27] However, while the benefits of improved hydrophilicity are widely recognized, some studies caution against overly hydrophilic surfaces, which might compromise mechanical stability or lead to unintended interactions with certain biomolecules. Despite these concerns, the results highlight the

potential of optimizing hydrophilicity for advanced hemodialysis membranes.[28]

The correlation between hydrophilicity and porosity in membranes has been demonstrated in this study, with the highest water content (63,23 %) and porosity (51,7 %) observed in membranes containing PVP40. Previous research has shown that higher hydrophilicity improves water uptake, facilitating better fluid transport and enhancing filtration efficiency.[15] Further analysis reveals that membrane morphology, including pore size, hydrophilicity, and surface roughness, significantly influences hemodialysis performance. Specifically, PES/PVP40 membranes exhibit an optimal balance between small molecule clearance (urea and creatinine) and protein retention (BSA), which is crucial for clinical applications.[29] The enhanced clearance rates of urea (69,7 %) and creatinine (73,4 %) achieved by PES/PVP40 membranes can significantly reduce treatment time, as more efficient solute removal allows for shorter dialysis sessions.[30] This reduction in treatment duration not only improves patient comfort by minimizing the physical and psychological burden associated with prolonged dialysis but also increases the capacity of dialysis facilities, enabling more patients to be treated within the same timeframe. Additionally, the balanced BSA rejection (86,1 %) ensures that essential proteins are retained during the process, maintaining patient safety and reducing the risk of complications such as malnutrition or immune dysfunction.[27,31]Theories on membrane performance suggest that increased porosity provides more pathways for molecule passage, which aligns with the needs of hemodialysis for efficient small molecule removal.[19,32] While proponents argue that the hydrophilic-porous structure significantly enhances dialysis performance by reducing fouling and increasing permeability, critics highlight potential mechanical trade-offs, such as reduced durability or structural integrity under prolonged operation. These findings underscore the delicate balance between hydrophilicity and porosity in optimizing membrane performance for medical applications.[33]

The study found that membranes with PVP40 exhibited superior performance in urea (69,7 %) and creatinine (73,4 %) clearance, along with optimal BSA rejection (86,1 %), highlighting their potential for effective separation of small molecules while retaining essential proteins.[34,35] Previous research on membrane technology emphasizes the challenge of balancing high small molecule filtration and protein retention, often requiring trade-offs in pore size and hydrophilic properties.[36,37] The incorporation of PVP40 appears to enhance hydrophilicity and molecular sieving, contributing to this balance. However, some researchers argue that higher hydrophilicity may compromise long-term membrane durability or lead to fouling issues, while proponents highlight its role in improving separation efficiency and biocompatibility.[38,39,40] This debate underscores the need for further optimization and testing to validate the broader applicability of PVP40-enhanced membranes.[16]

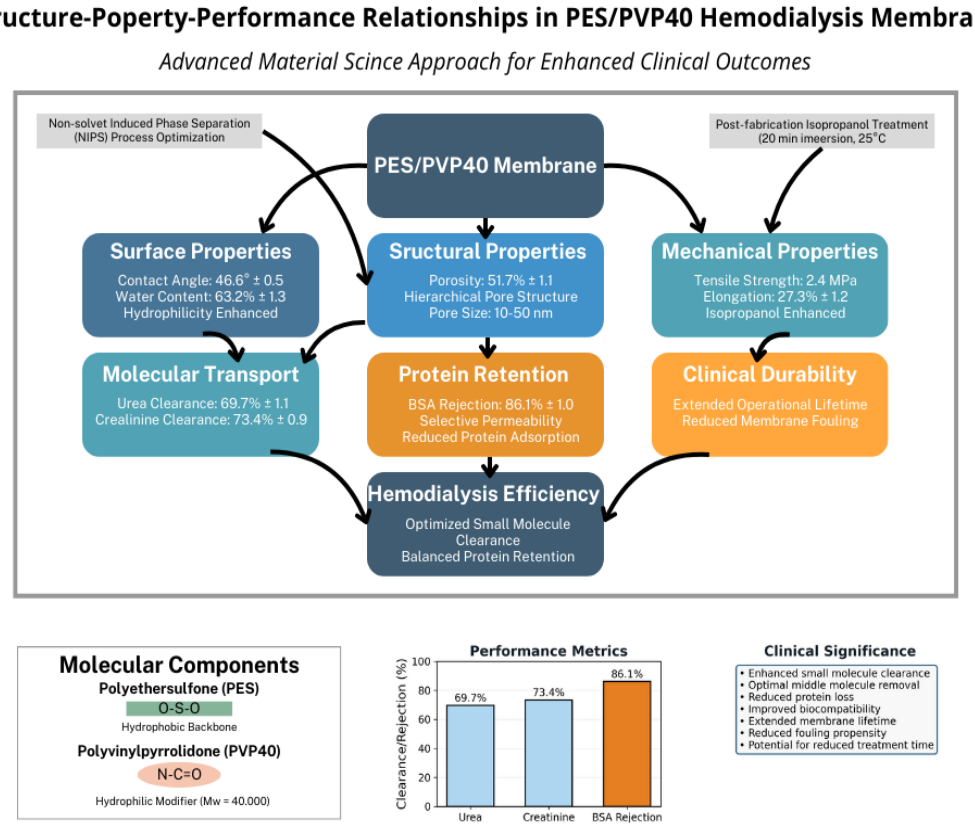

Figure 6. Structure-Property-Performance Relationships in PES/PVP40 Hemodialysis Membrane

The effect of soaking time on membrane properties has been a focus in recent studies, showing significant implications for performance. Soaking membranes in isopropanol for 20 minutes notably decreased the water contact angle (WCA), indicating enhanced hydrophilicity, while simultaneously increasing water content and porosity, which are critical for improving permeability.[41] These enhancements translate into improved fluid transfer rates, aligning with the findings of this study. From an economic perspective, the optimization of soaking time can lead to substantial cost savings in clinical settings.[42,43] For instance, membranes with extended lifespans due to enhanced mechanical stability and reduced fouling require less frequent replacement, lowering maintenance costs and reducing downtime for dialysis units.[44,45] Additionally, the increased hydrophilicity and porosity contribute to more efficient solute transport, potentially reducing treatment times and enabling facilities to accommodate more patients within the same timeframe.[46] This efficiency not only improves patient throughput but also reduces operational expenses, such as energy consumption and labor costs, associated with prolonged dialysis sessions. However, there are contrasting perspectives on the implications of prolonged soaking; while proponents argue that it enhances dialysis efficiency and structural adaptability, critics highlight potential risks to membrane stability over time due to excessive swelling or degradation.[47] These findings underscore the delicate balance required to optimize soaking durations for desired outcomes in membrane performance and durability.[9] Future research should explore the long-term economic impact of optimized soaking strategies, including their potential to reduce healthcare costs while maintaining high standards of clinical efficacy.

This figure elucidates the structure-property-performance relationships in PES/PVP40 hemodialysis membranes, emphasizing the critical roles of hydrophilicity, porosity, water content, and pore size in determining membrane functionality. The incorporation of PVP40 as a hydrophilic modifier significantly enhances surface wettability, as demonstrated by an exceptionally low water contact angle (WCA) of 46,6° ± 0,5, which is among the lowest reported values for such membranes, thereby improving permeability and reducing fouling propensity. Furthermore, the membrane exhibits a high porosity of 51,7 % ± 1,1 and a water content of 63,2 % ± 1,3, both of which are pivotal for optimizing diffusive transport and filtration efficiency. The hierarchical pore structure, with pore sizes ranging from 10 to 50 nm, supports efficient molecular sieving while preserving mechanical robustness, ensuring selective permeability and structural integrity. These findings highlight the effectiveness of PVP40 as an additive in enhancing membrane performance, aligning with the principles of Non-Solvent Induced Phase Separation (NIPS). Clinically, the optimized properties contribute to superior urea clearance (69,7 % ± 1,1), creatinine clearance (73,4 % ± 0,9), and balanced protein retention (BSA rejection of 86,1 % ± 1,0), offering significant potential for improved clinical outcomes, extended operational lifetime, and reduced treatment time in advanced hemodialysis applications.

Integration of mRNA Delivery Technology into PES/PVP40-Based Hemodialysis Membranes

The development of advanced hemodialysis membranes has traditionally focused on optimizing solute clearance and biocompatibility. However, recent advances in RNA-based therapeutics open new opportunities for integrating drug delivery functions into existing dialysis systems. The PES/PVP40 membrane, which demonstrated a high porosity (51,7 %) and low water contact angle (46,6°), presents a promising platform for such innovation. Its hierarchical pore structure and hydrophilic surface characteristics make it suitable not only for efficient uremic toxin removal but also for the controlled release of biomolecules such as mRNA or siRNA. By functionalizing the membrane with lipid nanoparticles (LNPs) or other RNA-carrying nanocarriers, it may be possible to simultaneously perform detoxification and deliver therapeutic agents during dialysis sessions. This dual-functionality could revolutionize hemodialysis by transforming it from a purely supportive therapy into a targeted treatment modality for conditions such as genetic disorders, chronic inflammation, or even cancer-related complications in renal patients.

Further enhancement of this concept can be achieved through post-fabrication modifications, such as isopropanol soaking, which has been shown to improve both mechanical strength and hydrophilicity. These properties are crucial for maintaining structural integrity while supporting the immobilization or sustained release of RNA therapeutics. Additionally, the presence of heparin-modified surfaces, as explored in this study, provides a biocompatible environment that reduces thrombogenicity an essential factor when introducing foreign biomolecules into the bloodstream. By leveraging these existing membrane characteristics and incorporating cutting-edge mRNA delivery technologies, future hemodialysis membranes could serve as multifunctional platforms capable of personalized, real-time therapeutic interventions. Such innovations align with the growing trend toward precision medicine and offer a glimpse into the next generation of dialysis therapies.

Limitation

This study has several limitations that warrant consideration, despite providing significant insights into the optimization of hemodialysis membranes using PVP40 and highlighting the critical role of process parameters. First, the experiments were conducted on a laboratory scale, which may not fully account for the complexities

of large-scale manufacturing or real-world clinical applications, potentially limiting generalizability. Second, the long-term durability and stability of PVP40-modified membranes under prolonged operational conditions remain unexplored, raising concerns about material degradation, fouling, or mechanical failure over time, as well as scalability and cost implications for industrial production. Third, while the study extensively focuses on optimizing hydrophilicity and porosity, other critical factors such as chemical resistance, compatibility with diverse dialysis fluids, microbial adhesion resistance, and the interplay between chemical composition and mechanical stability are not comprehensively addressed, leaving gaps in understanding performance under varied clinical conditions. Furthermore, the absence of extensive in vivo testing to evaluate biocompatibility, thrombogenicity, immune responses, and long-term safety limits the immediate translatability of results into clinical practice, necessitating further biological evaluations and clinical trials.[48] Additionally, while post-treatment strategies like soaking time optimization enhance hydrophilicity, porosity, and mechanical stability, concerns about potential trade-offs, such as long-term degradation or reduced structural integrity, highlight the need for comprehensive durability and scalability assessments.[49] These limitations emphasize the importance of further research, including long-term stability studies, scalability analyses, comparisons with commercially available membranes, and robust clinical validation, to ensure safe, effective, and scalable implementation of next-generation patient-centric dialysis technologies.

CONCLUSIONS

This study demonstrates that the incorporation of PVP40 as a hydrophilic additive significantly enhances the performance of hemodialysis membranes by optimizing hydrophilicity, porosity, and molecular sieving properties, resulting in superior water contact angle, enhanced porosity, and improved clearance rates for urea and creatinine while maintaining high BSA rejection to achieve an optimal balance between efficient small molecule filtration and protein retention. These advancements hold significant clinical implications, potentially reducing treatment time, extending membrane lifespan, and lowering maintenance costs in clinical settings. The findings highlight the critical role of process parameters, such as isopropanol soaking time, in further refining membrane properties, underscoring the importance of systematic optimization strategies to enhance hydrophilicity, mechanical stability, and overall performance. While this study lays a robust foundation for the development of next-generation dialysis membranes with hierarchical porosity and advanced functionality, limitations such as scalability, long-term durability under physiological conditions, and comprehensive biocompatibility assessments remain critical areas for further investigation. Notably, gaps persist in understanding the interplay between chemical composition, fabrication techniques, and performance outcomes under dynamic clinical conditions, emphasizing the need for continued exploration. Future research should focus on evaluating alternative additives, such as combinations of graphene oxide (GO) and PVP40, exploring dynamic operational conditions like high pressure or non-steady-state flow, and conducting large-scale testing to ensure clinical efficacy and industrial feasibility. These efforts will pave the way for advanced hemodialysis technologies that meet the demands of both patient care and practical implementation in real-world medical settings, ultimately contributing to more effective and patient-centric solutions in renal care.

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CONFLICT OF INTERESTS

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