New Membrane Technologies for Dialysis

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners. I understand that my thesis may be made electronically available to the public.

Statement of Contributions

I hereby declare that I have contributed to the majority of research work in this thesis wherein Chapters 4 and 5 include published articles.

My contributions to this thesis include design, development, characterization, testing and analysis of zeolite incorporated polymer membranes that can adsorb uremic toxins. Full citation of the articles along with the corresponding chapters is as follows:

Lu L, Samarasekera C., Yeow J.T. Creatinine adsorption capacity of electrospun polyacrylonitrile (PAN)-zeolite nanofiber membranes for potential artificial kidney applications. *Journal of Applied Polymer Science*. 2015. [**Chapter 4**]

Lu L., Chen C., Samarasekera C, Yeow J.T.W. Influence of zeolite shape and particle size on their capacity to adsorb uremic toxin as powders and as fillers in membranes. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*. 2016. [**Chapter 5**]

Abstract

Hemodialysis, developed in 1960s, has served as a treatment for patients with end stage renal disease. However, the 5 year mortality rate of hemodialysis patients is 65%. Research shows that some protein-bound toxins, which cannot to be cleared by hemodialysis, play an important role in mortality of hemodialysis patients. In order to improve the mortality rate of hemodialysis patients, we created a new type of hemodialysis membranes, which can remove more toxins than current hemodialysis membranes.

In this thesis, we first adopted electrospinning technology to synthesis hemodialysis membranes with adsorptive nanoparticles. Polyacrylonitrile-zeolite nanofiber composite membranes were fabricated and their ability to adsorb water soluble uremic toxins was tested. The results show that both the free zeolite powder and membranes with zeolite can adsorb creatinine at high level and fast speed. The creatinine adsorption level of 940-zeolite powders is 25423 μg g^{-1} in 625 μmol L^{-1} creatinine solution. 0.025 g of 940-zeolite powders can eliminate 91% of 2 μmol creatinine in 5 min.

In order to choose good zeolites, we also carried out experiments to study how their size and shape influence the creatinine uptake level. Spherical micro-particle 840, spherical nanoparticle P-87 and rod-like nanoparticle P-371 zeolites were tested. Experiments show that the zeolites have similar creatinine uptake ability as powders. However, they have significantly different creatinine uptake ability after being incorporated inside the membranes. Micro-particle and sphere-shaped particles perform better inside the membranes.

Although the membranes we fabricated through electrospinning can adsorb water soluble toxins, their pore size is too large for hemodialysis. In another part of the thesis, we used spin-coating technologies to synthesize polyethersulphone

zeolite composite membranes with suitable pore size. Experiments showed that these membranes can adsorb 4948 μg creatinine per g membranes. The effects of pH and salt on zeolite's adsorption and desorption of creatinine were also studied in order to infer the membrane's adsorption mechanism. We found that acidic environments enhance zeolite's creatinine adsorption while alkaline environments weaken it. The existence of various cations also decreases zeolite's creatinine adsorption.

Finally, we tested the adsorption of protein-bound toxin by our membranes. Studies have shown that these toxins are related to the progression of chronic kidney disease (CKD), and to the generation and aggravation of cardiovascular disease. Indoxyl sulfate, an important toxin in causing reno-cardiovascular syndromes, was chosen as a representative of protein-bound toxins. Experiments show that zeolite-PES membranes can adsorb 550 μg indoxyl sulfate per g membranes, and indicate that the adsorption mechanism is likely to be electrostatic attraction.

Acknowledgments

First, I would like to express my sincere thanks to my supervisor, Prof. John T.W. Yeow, who gave me the opportunity to embark on this Ph.D. journey. The academic freedom and amazing research opportunities you gave me have enabled me to try out new ideas without hesitation. Your support allowed me to try, fail and finally find a way for all the challenges I met in my research. Because of the freedom given to me on my project, I have learned how to do research independently and how to manage the whole project. My confidence and problem solving ability have also been strengthened.

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Lastly, but most importantly, I would like to thank my family for all their love and encouragement. To my parents, Junzhi Jiang and Jianxi Lu, who raised me to chase my dreams freely. My mother's weekly nagging, asking me to study harder and finish my Ph.D on time was the energy source I needed when my own energy was almost running out. To my siblings, Jie, Li, and Yong, who have always been very supportive on my pursuit. And most of all to my fiancé, Alinson, whom I admire deeply. My sincere thanks for all the programming knowledge you taught me and your company in these four years. I also really appreciate the good role model your set for me. Your study habit, reading habit, discipline and calm nature affected me deeply. I am a much happier, better, and more confident person because of you.

Dedication

This thesis is dedicated to my cousin Peng Jiang, who has recently been diagnosed with spinocerebellar atrophy, a disease with no cure. Your fighting spirit is forever an inspiration to me.

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Chapter 1

Introduction

Kidney failure is a widespread condition that affects millions of people. Worldwide, over 2 million people currently receive renal replacement treatment to stay alive, and this number likely represents less than 10% of those who need it. Kidney failure patients accounted for more than 661,000 in the US in 2015 [1]. In Canada, the number of people with kidney disease has more than doubled in the last 20 years. It is estimated that as many as one in ten Canadians have kidney disease, and millions more are at risk. Each day, an average of 15 people are told that their kidneys have failed.

When a patient's kidneys fail to clear waste from the body, hemodialysis is the major medical treatment to keep the patient alive. Hemodialysis is the process of removing waste and excess water from the blood to dialyzate through semi-permeable membranes. In US, 71% of patients with kidney failure are on traditional hemodialysis. In Canada, among all the 41,252 people being treated for kidney failure, 58% of them are on traditional hemodialysis.

The cost and the mortality rate of hemodialysis are high. On average, it costs $83,356 per patient per year for hemodialysis treatment. For end stage renal hemodialysis, the mortality rate of these patients is 20-25% after one year on hemodialysis and the 5-year mortality rate is 65% [1].

Furthermore, current hemodialysis, which depends on diffusion and convection for solute clearance through a low-flux or high-flux dialyzer, is not effective at clearing some important toxins that play an important role in the mortality rate. Although small and water-soluble toxins such as urea (66-75% reduction) and creatinine (66%) are readily cleared, potential uremic toxins including indoxyl sulphate (35%), 3 cardoxy4-methyl-5-propyl-2furanoproprionic acid (32%) and p-cresol (29%) [2], as well as middle sized toxins such as β_2 microglobulin (0.7-6.8%) [3] are cleared to a lesser extent. Davenport's studies [4, 2] showed that short-term survival (measured in days) and medium-term

survival (measured in months) crucially depends on a minimum removal of small molecular weight water-soluble toxins, and long-term (years and decades) survival requires improved elimination of protein-bound and middle-sized molecules [3]. Recently, phosphate, 2 microglobulin, indoxyl sulfate and p-cresol have been reported to be related to an increased risk of mortality in hemodialysis patients [5]. Eknoyan [3] undertook a five year randomized clinical study among 1846 patients undergoing thrice weekly hemodialysis, and showed that no mortality and morbidity benefits were gained from a higher hemodialysis dose or from using high-flux membranes in short term hemodialysis. The study suggested a benefit of high-flux membranes for patients who had been undergoing hemodialysis for more than 3.7 years.

In this thesis, we propose a membrane that can better clear uremic toxins when compared to traditional hemodialysis membranes. This membrane is able to clear water-soluble toxins as well as protein-bound toxins, therefore it has potential to reduce reno-cardiovascular syndrome as well as to reduce the mortality of patients who undergo long-term hemodialysis. The membrane is also able to eliminate the toxins very fast, having potential to reduce the hemodialysis time needed in each section (currently, 3-4 hours). Besides diffusion and convection, the conventional filtering mechanisms, this membrane can also eliminate toxins through adsorption.

A potentially feasible method to achieve all these purposes is to fabricate composite hemodialysis membranes with nanoparticles. Although Tijink [6] explored composite membranes with active carbon, the non-selective adsorbing properties of carbon adsorbs both toxins and biological molecules.

In order to fabricate membranes that can specifically adsorb uremic toxins, first we find adsorbents that can specifically adsorb them. Then, we incorporate them into them into the membranes through electrospinning and spin-coating technologies. Finally, we test the membranes' ability to eliminate toxins and we infer the adsorption mechanism.

The thesis has been broadly organized as follows: In Chapter 2, we present some general knowledge about kidney disease, hemodialysis, and the principles used in hemodialysis. We also present the theories related to electrospinning and spin-coating, the fabrication methods used in this thesis.

In Chapter 3, we do a literature review on renal medical treatments that involve adsorption mechanisms to eliminate toxins such as hemoperfusion and wearable kid-

ney. Among all the synthesized hemodialysis membranes, we choose polyacrylonitrile and polyethersulfone as polymer representatives, so their usage in hemodialysis is also reviewed.

In Chapter 4 and 5, we fabricate polyacrylonitrile and zeolite membranes through electrospinning and we test the membranes' creatinine adsorption level. We also study the the effect of particle size and shape on creatinine adsorption.

In Chapter 6 and 7, we fabricate polyethersulfone and zeolite membranes through spin-coating and we test these membranes to adsorb creatinine and indoxyl sulfate. We also study the adsorbing mechanism of zeolite.

Finally, in Chapter 8, we present an overall conclusion and future directions of research.

Chapter 2

Background

In this chapter, general background knowledge about kidneys, hemodialysis, membranes and uremic toxins are introduced. We also introduce electrospinning and spin-coating, which are methods to synthesize hemodialysis membranes. Since our membranes use zeolites as adsorbent, we also discuss the structure of zeolites.

2.1 Kidneys and medical treatments

Kidneys play an important role in maintaining human health. They sustain the equilibrium of water and minerals, clear acidic metabolism waste and function as part of the endocrine system. However, when kidneys fail to clear waste products from the body, medical treatments are needed to keep the patients alive. The most common form of treatment is hemodialysis. Most patients spend some time on hemodialysis before a donated kidney becomes available.

2.1.1 Kidneys

Kidneys are bean-shaped organs about 11 cm in length, 5–6 cm wide, and 3–4 cm thick. Each kidney weighs 120–160 g [7]. The function of a normal kidney involve removal of waste products, regulation the blood volume, blood pressure and blood's acid-base balance, adjustment of sodium and potassium level besides endocrinal functions.

2.1.2 Kidney failure

Kidney failure is the partial or complete loss of normal kidney functions. This is characterized by the inability to remove excess water and metabolic waste from the body. This subsequently has effects on blood pressure, blood volume and blood content. Re-

nal failure is classified into acute kidney injury (AKI) and chronic renal failure (CRF), depending on the cause.

The definition of AKI is "an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL ($\geq$ 26.4 μmol/L), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for more than six hours)"[8].

CRF is defined by the National Kidney Foundation as either kidney damage or a glomerular filtration rate below 60 mL/min/1.73 m^2 body surface area for at least three months.

2.1.3 Medical treatments

There are two options for treatment when a kidney fails. The most common form of treatment is hemodialysis. The other treatment option is kidney transplantation, but donor kidneys are limited. hemodialysis is performed as a "bridge to transplant" for patients because it sustains their life before a donor kidney becomes available.

2.2 Hemodialysis, membranes and principles

Hemodialysis is the process of removing waste and excess water from the blood, and is used primarily as an artificial replacement for patients with renal failure. Figure 2.1 illustrates a hemodialysis process. In hemodialysis, the patient's blood is pumped to the blood compartment of a dialyzer, which consists of a bundle of semi-permeable hollow fiber membranes. When the blood flows inside the hollow fiber, the dialyzate flows in the space surrounding the hollow fibers. Thus the excess wastes from the blood goes to the dialyzate through diffusion and convection. Then, cleaned blood is returned to the patient. In this process, the membrane is the most important part, since the pore size of the membranes decides which molecules can pass through the membranes. Dialysate is the solution in this process to pull toxins from blood. It normally consists of pure water, sodium chloride, sodium bicarbonate or sodium acetate, calcium chloride, potassium chloride and magnesium chloride.

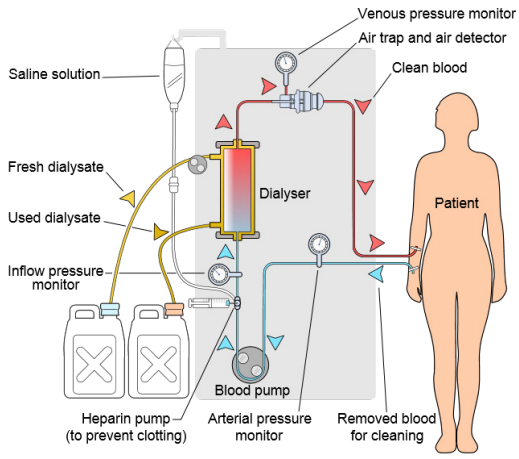


Figure 2.1: Illustration of a hemodialysis process (YassineMrabet/CC-BY-3.0).

2.2.1 Commonly used hemodialysis membranes

A hemodialysis membrane is a semipermeable membrane used to separate blood from dialyzate during hemodialysis. The pore size of the membrane determines the selective permeability of the molecules. In addition, it affects the biological response of the patients during and after the hemodialysis process. Commonly available hemodialysis membranes can be classified into three groups: regenerated cellulose, substituted cellulose and synthesized polymers (Table 2.1).

Cellulose

Cellulose membranes were one of the most commonly used membranes in 1960s since they are cheap to produce and they have uniform porosity and minimal thickness[9]. They are hydrophilic due to large amount of free hydroxyl groups on the cellulose monomers. Their disadvantages include being immunoreactive [10, 11] and only being available in low-flux form, so they have been gradually replaced by substituted cellulose and synthetic membranes.

Substituted cellulose

Substituted cellulose membranes are similar to cellulose membranes, but the free surface hydroxyl groups are substituted by acetyl residuals from acetate or triacetate [12, 13, 14]. Vitamin E [15] and polyethylene glycol grafted [16] cellulose membranes have also been

Table 2.1: Commonly available hemodialysis membranes.

Regenerated cellulose	Substituted cellulose	Synthetic polymers
Cuprophan	Cellulose acetate	Polyacrylonitrile
	Cellulose diacetate	Polymethylmethacrylate
	Cellulose triacetate	AN69
	Hemophan	Polysulfone
	Vitamin E coated	Polyethersulfone
		...

developed in order to improve the biocompatibility of cellulose membranes. In general, the substituted cellulose membranes have better bio-compatibility. The disadvantage of this group of membranes is that they still have low permeability for large solutes.

Synthetic membranes

Various synthetic membranes appearing since 1970s include membranes made from AN 69, polysulfone (PS), polyamide (PA), polyacrylonitrile (PAN), polymethylmethacrylate (PMMA), polyethersulfone (PES) and polycarbonate. They are collectively known as synthetic membranes. These polymer membranes can be manufactured with various pore sizes and desirable molecular weight cut-off, as well as high-flux ability. These membranes can also offer excellent biocompatibility. These membranes are mainly hydrophobic which can cause adsorption of cells and proteins onto the membrane surfaces.

2.2.2 Potential new hemodialysis membranes

Researchers are exploring other potentials materials for hemodialysis besides polymeric hollow fiber membranes, including silicon, alumina and composite membranes.

Silicon membranes

The kidney project, led by Shuvo Roy and William H. Fissell, dedicates to the fabrication of an implantable artificial kidney by using silicon nano-pore membranes [17]. The membrane used in their research has 10 nm by 45 μm slit pore arrays uniformly spaced with 2 μm separation across a 100 mm-diameter wafer, with thickness about 4 μm [18]. The membrane is made by surface micro-machining and micro-fabrication method. Johnson [19] incorporated a 30 nm thick silicon membrane made by Simpore Inc. into

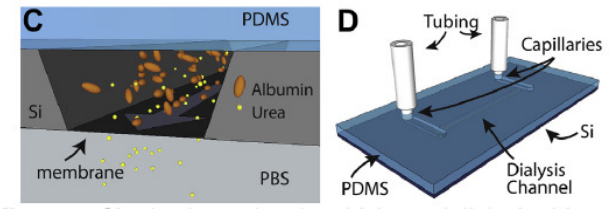


Figure 2.2: Lab-on-a-chip for urea clearance by using silicon membrane. Reprinted from [19], Copyright(2013), with permission from Elsevier.

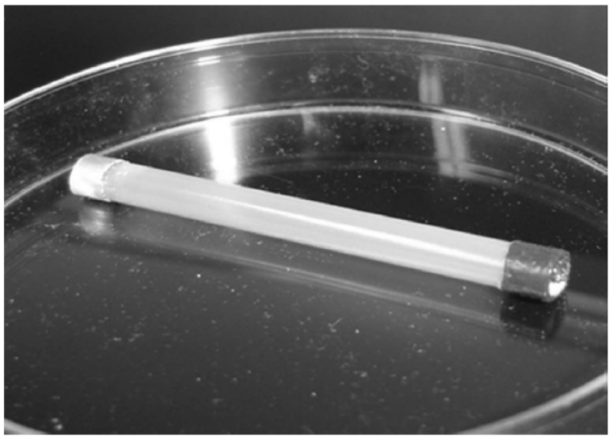


Figure 2.3: Alumina membrane as a dialyzer. Reprinted from [20], Copyright(2009), with permission from Wolters Kluwer Health, Inc.

micro-dialysis chip as a wearable dialyzer, as shown in Figure 2.2.

Alumina membranes

Attaluri [20] tested nanoporous alumina tubular membranes made from anodization for hemodialysis (Figure 2.3). He concluded that alumina membranes had better hemodialysis performance compared with PES membranes. However there have been no further hemodialysis research using alumina membranes.

Composite membranes

Composite membranes were proposed by Tijink[21]. She made composite membranes by loading activated carbon into a PES/PVP polymer blend in order to combine diffusion and adsorption of uremic toxin solutes in one step. This idea was novel and achieved a better uremic toxin clearance. The disadvantage of this composite membrane is that

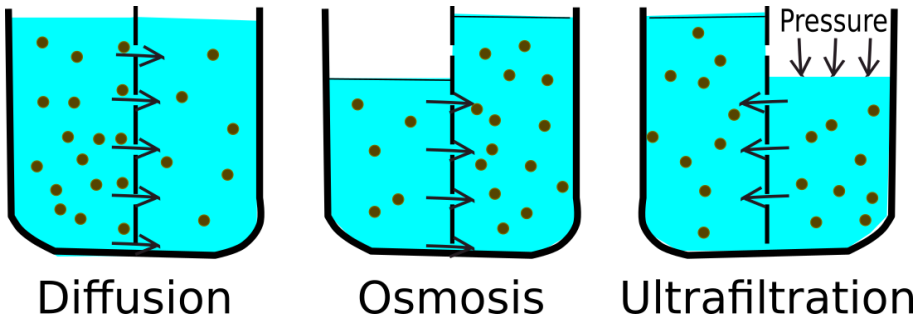


Figure 2.4: Illustration of diffusion, osmosis and ultrafiltration process.

the adsorbent is carbon, which adsorbs both toxins and biological molecules.

2.2.3 Basic principles of hemodialysis

Hemodialysis is a treatment which removes excessive uremic toxins and balance blood electrolyte components by the interchange between patient's blood and dialyzate, across semi-permeable membranes. The transport mechanism in current hemodialysis is mainly diffusion and convection. Osmosis, ultrafiltration, adsorption can also happen in hemodialysis process, and they are all explained as follows.

Diffusion

Diffusion is the spontaneous passive transport of solutes from higher concentration to lower concentration. The process is illustrated in Figure 2.4. Diffusion in hemodialysis is the transport of water soluble toxins from blood to dialyzate. The transport rate depends on diffusion coefficients of the solutes in blood, in membrane and in dialyzate; the concentration gradient across the membrane and the membrane area [22].

Convection

Convection process in hemodialysis is the simultaneous transport of water and solutes from blood to dialyzate across membranes due to pressure gradient. The rate of convection depends on the hydraulic permeability, the sieving coefficient of solutes, membrane area, the concentration of solutes in blood and the pressure gradient across the membrane.

Osmosis

Osmosis is the spontaneous net movement of solvent through semi-permeable membranes into a region of higher solute concentration so as to achieve a concentration balance. The driving force in osmosis is the concentration gradient. The process is illustrated in Figure 2.4. Osmosis in hemodialysis refers to the movement of water across cell-membranes into blood plasma or interstitial fluid.

Ultrafiltration

Ultrafiltration in hemodialysis is the process of removing excess water from plasma into dialyzate through difference of pressure. The pressure on the blood side is higher, so the water moves from a place of higher pressure to one of lower pressure, i.e., into the dialyzate. This is how fluid gets removed when a patient undergoes hemodialysis. A typical ultrafiltration process is illustrated in Figure 2.4.

Adsorption

Adsorption is the adhesion of atoms, ions, or molecules from a gas, liquid, or dissolved solid to a surface. Adsorption in hemodialysis happens when uremic toxins adhere to the surface of semi-permeable hemodialysis membrane or into the adsorbents inside the membranes.

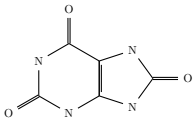
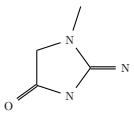
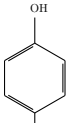
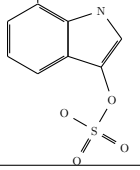
2.3 Uremic toxins

Uremic toxins are toxins that accumulate in chronic renal failure patients. These toxins show various cytotoxic activities in the serum, have different molecular weights and some of them are bound to other proteins, primarily to albumin. Their concentration in healthy people and patients with kidney failure are compared in Table 2.2. The detailed size and chemical structure of the toxins are showed in Table 2.3. These toxins are normally divided into three groups: water-soluble toxins, protein-bound toxins and large toxins.

Table 2.2: Concentrations of free water soluble and protein bond uremic measured in blood of healthy persons (mean C_N)and patients having kidney diseases ((mean C_U), maximum(C_{max})) Reprinted from [23], Copyright(2005), with permission from Elsevier.

Solute	$\mathbf{C_N}/\mu\mathbf{M}$	$\mathbf{C_U}/\mu\mathbf{M}$	$\mathbf{C_{max}}/\mu\mathbf{M}$	**Group**
Urea	< 6700	38,333 ± 18,333	76,667	Carbamides free water soluble solutes
Urea acid	< 400	496±265	873	Purines free water soluble solutes
Creatinine	< 106	1204±407	2124	Guanidines free water soluble solutes
p-Cresol	5.6±9	186±41	377	Phenols protein bond solutes
Indoxyl sulfate	2.4±22	211±365	940	Indoles protein bond solutes

Table 2.3: Size and structure of uremic toxic in blood. Reprinted from [23], with permission from Elsevier.

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

2.3.1 Water-soluble toxins

Water-soluble toxins are molecules with molecular weight (MW) less than 500 Da. Urea and creatinine are representatives[24]. They are highly water soluble and are absent of protein bounding, therefore easily removed by hemodialysis. They do not necessarily have toxic activity [25]. Creatinine is the marker of renal function and is chosen as a representative for water-soluble toxins in this thesis. The increase of creatinine in serum is usually the result of uremic retention, but it might also be caused by muscle breakdown. Morbidity and mortality in hemodialysis patients are positively related to their serum creatinine level [26].

2.3.2 Protein-bound toxins

Protein-bound solutes are a group of uremic toxins that tend to bound to proteins, such as albumin. They are routinely ignored, as hemodialysis adequacy is typically benchmarked by urea removal. Increasingly, studies have shown that protein-bound toxins are related to the progression of chronic kidney disease (CKD), and in the generation and aggravation of cardiovascular disease [27]. Indoxyl sulfate and p-cresol sulfate are two representatives. Indoxyl sulfate is derived from tryptophan in dietary proteins (Figure 2.5) while p-cresol sulfate is derived from tyrosine and phenylalanine. They are excreted to urine through the kidney. Their increase in serum indicates the deteriorating of kidney functions [28].

2.3.3 Large toxins

Large toxins are toxins with molecular weight larger than 500 Da. β-microglobulin is a prototype. An accumulation of molecules is independently associated with an increased mortality risk [30]. These molecules can only be cleared by hemodialysis membranes with pore sizes larger enough for these molecules to cross.

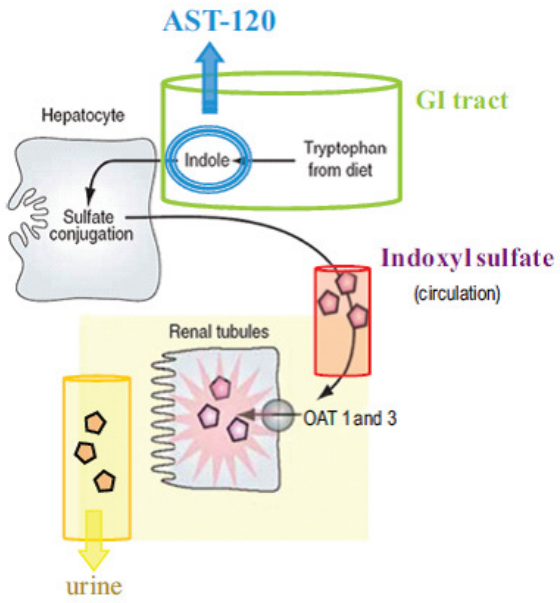


Figure 2.5: Indoxyl sulfate metabolism. The diagram shows the protein metabolite hypothesis of indoxyl sulfate (IS) production that is derived from dietary tryptophan. Inhibition of indole uptake by a gut adsorbent AST-120 reduces IS synthesis. GI tract indicates gastrointestinal tract; OAT, organic anion transporter. Reprinted from [29].

2.4 Electrospinning

Electrospinning is a technique that can be used to fabricate fibrous composite membranes. A basic electrospinning setup contains three major parts: a high voltage power supply, a syringe pump and a collector. The setup can be found in Figure 2.6. The syringe is used to host the polymer solution. When high voltage is applied, the polymer drop at the tip of the syringe is polarized and then the charged polymer flies to the collector under strong electrostatic field.

In this thesis, we use electrospinning to fabricate nanofiber composite membranes. More specifically, these membranes contain polymeric nanofiber as high porous nanowoven matrix. They also contain nano-filler as adsorbent for the toxins. These membranes are better than currently used hemodialysis membranes and silicon membranes. Comparing with currently used polymer membranes, composite membranes have clear pore channels and higher porosity. Comparing with potential silicon membranes, they have much higher porosity and they are more flexible. Another advantage of these membranes is that they combine diffusion and adsorption mechanisms together. Silicon and

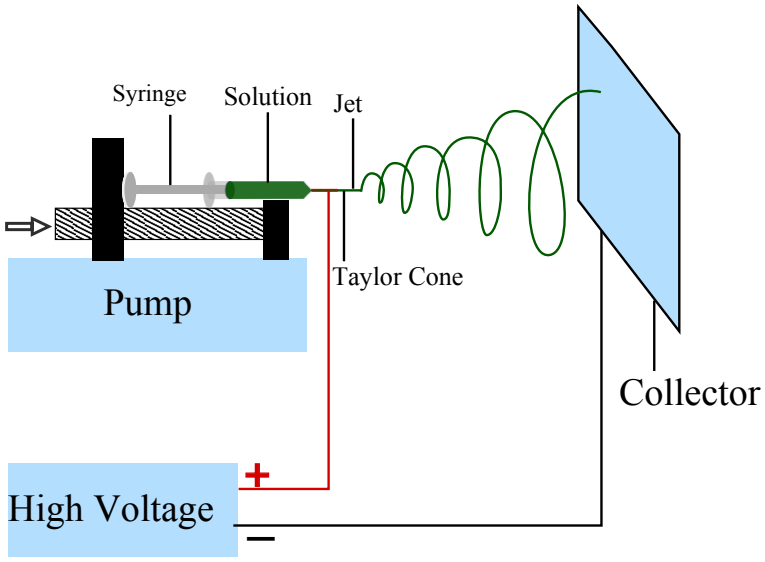


Figure 2.6: Electrospinning setup.

polymer membranes eliminate toxins only by diffusion. With the addition of adsorption, we can expect composite membranes to have faster toxin clearance speed.

In this section, we study the theory of electrospinning, which includes charge generation, taylor cone theory, jet thinning and jet instability. We also discuss the factors that influence the formation of membranes.

2.4.1 Charge generation

Electrospinning works by generating charge carriers which respond to the applied electric field. Charge carriers are created by high electric field induced emission (on the order of 10^9 to 10^{10} V/m) and by dissociation processes [31]. Figure 2.7 is the illustration of charge carries in the needle. We define the syringe needle and solutions within it as a capillary electrode. With a positively polarized capillary, the negative ions will migrate to the inner surface of the needle where they will be immobilized. This leaves the inner volume of the solution with an excess mobile positive charge which can respond to the electrostatic stress of the opposite electrode. The sharp edges might have field emission of charges.

For high electric field emission to occur, the electrospinning setup uses a needle and

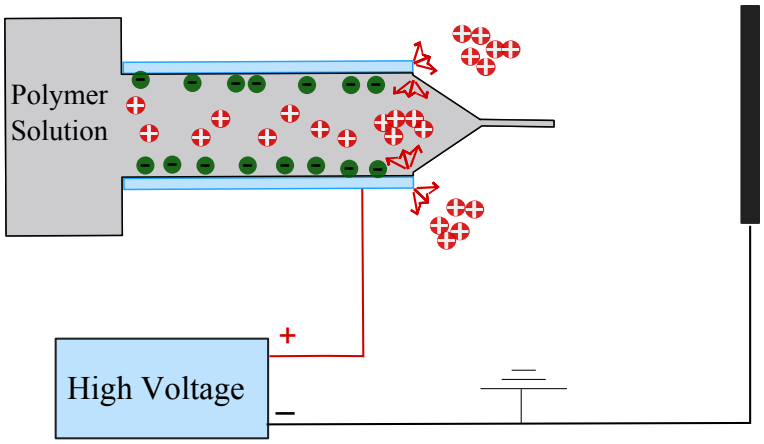


Figure 2.7: Illustration of charge carries in a syringe needle.

a plate electrodes configuration, called "point-plane" geometry. The electric field under this configuration has highly non-uniform electric field. The increased electric field at the needle tip can be expressed by the following equation [32]

$$E_{\text{tip}} = \frac{2V}{r \ln\left(\frac{4d}{r} + 1\right)}, \tag{2.1}$$

where V is the externally applied voltage, d is the distance from the needle tip to plane collector, and r is the radius of curvature of the needle point.

Dissociation process happens in liquid solution. The process is affected by ion diffusion and migration in the electric field. Lars Onsager's equations (2.2)-(2.3) describe that the electric field can enhance the dissociation process.

$$K(E) = K(0)\left(1 + b + \frac{b^2}{3} + \frac{b^3}{18} + \frac{b^4}{180} + \frac{b^5}{2700} + \frac{b^6}{56700} + \ldots\right) \tag{2.2}$$

$$b = \frac{z_1\omega_1 + z_2\omega_2}{\omega_1 + \omega_2} z_1 z_2 \frac{Eq^3}{2\epsilon k^2 T^2} \tag{2.3}$$

where, $K(E)$ is the dissociation constant in the presence of an electric field, $K(0)$ is the dissociation constant at equilibrium without electric field, z_1 and z_2 are the valences of the ions, ω_1 and ω_2 are ion mobilities, q is the electronic charge, E is the electric field, k is the Boltzmann constant, T is the temperature, and ϵ is the permittivity of the liquid.

After ions dissociate, the negative ions will migrate to the cathode, while the pos-

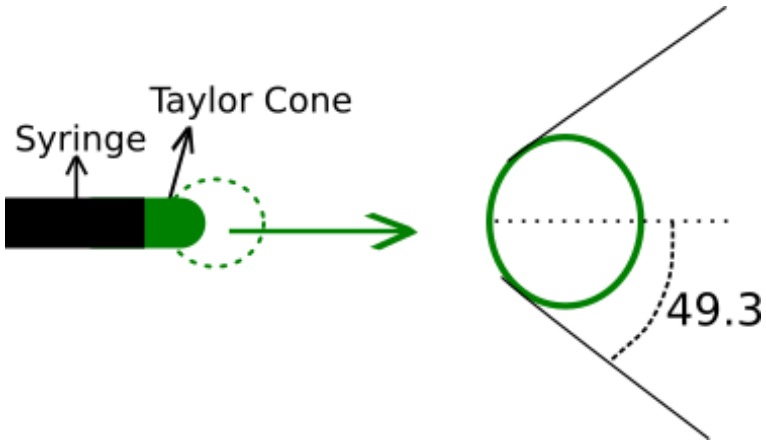


Figure 2.8: Schematic diagram of the Taylor cone.

itive ions to the anode, leading to a disrupted dissociation-recombination equilibrium. The ions will be further immobilized or annihilated by the electrochemical process at electrodes, which makes recombination impossible [33].

2.4.2 Taylor cone theory

Taylor cone theory was established in 1964 by G.I. Taylor to describe the deformation of small-volume liquid under high electric field. It asserts that, when a small volume of electrically conductive liquid is exposed to electric field, it keeps a shape due to the balance between electric forces and surface tension. If the potential increases to a critical level, further increase will destroy the balance, and the liquid will acquire a conical shape with half angle of 49.3°, called Taylor cone, as shown in Figure 2.8. A.L. Yrin and D.H. Reneker later modified Taylor cone theory based on experimental data. They found that Taylor cone theory was only correct for self-similar solution and that the angle of the cone was 33.5° instead of 49.3°. For non self-similar solution, the further increased potential after critical potential point will cause the cone to have a more prolate shape [34].

2.4.3 Jet in flight

Jet in flight describes the process after the jets (solution) are ejected from the Taylor cone. The jets usually pass by in a straight line followed by bending into a complex

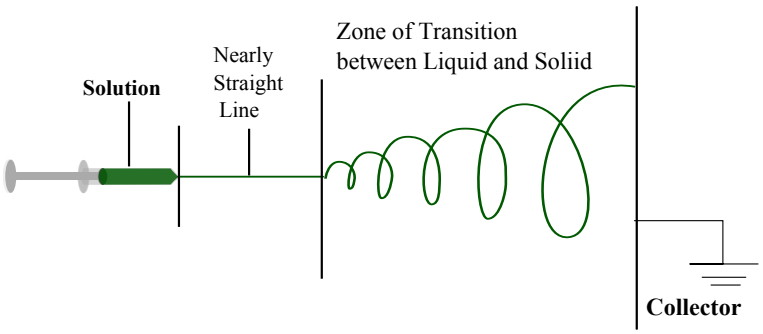


Figure 2.9: Schematic illustration of the jets path between the tip of syringe and collector.

path, during which the electrical forces stretch and thin them into a nanofiber, before arriving at the collector. The process is shown in Figure 2.9.

Jet thinning (Steady region)

As the fluid is ejected from the cone, a continuous thinning liquid jet can be seen. Hohman and Feng [35, 36] indicated that the surface charge density and the local electric field determine the shape of the jet. The thinning regime length L is decided by the equation (2.4).

$$L^5 = \frac{K^4 Q^7 \rho^3 (\ln\chi)^2}{8\pi^2 i^5 \varepsilon^2 e_\infty} \tag{2.4}$$

where K, Q, ρ, χ, E_∞,I, and ϵ are the conductivity, flow rate, density, aspect ratio ($\chi = D/h_0$), applied field, electric current, and dielectric constant of air. The current for electrospinning "circuit" is typically < 1 μA. The measured current follows the equation (2.5) [38].

$$i = Q\rho_c = C^\chi e^{-H} K_{\exp} M^\gamma Q^\beta V^\alpha \tag{2.5}$$

where, ρ_c, V, Q, C, M, and H are the initial charge per unit volume, applied voltage, volumetric solution flow rate, polymer concentration, molecular weight, and needle to plate distance, respectively. The variables α, β, γ and χ depend on the type of solution.

Beyond the length L, the jet thins much more slowly.

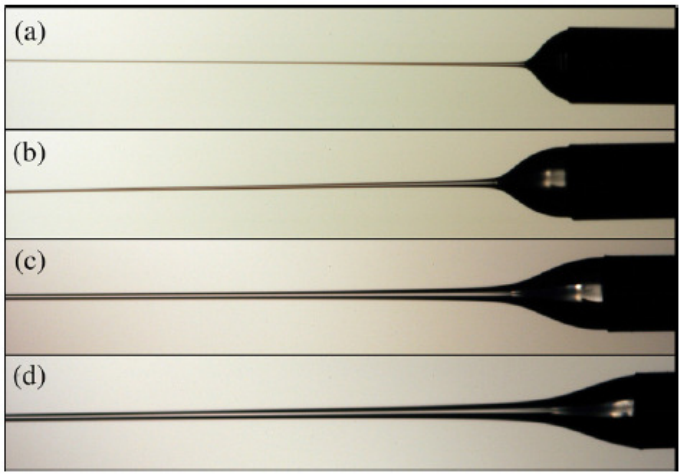


Figure 2.10: Cone-jets of solution of polyethylene oxide(MW=920 kg/mol). D=45 cm in all cases. (a) Q=0.02 ml/min, E=0.282 kV/cm; (b) Q=0.10 ml/min, E=0.344 kV/cm; (c)Q=0.50 ml/min, E=0.533 kV/cm Q=1.00 ml/min, E=0.716 kV/cm. Reprinted from [37], Copyright(2007), with permission from Elsevier.

Jet instability (Unsteady region)

During the experiment, as the jet grows, it is distorted by one or more fluid instabilities. The most common mode of instability is whipping (shown in Figure 2.11) [37].

2.4.4 Collector

Collector is the device that collects jets. The shape of the collector can be plate, rotating drum, wire drum, rotating discs, parallel electrodes and other collecting array, depending on the purpose of the nanofiber assembly [39].

2.4.5 Parameters influencing electrospinning

In the electrospinning process, the governing parameters that influence volume charge density and current are the applied voltage (V), the solution flow rate (Q), the polymer weight concentration (C), the molecular weight of the polymer (M) and the nozzle-to-ground distance (H). The volume charge density follows power law which depends on V, Q, C, and M, and at the same time exponentially depends on H: [40].

$$\rho = C^{\chi} K_{\exp} M^{\gamma} Q^{\beta} V^{\alpha} e^{-\frac{H}{h}} \tag{2.6}$$

Figure 2.11: Fiber instability-whipping.

where, K_{exp} depends on parameters such as intrinsic solution properties, temperature and humidity, and h is a function of molecular weight (M).

2.5 Spin coating

Spin coating is a commonly used technique to apply thin films to substrates. It was chosen as another technique to fabricate composite membranes in this thesis. Spin coating has been used in various applications such as coating of photoresist on silicon wafers [41, 42, 43], sensors [44, 45], protective coatings [46], paint coatings, optical coatings [47] and membranes [48]. It can be used to quickly and easily to produce uniform films over a large area ($\phi \geq 30$ cm), ranging from a few nanometers to a few micrometers in thickness [49]. The general spin-coating process is shown in Figure 2.12. It consists of (1) a dispense step in which the polymer solution is deposited onto the substrate, and then (2) a speed spin step to thin the solution, and (3) a drying step to eliminate excess solvents from in step (4) the resulting film.

Spin speed, acceleration, spin time, fume exhaust, viscosity of the solution are factors

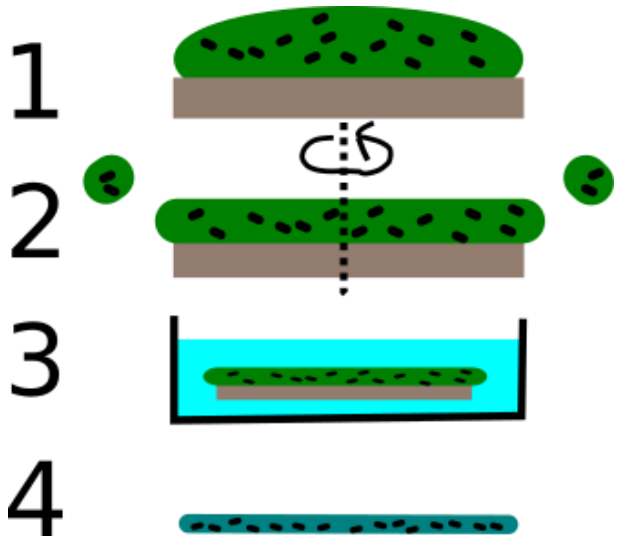


Figure 2.12: Demonstration of a typical spin coating process.

related to film thickness and uniformity.

2.6 Zeolites

Zeolites are microporous, aluminosilicate minerals commonly used as commercial adsorbents and catalysts. Zeolites have been chosen as adsorbent in this thesis. Here we discuss their structure and chemical composition.

2.6.1 Chemical composition of zeolites

The general formula for most zeolite are given as [40, 50]:

$$|M_x(H_2O)_\gamma|[Al_xO_{2t}Si_{t-x}] - IZA,$$

where, the guest species are represented in bars(| |). The host framework is represented inside brackets ([ ]). M represents a cation, x is the number of framework Al atoms in the unit cell, γ is the number of adsorbed water molecules, t is the total number of framework tetrahedral atoms in the unit cell (Al+Si) and IZA (International Zeolite Association) is the code for the framework type assigned by the Structure Commission of the International Zeolite Association.

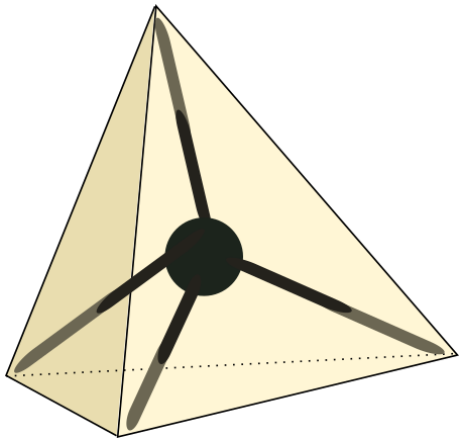


Figure 2.13: Several representation of the basic building unit of zeolites, the tetrahedron.

2.6.2 Structure of zeolites

Zeolite's structure is based on a connected framework of SiO_4 and AlO_4 tetrahedra by sharing of oxygen atoms. Here we introduce the basic building and composite building units of zeolites.

Basic building unit (BBU): the tetrahedron

All zeolite frameworks can be built by periodically linking the a basic building unit (BBU), the tetrahedron (Figure 2.13). In the center of the tetrahedra are atoms Si^{4+}, Al^{3+} or P^{5+}, while in the corners are oxygen anions (O^{2-}). The combination could be SiO_4, AlO_4 ,PO_4, etc.

Composite building unit (CBU)

Composite building units (CBUs) of zeolites can be formed by linking together groups of basic building units (BBUs). The simplest example of CBUs are rings. In general, a ring containing n tetrahedra is called n-ring. The most common rings contain 4, 5, 6, 8, 10 or 12 tetrahedral [51, 52]. Figure 2.14 shows the pore size and structure of 8-ring. The size of other rings is shown in Table 2.4. Further combining n rings can lead to larger CBUs with diverse and interesting structures, as shown in Figure 2.15. Cages can contain cation, water molecules, small organic molecules, and so on. One-dimensional CBUs which are composed by rings (either identical or different) are called chains.

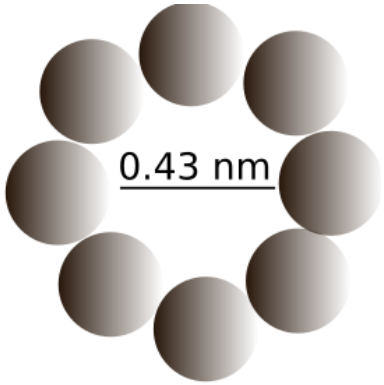


Figure 2.14: Illustration of 8-ring.

Table 2.4: The free apertures of 4,5,6,8,10,12 rings.

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

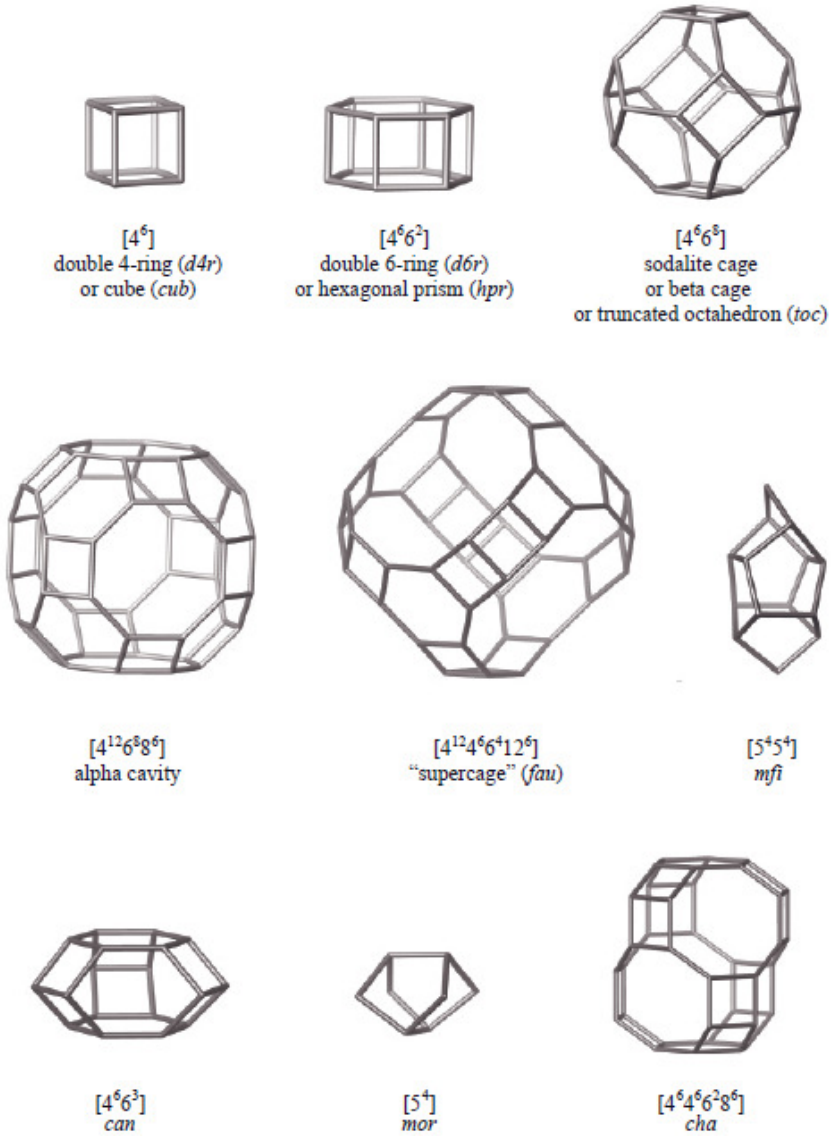


Figure 2.15: Some examples of polyhedral composite building units (cages) with their corresponding pore symbols and common names. The nodes are tetrahedrally coordinated atoms such as Si or Al. Bridging oxygen atoms have been left out for clarity. Reprinted from [50], Copyright(2003), with permission from Elsevier.

Pores, cages, cavities and channels

The n-rings defining the face of a polyhedral CBU are called windows or pores. Polyhedra whose faces are no larger than 6-rings are called cages, since they are too narrow for molecules larger than H_2O to pass. Polyhedra with at least one face larger than 6-rings are called cavities. The extended pores in one, two, or three dimensions which allow diffusion of guest species (larger than 6-rings) are called channels. An important characteristic of zeolites is the effective width of channels, which is limited by the smallest free aperture along the channel. By knowing the structure of zeolites, it is possible to calculate the effective width of the channels.

2.6.3 Molecular sieving

Molecular sieves are porous materials that selectively adsorb molecules of specific sizes. Zeolites are the most commonly used crystalline materials for molecular sieves. They have pore sizes from 0.3 to 1.0 nm and pore volumes from 0.10 to 0.35 cm^3/g. Typical zeolites' pore sizes include: (1) small pore zeolites that have eight-ring pores with free diameters of 0.30-0.45 nm (eg, zeolite A), (2) medium pore zeolites that have ten-ring pores with free diameter of 0.45-0.60 nm (eg, stilbite and silicalite (MFI)), (3) large pore zeolites that have 12-ring pores with free diameters of 0.6-0.8 nm (eg, Mordenite and Faujasite) and (4) extra-large pore zeolites that have 14-ring pores (eg. UTD-1). Additionally, the zeolite frameworks are somewhat flexible; their size and shape change in response to changes in temperature and substituted guest species.

Chapter 3

Literature review

The composite membranes we propose mainly depend on adsorbents to eliminate toxins. In this chapter, we present a literature review on adsorbents used in renal therapy. This provides us a good guidance in choosing suitable adsorbents. We also survey other renal replacement therapies that use adsorbent technologies, such as hemoperfusion and wearable kidneys.

3.1 Hemoperfusion

Hemoperfusion (HP) is a procedure to treat drug overdose and poisoning [54], which was introduced in the 1940s [55]. It was adopted in clinic in the 1970s and 1980s [56, 57, 58] and used infrequently for treating acute intoxication [59]. A typical hemoperfusion system is shown in Figure 3.1. It consists of a blood circuit including blood pumps and pressure monitors that are identical to hemodialysis, but with a cartridge containing adsorbents (charcoal, activated carbon or resin). Anticoagulated blood is pumped through the cartridge, where drugs or poisons are removed by adsorption. Table 3.1 lists several adsorption cartridges available [60]. HP can lead to a number of medical complications, including thrombocytopenia, leukopenia, hypocalcemia, and hypoglycemia. Its use has been declining due to the development of high-flux hemodialysis, which has a lower cost and lead to fewer medical complications. However, HP is still a valid alternative for

Table 3.1: Some available hemoperfusion devices.

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

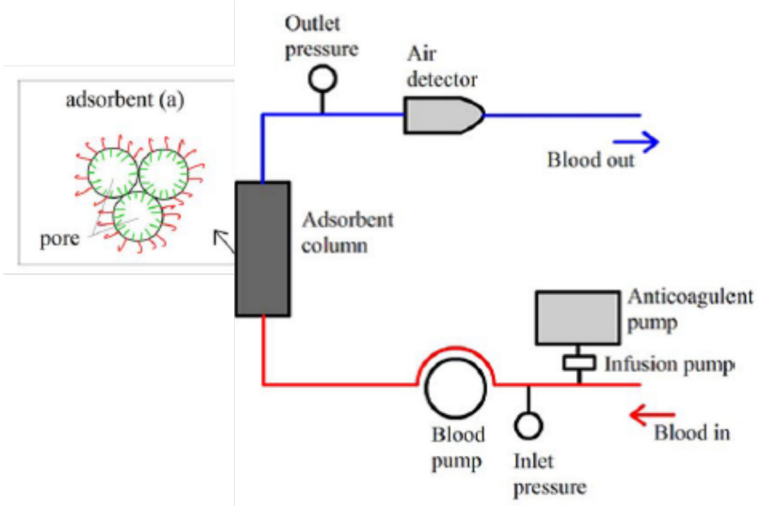


Figure 3.1: Schematics of a typical hemoperfusion system. Reprinted from [53], Copyright(2016), with permission from John Wiley and Sons.

poisons with a low concentration distribution and high degree of protein binding [61].

3.2 Wearable kidney (WAK)

Current hemodialysis uses large amounts of hemodialysis fluid in a one time pass [53]. The size of existing hemodialysis system can be scaled down significantly if the amount of required dialyzate is significantly reduced. This can be achieved with the utilization of an adsorbent system to regenerate dialyzate [64, 65, 66].

Wearable kidneys are miniatured hemodialysis devices that patients can "wear" and perform hemodialysis as they move around. These devices work by regenerating and reusing a small volume of hemodialysis fluid in a closed-loop cycle. Miniaturized hemodialysis models that are wearable can eliminate one of the long-standing hemodialysis problems, specifically patient mobility and non-continuous hemodialysis. Although the models of WAK may differ from each other, the dialyzer is the heart of the system. A schematic of a WAK is shown in Figure 3.2 (a) while a prototype is shown in Figure 3.2 (c). Some famous patented designs of WAKs that predominantly utilize adsorbents to generate dialyzate include Yoshida [67], Henne[68], Davankov [69], Granger [70], and Gura [62, 71]. The Gura WAK is currently undergoing clinical trials[72] and is one of the most viable design.

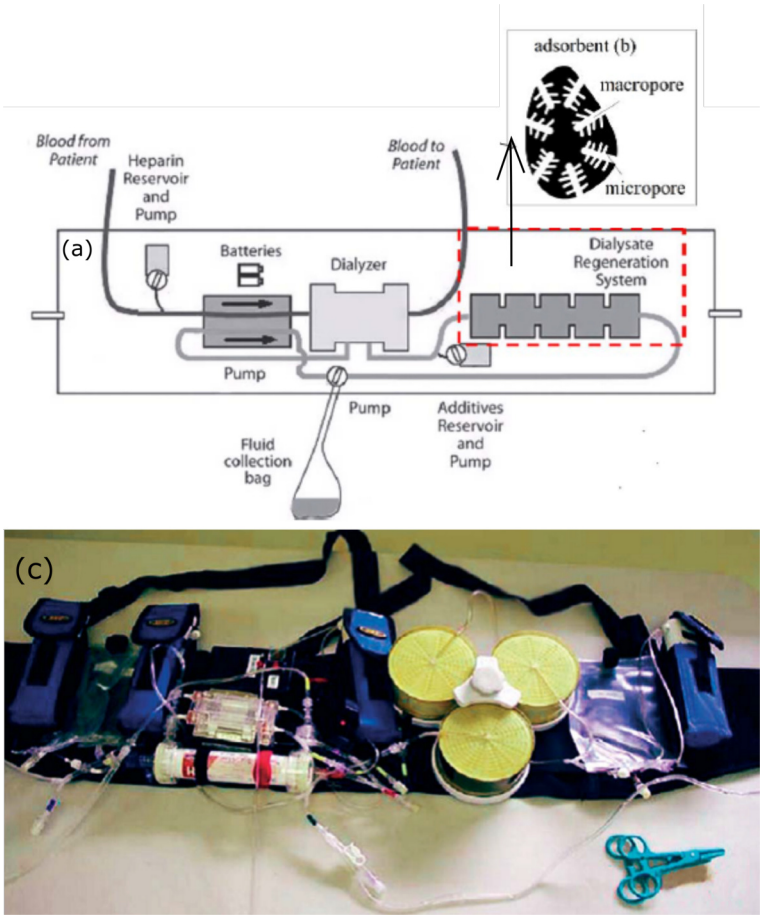


Figure 3.2: A wearable kidney schematic (a), adsorbent(b) and the Gura wearable kidney(c). (a) Reprinted from [62], Copyright(2008), with permission from John Wiley and Sons, (b) Reprinted from [53], Copyright(2016), with permission from John Wiley and Sons, (c) Reprinted from [63], Copyright(2007), with permission from Elsevier.

Table 3.2: Comparison of hemoperfusion,hemodialysis and wearable kidney.

Categories	**Hemoperfusion**	**Hemodialysis**	**Wearable Kidney**
Mechanism	Adsorption	Diffusion convection	Diffusion
Usage	Poisoning/Drug overdose	Kidney failure	Kidney failure
Key parts	Adsorption cartridge	Dialyzer/Dialyzate	Dialyzer /Adsorption cartridge

All the wearable kidneys design need regeneration cartridges. The serial REDY models of regeneration cartridge [73], based on sorbent and enzyme technology, were the first truly portable hemodialysis systems and were widely used throughout Australian hospitals. This cartridge was used for purification of the recirculated hemodialysis fluid. It consists of urease layer to convert urea, activated carbon layer for adsorption of non-urea organic toxins, zirconium phosphate to bind potassium and (urease-generated) ammonium, and zirconium oxide & zirconium carbonate layer to remove phosphate [57]. This combination of sorbents and urease formed the basis for the WAK developed by Davenport et al [63].

In this chapter, we discussed hemoperfusion and wearable kidneys. In the previous chapter, we also discussed the hemodialysis process. Table 3.2 compares these three therapies in terms of mechanism, usage and the key components.

3.3 Adsorbents

Adsorbents are materials that can adsorb molecules into/onto their surface. They are the key components in hemoperfusion and wearable kidneys. Resin, charcoal and activated carbon are the adsorbents that have been used to eliminate uremic toxins.

Charcoal was the first adsorbent used to remove uremic toxin, as reported by Yatzidis [74]. From 1964 until now, activated carbon has been used in hemoperfusion, which is especially useful to treat acute poisoning, intoxication and hepatic failure [75, 76, 77]. Activated carbon is a logical choice as an adsorbent because it has a large surface area

[78, 79], good affinity for both organic and inorganic contaminants [80] and amphoteric properties [81]. However, activated carbon's major drawback lies in the indiscriminate adsorption of both uremic toxin molecules as well as life sustaining molecules from blood [82].

Zeolites are other promising candidates to adsorb uremic toxins. Wernert and colleagues reported that MFI zeolites are able to adsorb uremic toxins that have small molecular size [23, 83]. The adsorbent level for urea is slightly lower or equal to that of activated carbon. Physical and chemical modification of zeolites through ion exchange or surfactant can improve their affinity towards some specific uremic toxins, thus improving the overall adsorption capacities of zeolites [23]. Unlike activated carbon, zeolites possess better selectivity and affinity toward specific uremic toxins. The ability for selective adsorption alone is helpful in solving problems existing in hemodialysis [53].

Although the incorporation of adsorbents into the membranes could minimize the shortcoming of hemodialysis. However, a direct contact between adsorbents such as activated carbon and blood leads to various problems and complications, such as hemolysis and blood coagulation [83]. Even though heparin can be used as a conventional way to prevent blood from clotting [75], heparin overdose could lead to further complication such as bleeding and bruising [84].

A growing and feasible trend to reduce complications caused by the contact of adsorbents with blood is to improve the biocompatibility of adsorbents [85]. Attempted methods to improve the hemocompatibility of activated carbon and carbon nanotube adsorbents include coating and encapsulation of the adsorbents. A wide range of hemocompatible membranes such as cellulose nitrate [86] and plyhydroxyethyl methacrylate [87] have been used to coat adsorbent particles. Heparin [88, 89] has been used to coat adsorbent particles in order to prevent platelet adhesion and blood coagulation. However, the uremic toxin adsorbing efficiency of coated or encapsulated adsorbent systems is lower than that of bare adsorbents due to partial blocking of adsorption sites [90]. Other than coating and encapsulation, functionalization method proved to be beneficial in improving hemocompatibility of adsorbent particles. This method involves the introduction of hydrophilic functional groups into the surface of adsorbent particles [91].

Our proposed composite membranes incorporate zeolites inside the membranes. It has good biocompatibility and it has been used as drug delivery material [92] and as

coating material for biomedical implants [93].

3.4 Dialyzer membranes

Dialyzer membranes are the semi-permeable membranes in a dialyzer that allow toxins to pass while retaining biological molecule during hemodialysis. Synthetic membranes are by far most frequently used hemodialysis membranes, with an increasing market share. They are regarded as the most biocompatible hemodialysis membranes, and, for that reason, have replaced cellulose membranes since mid-1990s. It is expected that they will also replace modified cellulose membranes in the near future.

The majority of synthetic hemodialysis membranes currently used is hydrophobic. The addition of additives or copolymers in the production process can make them more hydrophilic. These membranes are in the shape of hollow fibers. These hollow fiber membranes are extruded through a spinneret followed by phase inversion and immersion. Their skin is formed by partial evaporation of the solvent and their structure is defined by phase separation. The major purpose of these membranes is to achieve a high porosity, in order to mimic the kidney filtration process [94], and to remove middle molecules and higher molecular uremic toxins. It was calculated that the pore size of the membranes should be larger 5 nm in order to remove large molecular uremic toxins and smaller than 8 nm in order to prevent the leaking of albumin [95].

Commonly available hemodialysis membranes can be classified into three groups: regenerated cellulose, substituted cellulose and synthesized polymers. These synthesized polymers include AN 69, PS, PA, PAN, PMMA, PES and polycarbonate(PC). PAN and PS have relatively more publications compared with other polymers. Bazargan [96] shows that by electrospunning 12 wt% PAN in DMF we can get PAN fiber membranes with diameter of 165 $\pm$ 16 nm and porosity of 91.7%. Bastani [97] fabricated PAN nanofiber membranes with pore size around 5-65 nm which could filter 7-40 nm particles from waste water. Since PAN nanofiber membranes have pore size similar to hemodialysis membranes, as well as high permeability, it was chosen as candidate for our electrospinning experiment. On the other hand, PES[21, 98] is a good polymer to make membranes through spin-coating. PAN and PES are two polymers used in this thesis, thus the following section reviewed their histories and current status as hemdodialysis

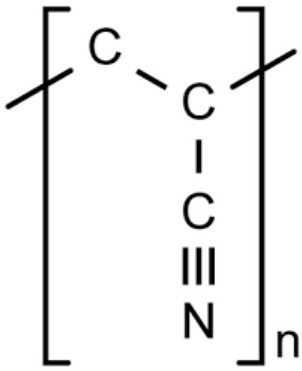


Figure 3.3: The molecular structure of polyacrylonitrile.

membranes.

3.4.1 Polyacrylonitrile

The first dialyzer with polyacrylonitrile (PAN) (structure shown in Figure 3.3) membrane was produced by Gambro and marketed under brand name AN69®. This membrane is highly permeable and symmetric. It is a blend of hydrophobic polyacrylonitrile with hydrophilic methallylNa-sulfonate. It has good distributed medium-sized pores in high density over the homogeneous polymer. It is used till date and has been a great success over the years.

Another PAN producer is ASAHI (PAN, PAN DX, ASAHI Medical, Japan). Their membrane consists of hydrophobic monomers, acrylonitrile, methacrylate, and hydrophilic acrylic acid. The membrane is asymmetric and has a skin layer with pores in a wide range.

Since 1990, it has been reported that the electronegativity of AN69® is responsible for the anaphylactoid reactions in patients who are taking angiotensin-converting enzyme (ACE) inhibitors, since contact phase system was activated due to the generation of bradykinin [99, 100]. Therefore, AN69® is contraindicated in patients on ACE inhibitor therapy. To eliminate contact activation, AN69®ST was developed through surface-modification. Polyethyleneimine was used to coat the surface of the membranes in order to neutralize the negative charges [101]. Additionally, heparin binds to the surface of AN69®ST during priming process and no further heparin is needed during treatment, which may be beneficial in patients at bleeding risk [102].

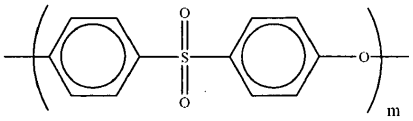


Figure 3.4: The molecular structure of polyethersulfone.

3.4.2 Polyethersulfone

More than 18 models of dialyzers made from polysulfone and polyethersulfone (structure shown in Figure 3.4) are currently used in clinic, which attest the great success of these membrane polymers for hemodialysis. They fit all the requirements of hemodialysis membranes such as good physical strength and chemical resistance, biocompatiblility, and easy sterilization. The first polysulfone membrane, Fresenius Polysulfon® was introduced by Fresenius in 1983. It has an asymmetric and microreticular structure. DIAPES® and Polyamix are other commonly used polyethersulfone membranes. Both polysulfone and polyethersulfone are hydrophobic polymers. Blending with a hydrophilic copolymer (polyvinylpyrrolidone) is a common method to make the membranes more hydrophilic, which can lead to a better diffusive performance.

3.5 Design Methodology

In this section, we first summarized the membrane design criteria, and then presented experiment testing methods used in this thesis.

3.5.1 Membrane design criteria

In order to make better hemodialysis membranes, the following criteria need to be followed:

- Membrane fabrication methods should be easy to realize in the lab.
- Adsorbents used in the membranes should be stable and non_toxin in biological environment, they should also be selectively adsorb uremic toxins and not to adsorb biological molecules.

- Pore size of membranes should be large enough for toxins to pass and small enough to prevent albumin to pass.
- Membranes should be biocompatible.
- Membranes should have suitable permeability.
- Membranes should be able to remove both water_soluble toxins and protein_bound toxins.

3.5.2 Experiment methods

In this thesis, we used two simple membranes fabrication methods (electrospinning and spin_coating) to fabricated hemodialysis membranes in the lab. We also tested whether these membranes could fulfill the membrane design criteria we mentioned above through the following experiment methods.

Scanning electron microscope and Si_mapping

Scanning electron microscope (SEM) is a common technique to produces images of a sample by scanning it with a focused beam of electrons. In this thesis, we used scanning electron microscope (SEM) method to test the morphologies of membranes. These images can not only infer the fiber diameters of electrospinning membranes, but also show the channel of spin_coated membranes. Si_mapping membranes show the distribution of Si elements in the membranes and we can infer the distribution of zeolites in the membranes.

Thermalgravimetric analysis

Thermalgravimetric is a common method to measure the sample weight changes as a function of increasing temperature. It is normally used to determine mass loss or gain due to materials' decomposition, oxidation or evaporation of chemical with low boiling points. In this thesis, we use this method to determine the weight percentage of zeolites in polymer membranes.

The uncertainly of this method might caused by the initial samples, the sample need to be dry before the tests. In order to avoid the uncertainly, we dried our sample in the

oven over night.

Dynamic laser scattering

Dynamic laser scattering can be used to determine the size distribution of particles. It normally consists of a laser, a sample, a photo detector and a correlator. When the laser lights hits the small particles in the sample, the light scatters in all directions. The photo detector detects the intensity fluctuates over time and the correlator correlates the particle size with scattering intensity.

The uncertainly of this test can be caused by the size of particle core and surface structures, particle concentration, and types of ions in the medium. In order to minimize the uncertainly of this test, all the particle size are tested and compared at same concentration and in the same medium.

Zeta potential

Zeta potential of particle is measured by applying an electric field across the sample dispersion. Particles with a zeta potential will migrate toward the electrode with a velocity proportional to zeta potential. By measuring the migrating velocity of these particles, zeta potential of particles can be deduced.

The uncertainly of zeta potential can caused by pH of medium and ions strength in the medium.

Ultraviolet spectroscopy

Ultroviolet spectroscopy is a common method to measure the concentration of molecules. It happens because molecules containing π-electrons can adsorb ultraviolet to excite these electrons to higher molecular orbitals.

Measurement uncertainly can caused by spectral bandwidth, wavelength of excitation light, purity of light and high concentration of samples.

Fluorescence spectroscopy

Fluorescence spectroscopy intensity can be used to represent sample concentrations. In fluorescence, the molecular is first excited by adsorbing a photo from its ground

electronic state to various vibrational states. Collisions with other molecules caused the excited molecule to lose vibrational energy and reaches the lowest vibrational state. In the process, a photo is emitting.

Measurement uncertainly can caused by the instruments, such as light source intensity, wavelength characteristics, intensity of wavelength at all wavelengths, and cuvettes. It can also caused by sample distortions, re-adsorption and high concentrations of samples.

Water flux

Water flux of membranes is the rate at which water permeates a membrane.

Water flux uncertainly is related to membrane thickness, membrane pore size and pore channels and membrane surface properties.

3.5.3 Data calculation methodology

Fiber diameter

The fiber diameter data of polyacrylonitrile-zeolite are presented either as histogram figure or average bar figures. We collected around 50 sample diameter by using 5 images from scanning electron microscope and measured the fiber diameter with the help of Image J.

Ultraviolet adsorption

All the data related to creatinine adsorption are measured through ultraviolet adsorption. We first get a standard creatinine adsorption function trough linear regression between the ultraviolet intensity with creatinine concentration. Then, we tested our samples for three times and calculated the sample concentration through the linear function. The data is presented in bar figure with the height of the bar represents the average, the error bar represents the min and max data of these three repeated samples.

Fluorescence adsorption

Fluorescence spectrum are used to represent the concentration of indoxyl sulfate in samples. As we know, the environment change such as pH and types of ions will affect the fluorescence intensity of indoxyl sulfate. For each environment, both background data (as control) and sample data are presented.

Others

Scanning electron microscope and thermalgravimetric analysis data are used without further change. The water flux table in this thesis is created with the average data of three repeated water-flux test.

Chapter 4

Toxin adsorption capabilities of PAN-zeolite electrospun membranes

In this chapter, we show that the proposed composite membranes are able to adsorb water-soluble toxins. Four types of zeolite powders are tested and their abilities to adsorb creatinine are compared. An electrospinning device is set up in order to fabricate fibrous membranes with these adsorbents. Finally, the membranes are tested and their abilities to eliminate creatinine are compared.

4.1 Introduction

Although several types of hollow fiber hemodialysis membranes which can eliminate uremic toxins though diffusion process are used in clinics [16, 103, 104, 105], the hemodialysis process is still inconvenient, time consuming and expensive.

Patients with kidney failure have uremic toxins buildup, which are toxic to the body at high concentration and lead to a complex mixture of organ dysfunctions if left untreated [106]. Urea and creatinine are the common uremic toxins accumulated in chronic renal failure patients. The average concentration of urea and creatinine in patients are 38,333 $\pm$ 18,333 and 1204 $\pm$ 407 μmol, while that of normal health persons are less than 6700 and 106 μmol respectively [23].

Uremic toxins can also be eliminated by adsorption mechanisms other than the traditional diffusion mechanisms used in dialyzers nowadays. In previous research[107, 108, 109, 110], zeolite powders were used to adsorb uremic toxins. Zeolites are the most commonly used crystalline materials for molecular sieves since various types can be easily obtained either from nature or synthesized in labs. The molecular sieve properties of

zeolites as well as the fact that zeolites are non-toxic and very stable under physiological conditions make them a good alternative method to eliminate uremic toxins. By analyzing the structure of a given zeolite, especially its pore size information, one can estimate what molecules the zeolite can adsorb.

In order to use zeolites to adsorb uremic toxins, zeolites can be incorporated into a nonporous polymer to form a composite membrane which has both the properties of molecular sieving and processability [111]. Polymer membranes with zeolite fillers were investigated in depth for water purification [112, 113] and gas separation [114, 115]. Nonwoven nanobrous membranes, which can be produced through a simple electrospinning method, are an excellent choice for incorporating zeolite powders. The fibrous membranes produced by electrospinning have high porosity, fine fiber diameters, large surface area-to-volume ratio, good interconnected pore structures and great permeability [116, 117].

To fabricate a hemodialysis membrane, zeolites were incorporated into electrospun PAN (polyacrylonitrile) polymeric nanofiber membranes. PAN porous membranes have a variety of excellent characteristics including good thermal and mechanical stability, tolerance to bacteria and photo irradiation [118], and excellent membrane forming properties [117]. PAN membranes made through traditional phase inversion method are used as dialyzer membranes in clinic [119, 120, 121].

In this chapter we fabricated and characterised PAN nanofiber membranes and PAN-zeolite composite membranes with two types of zeolite, 840-NHA and 940-HOA, at differing concentrations (5, 10, 15, 20, 25, 30 & 35 wt%). Then, the creatinine absorption capacity of both free zeolites and incorporated zeolites were evaluated. We anticipate that PAN-zeolite membrane will have a quick speed to eliminate uremic toxins because of the fast adsorption speed of zeolites. The fibrous PAN-zeolite membrane, which combines adsorption and diffusion together, could be a new choice for hemodialysis membranes.

4.2 Materials and methods

4.2.1 Materials

Polyacrylonitrile (PAN) with molecular weight of 150,000, dimethylformamide (DMF) and creatinine were purchased from Sigma Aldrich, Co. HSZ-series zeolites 500-KOA (L), 720-KOA (Farrierite), 840-NHA (ZSM-5) and 940-HOA (Beta) powders were purchased from Tosoh. Ultrapure water was also used.

4.2.2 Sample preparation

Preparation of nanofibrous PAN membranes

PAN electrospun solutions were prepared by dissolving 6 wt%, 8 wt% and 10 wt% PAN powders in DMF at 60 °C for 12 h. The PAN nanofibrous membranes were prepared using a laboratory set-up electrospinning equipment. The electrospun voltage was 22.5 kV, feed rate was 1 ml h^{-1} and tip to collector distance was 15 cm. The relative humidity and temperature were kept between 48-52% and $23 - 26\,^{\circ}\mathrm{C}$ respectively. In all experiments, 21 gauge needles were used.

Preparation of PAN-zeolite composite membranes

PAN-zeolites solutions were prepared by adding zeolite powders into 10 wt% PAN electrospun solution from section 2.3.2. The composite solution was further stirred at room temperature for 12 h and ultrasonicated for 1 h during the stirring process. Composite solutions with zeolite to PAN polymer ratio varied from 10:100, 15:100, 20:100, 25:100, 30:100 to 35:100 were prepared. If a sample contains 10 wt% 840-NHA in PAN polymer, the samples were named 10-840, other samples were also named accordingly. The electrospinning factors were kept the same as section 2.3.2 except for the tip to collector distance, which was 19 cm. At this distance, a flat composite membranes were obtained smoothly.

4.2.3 Measurement

Scanning electron microscopy (SEM)

The morphology of PAN and PAN-zeolite membranes was examined using a Zeiss scanning electron microscope. The diameter of the fibers was measured by ImageJ software for 50 times. The PAN membranes and PAN-zeolite membranes were also examined by energy dispersive X-ray spectroscopy (EDX) equipped in SEM.

Thermal gravimetric analysis (TGA)

Thermal gravimetric analysis (TGA) of the samples was conducted using the Q500 TGA instrument from TA Instruments. The temperature scans were taken from room temperature to 800 °C at 10 °C min^{-1} in an ambient atmosphere at an air ow of 20 ml min^{-1}.

Adsorption studies of zeolite powders

UV-Visible spectrophotometer (Ultraspec 2100 pro) was used to measure the absorbance of the creatinine solution. Creatinine solutions with various concentrations (50, 100, 150, 200, 250, 312.5 and 400 μ mol L^{-1}were made by adding creatinine powders into beakers with ultrapure water and then stirred overnight. An UV calibration standard line for creatinine in ultrapure water was prepared based on the absorption value of creatinine solutions at 234 nm. Creatinine solutions with concentration of 0, 50 , 100 , 150 , 200 and 312.5 and 400 μmol L^{-1} were tested for drawing the UV calibration standard line. Creatinine adsorption capacity of free zeolite was first tested by the following procedure. 0.025 g 500 KOA, 720 KOA, 840-NHA and 940-HOA powders were added into 4 vials with 10 ml 200 μmol L^{-1}creatinine solution and were shaken at 37 C for 3 h at a speed of 165 rpm in a shaker (C25, New Brunswick Scientific, USA). The adsorption speed of 940-HOA powders was further measured using the same procedure by shaking them for 0, 5, 10, 20 minutes and 3 h. Finally, the adsorption capacity of 940-HOA powders in 50 , 200 , 312.5, and 625 μmol L^{-1} creatinine solutions were also measured for 20 minutes.

Adsorption study of zeolites incorporated in membranes

Creatinine adsorption capacities of different composite membranes were tested in a flow state according to the following procedure. First, composite membranes with a diameter of 10 mm were cut and positioned in a syringe filter cartridge (EMD Millipore, CA). Then, 200 μmol L^{-1} creatinine solution was introduced into the inlet of the cartridge to flow through the membrane and exit through the outlet at the flow rate of 1 ml h^{-1} for 3 h. Finally, UV absorption spectrums of solutions collected from the outlet were measured. Three samples of each type of membrane were tested. The creatinine adsorption capacity of 30-940 membranes with different thicknesses were further measured following the same procedure.

4.3 Results and discussion

4.3.1 Data presentation methods

In this chapter, all the data related to adsorption test are presented through bar figures. In these figures, the height of the bar is the average value and the error bar is the range of value. The data are presented in this way to show the value range of these data.

The average diameter of fibers are also presented using bar figure. The height represents the average fiber diameter of 50 samples measured using Image J based on 5 SEM images.

4.3.2 Fabrication of PAN membranes

Electrospinning is a process based on electrohydrodynamics to form continuous thin fibers, which can further form fibrous membranes [122]. This membrane fabrication method is simple, easy and cost-effective. Various polymers have been used in electrospinning processes [123, 124, 125, 126]. Among them, electrospun PAN membranes have attracted much attention due to its excellent thermal stability and insolubility to most solvents [127]. PAN based membranes have been widely used in water treatment [128, 129], protein filtration and dialysis. In this chapter, PAN fibrous membranes with different concentrations were fabricated by adjusting voltage, tip to collector distance,

flow rate, temperature and humidity during the electrospinning process. The best conditions to get smooth fibers were at 22.5 kV with a flow rate of 1 ml h^{-1} in a relative humidity of 50% at 25 °C. These conditions were used in the following experiments. The morphology of the fibers with 6 wt%, 8 wt% and 10 wt% of PAN in DMF is shown in Figure 4.1. Smooth fibers with rare beads are observed in all the figures. The rare beads in Figure 4.1 have probably formed due to the disturbance of electrospinning parameters, such as flow rate, humidity, voltage and current. The diameter of fibers with 6 wt% of PAN is 141 nm, which is the thinnest among all the three samples. The diameter of 8 wt% of PAN is 411 nm and that of 10 wt% of PAN is 673 nm. These average fiber diameters are measured by collecting 50 samples by Image J using 4-5 different SEM images. Typically, the fiber diameter would increase with increased polymer concentration when other fabrication factors are unchanged. Solutions with more than 15 wt% of PAN in DMF were not used since their viscosities were too high for the electrospinning apparatus.

4.3.3 Fabrication of PAN-zeolite membranes

Polymeric membranes filled with zeolites have their advantages since they combine molecular sieve property of zeolites and processability of polymers12. Polymer-zeolite membranes have been used for gas separation [130, 111], ethanol-water separation [131] and water treatment [132]. To maintain a relatively high flow rate of 1 ml h^{-1}, the 10 wt% PAN in DMF was chosen as the polymer solution base for incorporating zeolites. To better distribute the zeolites within the polymer, the composite solution was stirred for over 12 h before electrospinning. Furthermore, the solutions were ultrasonicated twice for 30 min during the stirring process.

Figure 4.2 shows SEM images of PAN-zeolite composite membranes with 940 (10 & 30 wt%) and 840 (25 & 30 wt%). In these images, a mix of bead and fiber morphology can be observed. The formation of beads was due to relatively large zeolite particle sizes (0.67-2 μm) when compared with fiber diameters (277-419 nm, shown in Figure 4.4). The average fiber diameters used in Figure.4.4 were collected using 5 SEM images by Image J, the data presented in the figure is the average of 50 measured data. Another potential reason was due to poor distribution or aggregation of zeolite

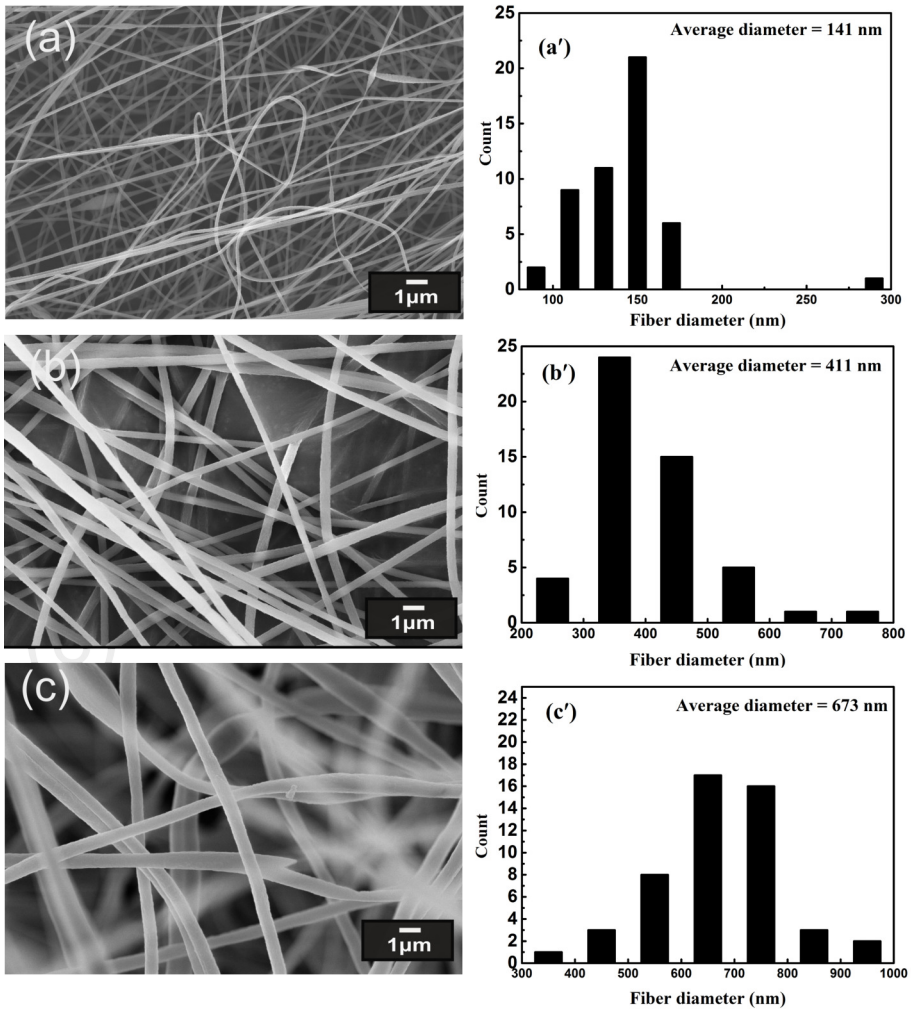


Figure 4.1: SEM images and diameters of electrospun PAN nanofibers produced in DMF with polymer concentrations of 6 wt% (a), 8 wt% (b) and 10 wt% (c).

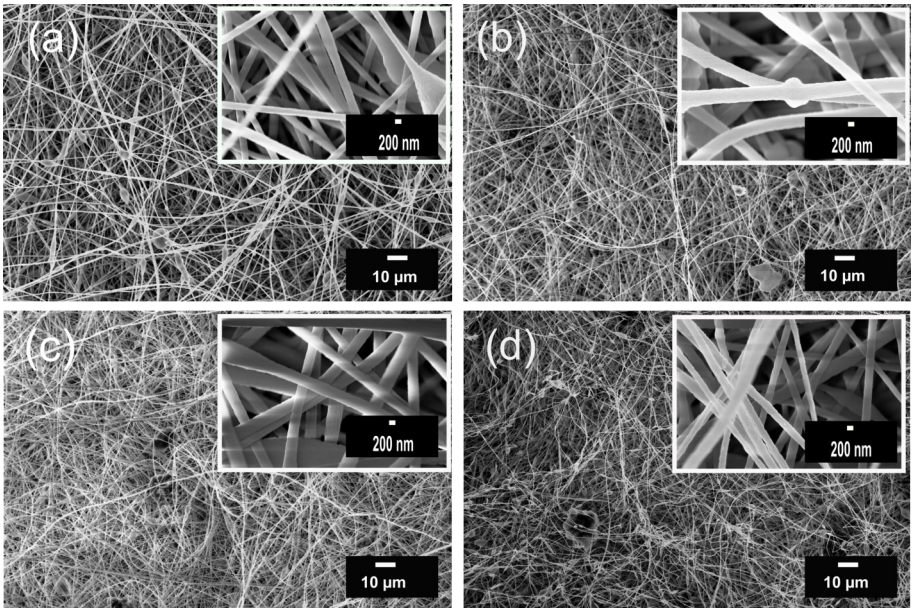


Figure 4.2: SEM images of PAN-zeolite nanofibrous composite membranes. 10-940 (a), 30-940 (b), 25-840 (c) and 30-840 (d). (PAN is 10 wt% based)

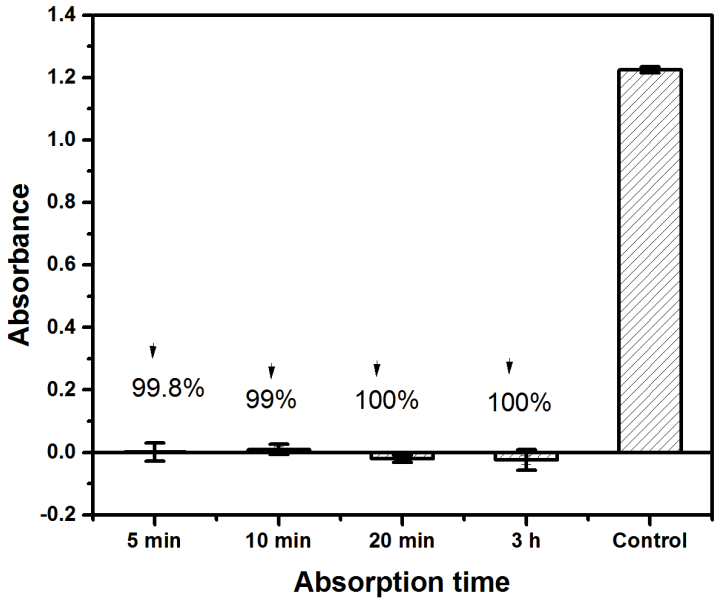


Figure 4.3: Creatinine adsorption speed of 940 zeolites in 200 μmol L^{-1} creatinine solution.

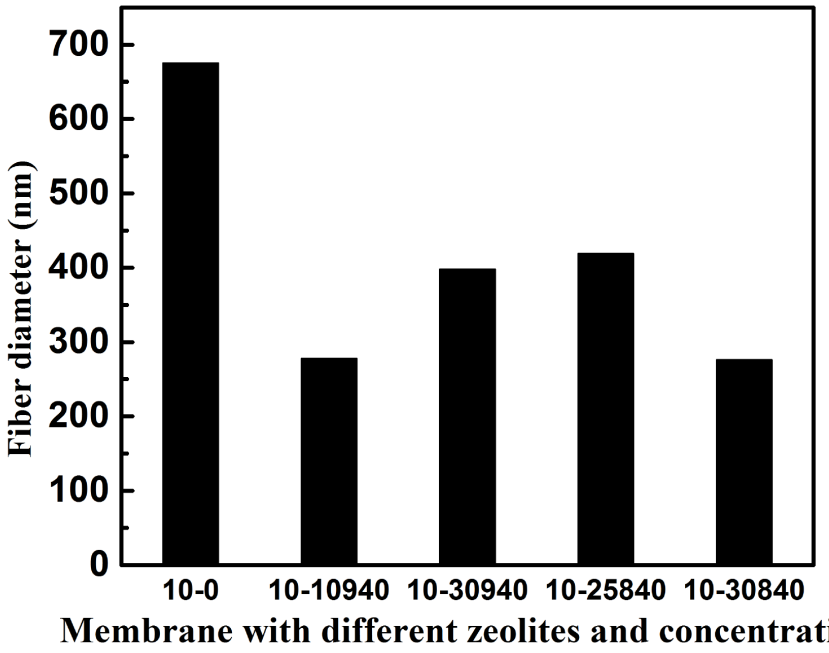


Figure 4.4: Fiber diameters comparison between membrane with various zeolite at different concentration.

particles. However, smooth nanofibers existed between the beads. Figure 4.4 shows a comparison between the average fiber diameter of PAN and PAN-zeolite membranes. The fiber diameter of 10 wt% PAN membrane without zeolites was 675 nm while the fiber diameter in the membrane with 10 wt% 940 (Figure 4.2 (a)) was 277 nm and that in the membrane with 30 wt% 940 (Figure 4.2 (b)) was 398 nm. It further indicated that the fiber diameter in the membrane with 25 wt% 840 (Figure 4.2 (c)) was 419 nm while that in the membrane with 30 wt% 840 (Figure 4.2 (d) was 277 nm. From these data we know that the membrane with zeolites had decreased fiber diameter when compared with PAN membrane and the fiber diameters in PAN-zeolite membrane were relevant to zeolite type (size and shape) and concentrations. The properties of zeolites used in this paper are provided in Table 4.1.

To further determine the successful incorporation of zeolites into the membrane, SEM/Si-mapping images are presented in Figure 4.5. Silicon atom was chosen for it existed in zeolites, but not in PAN polymers. Si-mapping analysis further presented the Silicon atomic percentages in PAN and PAN-zeolite membranes, show in Table 4.2. There are merely 0.07% Silicon atoms in PAN membranes while 14.01% in the mem-

Table 4.1: Characteristic data of various zeolites used in this study, supplied by Tosoh Corporation.

	500KOA	**720KOA**	**840NHA**	**940HOA**
Cation Type	K	K	NH_4	H
SiO_2/Al_2O_3(mol/mol)	6.1	18	40	40
Na_2O(wt%)	0.25	1.3	0.05	0.05
K_2O(wt%)	16.8	5.6	-	-
Surface Area(BET, m^2/g)	290	170	330	530
Cystal Size(μm)	0.4	≤ 1	2x4	0.5-1.0

brane with 10 wt% 940. Figure 4.5(a, b) is the Si-mapping of 10 wt% 940-HOA PAN membranes; no aggregation of Si was observed. Contrarily, large areas of Si aggregation were observed in membranes with 30 wt% 940-HOA (Figure 4.5 (c, d)). Uniform distributions of zeolite within the membrane were harder to achieve when incorporating higher concentration zeolite. Similarly, mildly aggregation were observed in Figure 4.5(e, f), which had 25 wt% of 840-NHA.

TGA testing was further carried out to precisely determine the percentage of zeolites inside the membranes. At 800 °C, PAN polymer is totally burned and only zeolites are left on the pan. As indicated in Figure 4.6, PAN membrane (Figure 4.6(a)) had 0 weight left at 800 °C. 10-10940 (Figure 4.6(b)) had 10% weight left at 800 °C. This indicated that 100% of the fed zeolites are incorporated inside the membranes. Similarly, 10-20940 (Figure 4.6(c)) had 18% weight left at 800 °C, which indicated that 90% of the fed zeolites (20 wt% 940) were incorporated into the membranes. The membranes fed with 30 wt% zeolite had around 24 wt% of zeolites inside the membrane (as shown in 10-30 940, Figure 4.6(d)). From the TGA analysis we can see that the deviation between the zeolite in feed and zeolites in membrane grew larger with increased zeolite feeding percentages. The date from Table 4.2 further supported this.

The above analysis shows that zeolite-PAN nanofiber membranes can be successfully fabricated through the electrospinning method. However, with increased zeolite fed percentage, it is harder to incorporate all the zeolites in the membrane and higher percentage of zeolites tend to coagulate inside the membranes.

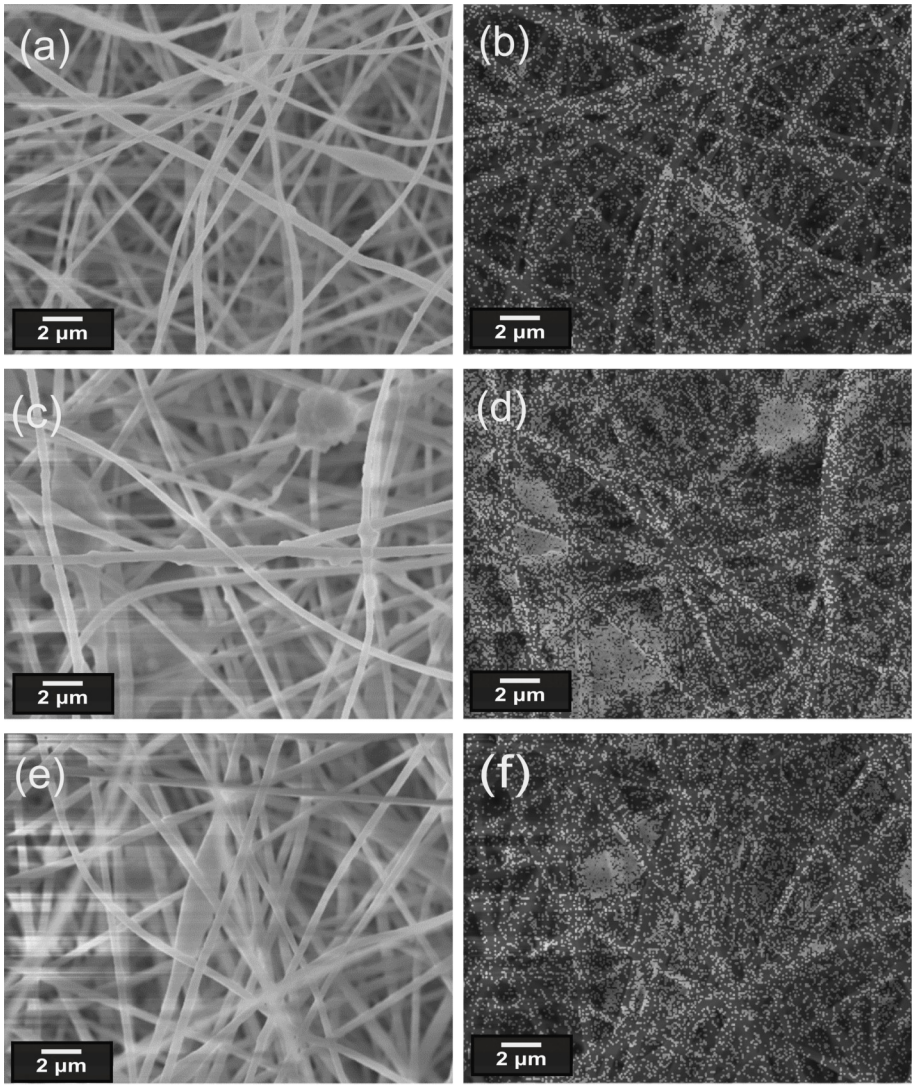


Figure 4.5: SEM/Si mapping images of zeolite-PAN membrane with zeolites: 10-940 (a) with Si-mapping (b), 30- 940 (c) with Si-mapping (d) and 25-840 (e) with Si-mapping (f).

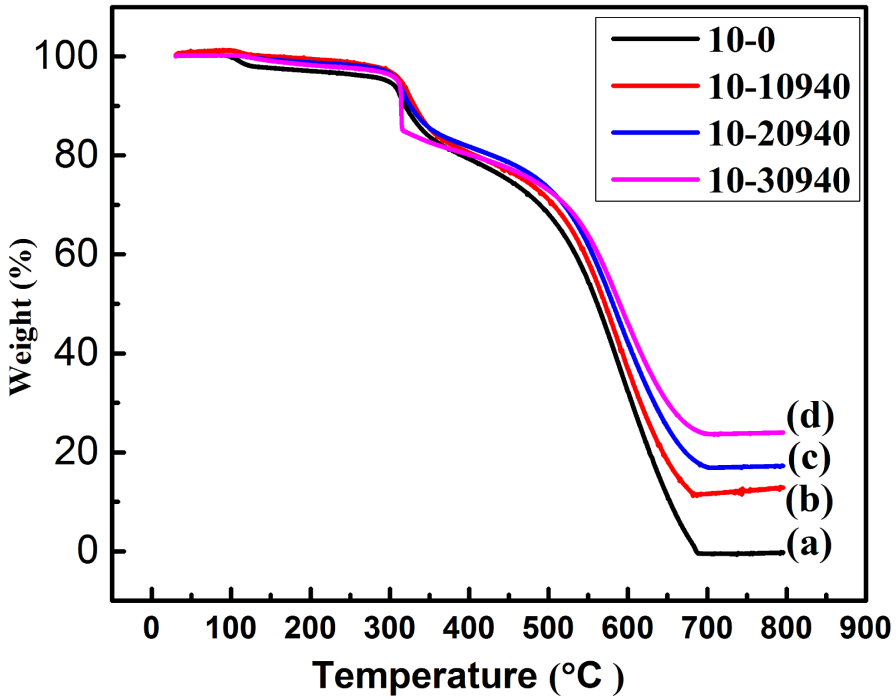


Figure 4.6: TGA analysis of composite membranes.

Table 4.2: Summaries of TGA test results: Comparison of zeolite percentages in feed and in membrane.

Sample	Zeolites in feed(%)	Zeolite in membrane(%)	Deviation(%)
10	0	0	0
10-10940	10	10	0
10-15940	15	15	0
10-20940	20	17.5	12.5
10-25940	25	21	16
10-30940	30	24	20
10-35940	35	24	31
10-10840	10	10	0
10-20840	20	15	25
10-25840	25	22	12
10-30840	30	22	26.67

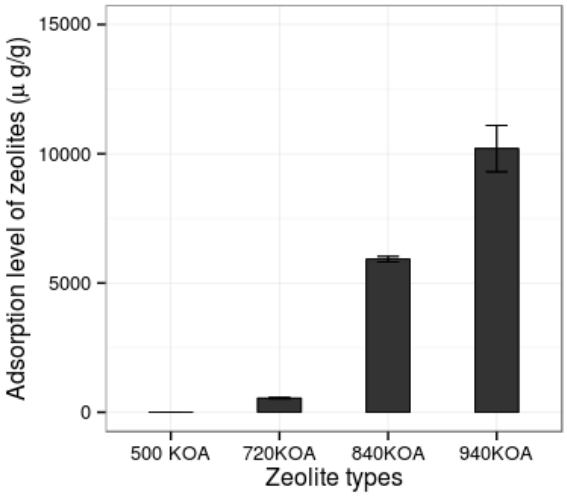


Figure 4.7: Creatinine adsorption level of zeolites in 200 μmol L^{-1} creatinine solution for 3 h.

4.3.4 Creatinine adsorption capacity of zeolites

To determine the creatinine adsorption capacity of zeolite, several experiments were designed and carried out. Figure 4.7(a) presents the adsorption capacity of various zeolite in both 200 μmol L^{-1} creatinine solutions for a 3 h period. 500-KOA were non-adsorbent to creatinine since their pore size was smaller than that of creatinine [133]. 720-KOA and 840-NHA reduced 10% and 42% of creatinine in 200 μmol L^{-1} creatinine solution. 940-HOA had the best creatinine adsorption capacity; almost all the creatinine from both 200 μmol L^{-1} and 50 μmol L^{-1} creatinine solution was adsorbed. Figure 4.7(b) exhibits the creatinine adsorption capacity of zeolites by zeolite mass. 940-HOA$'$s creatinine adsorption capacity is as high as 9050 μg g^{-1} in a 200 μmol L^{-1} solution. This experiment revealed that creatinine adsorption capacity was related to zeolite type.

940-HOA was chosen to further evaluate its creatinine adsorption speed. Figure 4.3 demonstrates that the adsorption speed of zeolites was very quick, 0.025 g of 940-HOA powders adsorbed all of creatinine from 10 ml 200 μmol L^{-1} creatinine solution in 5 min.

To further reveal how initial creatinine solution and adsorption time affected creatinine adsorption capacity of zeolites, 940-HOA powders were added to creatinine solu-

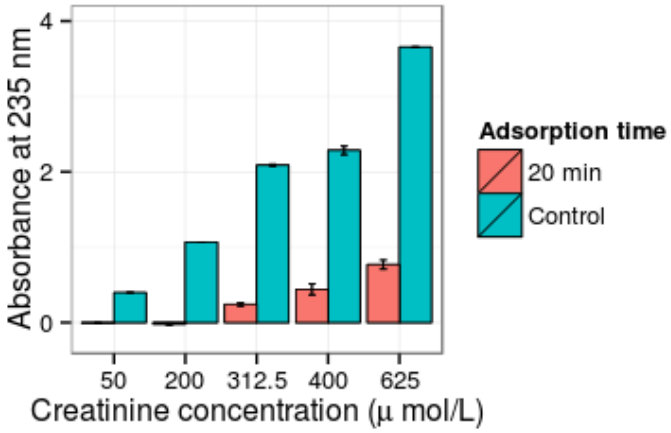


Figure 4.8: Creatinine adsorption percentages of 940-HOA zeolites in different creatinine concentrations for 20 min.

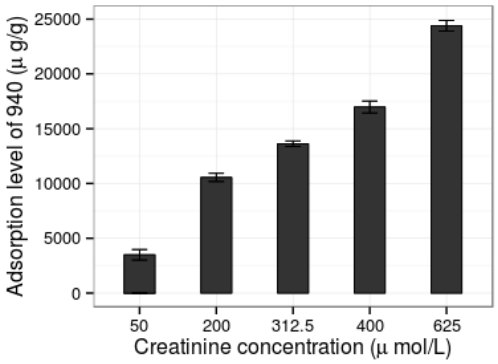


Figure 4.9: Creatinine adsorption capacity of 940-HOA zeolites in different creatinine concentrations for 20 min.

tions with concentrations from 50 to 625 μmol L^{-1} for 20 min. Figure 4.8 showed that, in 20 min, 940 could adsorb 100, 100, 90, 76 and 70% of creatinine from 10 ml 50, 200, 312.5, 400 and 625 μmol L^{-1} creatinine solution correspondingly. To express the data in adsorption capacity method, 940-HOA zeolite exhibited higher adsorption capacity with increased creatinine concentration, as shown in Figure 4.9. It had the lowest capacity (4930 μg g^{-1}) in 50 μmol L^{-1} creatinine solution, a gradually increased capacity in (11236, 13621 &16126 μg g^{-1}) 200, 312.5 & 400 μmol L^{-1} creatinine solution, and the greatest capacity (24452 μg g^{-1}) in 625 μmol L^{-1} creatinine solution. From this figure, we can tell that the higher creatinine solution concentration, the higher 940's adsorption level.

4.3.5 Creatinine adsorption capacity of zeolite-PAN membranes in a flow state

All the membranes used in this experiment were electrospun for 1 h at a flow rate of 1 ml h^{-1}. To test the creatinine adsorption capacity of PAN-zeolite membranes, the membranes were cut into 10 mm disks and then mounted in syringe filter cartridges. A solution of 200 μmol L^{-1} creatinine was filtered through the membrane at a rate of 1 ml h^{-1} for 3 h. Figure 4.10(a) reveals that the membranes with 840-NHA or 940-HOA zeolites could successfully adsorb creatinine at distinct levels. Among the membranes with 840-NHA, the membrane with 25 wt% zeolites (10-25) reduced as much as 43% creatinine in 3 h. Similarly, within all the membranes with 940-HOA, 10-30 reduced 52% of the creatinine in solution. Figure 4.10(b) presents the creatinine adsorption capacity of each membrane by membrane mass as well as zeolite mass. Similarly, 10-25 membranes with 840-NHA and 10-30 membranes with 940-HOA both showed the highest creatinine adsorption capacity by membrane mass: 2545 μg g^{-1} and 2658 μg g^{-1} respectively. Figure 4.10(b) demonstrates that the membrane with 10 wt% zeolite had the highest creatinine adsorption value by zeolite mass (19117 μg g^{-1} for 840-NHA and 14140 μg g^{-1} for 940-HOA). A potential reason was that the zeolite distribution was more uniform and less aggregated inside the membrane at low zeolite level, as supported by Figure 4.5.

By collecting the membranes over different spinning times while keeping all the

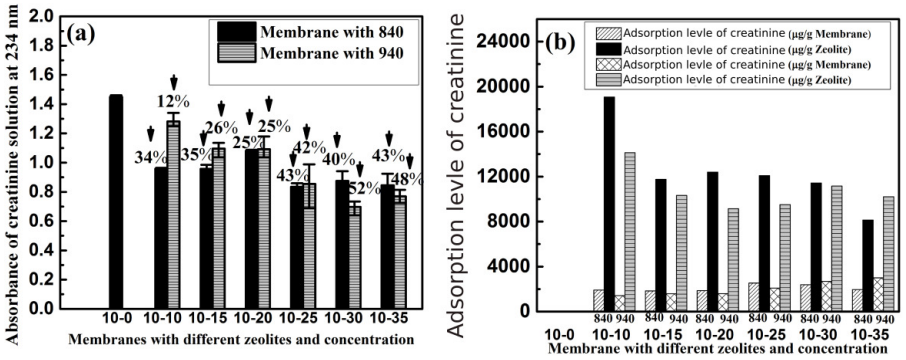


Figure 4.10: Creatinine adsorption capacity of membranes with different concentration of 840-NHA and 940-HOA under flow state in 200 μmol L^{-1} creatinine solution for 3 h. The absorbance value of creatinine solution and the creatinine adsorption percentage was shown in (a); Creatinine adsorption capacity of zeolites by fiber mass and zeolite mass were presented in (b).

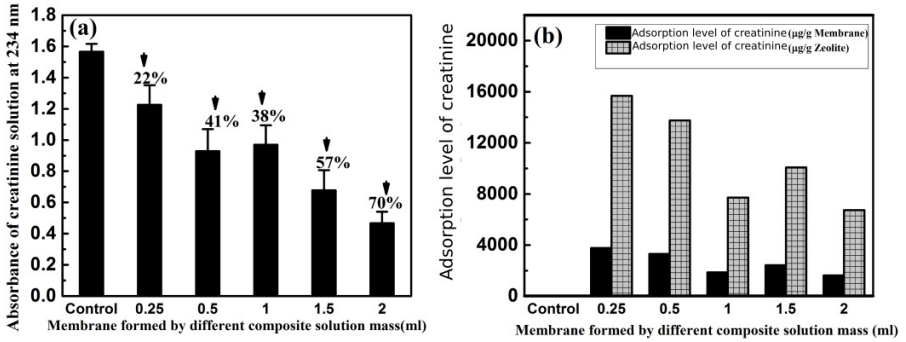


Figure 4.11: Creatinine adsorption capacity of membrane with 30 wt% 940 zeolite with various thickness under flow state in 200 μmol L^{-1} creatinine solution for 3 h. The absorbance value of creatinine solution and the creatinine absorption percentage (a); Creatinine adsorption capacity of zeolites by membrane and zeolite mass (b).

other experimental factors the same, we could get membranes with various thicknesses. Figure 4.11 shows the creatinine adsorption capacity of membranes with various thicknesses. It shows that, the thinner the membrane, the higher the creatinine adsorption capacity by membrane mass and zeolite mass. The membranes collected for 0.5 h at a flow rate of 1 ml h^{-1} is recommended, since it had good creatinine absorption capacity as well as the potential for high mechanical strength. Creatinine concentration for a healthy person is normally less than 106 μmol, while that of patients with kidney disease is around 1204 407 μmol. The creatinine adsorption capacity of 940-HOA increased from 2262 μg g^{-1} in 50 μmol L^{-1} creatinine solution to 25423 μg g^{-1} in 625 μg L^{-1} creatinine solution. We can expect better creatinine adsorption capacity of 940-HOA in solutions with higher creatinine concentration. Furthermore, the adsorption speed of 940-HOA is very quick (0.025 g 940-HOA will eliminate 91% of 20 μmol creatinine in 5 min). When we compared the creatinine adsorption capacity of zeolite powder and that of zeolite incorporated in membranes, zeolite showed improved capacity inside the membrane. Specifically, the creatinine adsorption capacity was 3733 μg g^{-1} for 840 powders while it was 19230 μg g^{-1} for 840 inside the membrane. On the other hand, the capacity of 940-HOA powders was 8823 μg g^{-1} while it was 13574 μg g^{-1} for 940 inside the membrane. The fact that 840 and 940 zeolites had improved capacity inside the membranes might be because of the following two reasons. First, the zeolites particles tended to coagulate even though they were shaken at 165 rpm during test since there is no force to separate zeolites particles. However, they were better distributed in the polymer matrix after stirring overnight. As a result, the effective surface area of zeolites to adsorb creatinine was largely increased in the membranes. The second reason is related to the testing method. The adsorption capacity of zeolite powder was tested inside vials by shaking them at 165 rpm. And the composite membrane was tested in flow state.

We also noticed that the creatinine adsorption capacity of 840 in membrane improved four times compared with that of 840 powders while that of 940-HOA improved merely 0.5 times in the membrane when comparing with 940 powder. This is possibly because the mean particle size of 840-NHA was 2 μm while that of 940-HOA was 0.67 μm. 840-NHA powders had significantly larger particle diameters when compared with the PAN fiber diameters (277-410 nm), so a lower percentage of zeolite particle surface

was blocked by fibers. On the other hand, 940 had closer particle size to the PAN fiber diameters (276-398 nm), thus 940 zeolite powders can be buried inside the zeolites easily. Future work will investigate how the particle size of zeolite affects the adsorption capacity of PAN-zeolite membranes as well as explore the possibility of using PAN-zeolite to eliminate creatinine from blood.

4.4 Conclusion

In summary, in this chapter we have successfully 1) identified 940 and 840 zeolite as excellent uremic adsorption adsorbents; 2) fabricated PAN-zeolite nanofibrous membranes through an electrospinning process; 3) compared creatinine adsorption capacity of zeolites as free powders to that of zeolites incorporated into membranes.

The results showed that PAN-zeolite membranes are promising hemodialysis membranes, since they can adsorb water-soluble toxins at a fast speed. These membranes proved able to eliminate toxins through adsorption which is an excellent result. Together with diffusion and convection mechanisms, we can expect these membranes to perform better as hemodialysis membranes. The quick adsorption speed can also potentially reduce the hemodialysis time needed for hemodialysis.

Furthermore, by comparing the creatinine adsorption capacity of 840-NHA and 940-HOA, we noticed that the particle size and the surface area play an important role in determining the adsorption capacity of the membranes. In next chapter, we carry out an study to determine how the particle size and shape affects the membranes' adsorption.

Chapter 5

Effect of size and shape on zeolite adsorption

In this chapter, we study how do the size and shape of zeolites affect their adsorption when incorporated inside fibrous membranes. Our goal is to obtain an insight on how to choose zeolites.

5.1 Introduction

Previous studies showed that zeolite and active carbon can be used as uremic toxins adsorption materials. More specifically, MFI-type zeolites eliminated 85% of p-cresol in the pathologic uremic concentration range [134]. 940-HOA and 840 NHA zeolite had a 200 μmol g^{-1} creatinine adsorption capacity in 200 μmol g^{-1} creatinine solution [133]. Activated carbon was used to adsorb uremic toxins such as creatinine, p-cresylsulfate, indoxyl sulfate and hippuric acid [135, 21]. Na-STI (stilbite) was used to adsorb urea while Ca-STI, K-STI and Na-STI displayed the ability to adsorb urea acid [23].

In Chapter 4 [136], we found that PAN-zeolite fibrous membranes can adsorb uremic toxins. We also found that zeolites with different molecular structures have different adsorption capacity. Zeolite particle size was an important factor which affected the creatinine uptake ability when incorporated inside the membranes. Despite evidence that zeolite particle size and shape matters on its adsorption ability as powders and as fillers, this has not yet been investigated in detail [137].

To compare uremic toxin uptake of zeolites with different particle sizes and shapes, three types of zeolite from the ZSM-5 group were chosen. Besides comparing their creatinine uptake ability as powders, zeolites were also incorporated into polyacrylonitrile (PAN) polymeric nanofibers that formed composite membranes [137, 111]. The PAN fibrous membranes are good candidates for hemodialysis membranes since they have high

porosity, fine fiber diameters, large surface area-to-volume ratio, good interconnected pore structures and high permeability [116, 138]. The PAN polymer also has a variety of excellent characteristics including good thermal and mechanical stability, tolerance to bacteria and photo irradiation [139], and excellent membrane forming properties [117].

Creatinine is the most common molecule used in studies to represent uremic toxins. It is one type of uremic toxin and it is produced by the breakdown of creatine phosphate in muscles. Free creatinine concentration in the blood of healthy persons is relatively low, around 106 μmol, but can reach up to 1204 $\pm$ 407 μmol in cases of renal failure [23]. For this reason, creatinine is also used in this chapter as a representative uremic toxin.

The aim of this chapter is to examine how do particle size and shape affect creatinine uptake by ZSM-5 zeolites. First, we study the creatinine uptake ability of spherical microparticle 840, spherical nanoparticle P-87 and rod-like nanoparticle P-371 zeolites in creatinine solutions. Their creatinine uptake levels are measured in creatinine solutions with different concentrations, volumes and adsorption times. Then, we incorporate the three zeolites inside their respective nanofibrous membranes and measure their creatinine uptake abilities. Finally, the creatinine uptake ability by zeolites in membrane is compared with that of their respective powders'.

5.2 Sample preparation

5.2.1 Materials

Polyacrylonitrile (PAN) with molecular weight of 150,000, dimethylformamide (DMF) and creatinine were purchased from Sigma Aldrich, Co. HSZ-series zeolite 840-NHA (ZSM-5) powders were purchased from Tosoh. Nano ZSM-5 P-87 and P-371 were purchased from ACS Materials, LLC. Ultrapure water was also used.

5.2.2 Preparation of PAN-zeolite composite membranes

A 10 wt% PAN solution was made first by dissolving PAN powders in DMF and stirring overnight at room temperature. PAN-zeolite composite solutions were prepared by adding zeolite powders into the 10 wt% PAN solutions. The composite solutions were

stirred overnight again and ultrasonicated for 1 h during the stirring process. PAN-zeolite composite solutions of 840, P-87, and P-371 were prepared with zeolite to PAN ratio of 3: 10. PAN-zeolite composite membranes were fabricated using self-built electrospinning equipment. The voltage, feed rate, tip to collector distance, relative humidity and temperature were set as 22.5 kV, 1 ml h^{-1}, 15 cm, 10% and 22 °C respectively.

5.2.3 Measurement

Dynamic light scattering (DLS)

A dynamic light scattering (DLS), Zetasizer Nano ZS (Malvern) was used to analyze the particle size distribution of the zeolite powders. The powders were dissolved in water at a concentration of 8.6 g L^{-1} and all samples were tested three times.

Adsorption studies of zeolite powders

Creatinine adsorption capacity of three zeolites with different size and shape was tested by the following procedure. To test the effect of the creatinine concentration on zeolites' adsorption capacity; 0.025 g 840, P-87, and P-371 powders were respectively added into vials with 10 ml 50, 200, 400, and 625 μmol L^{-1} creatinine solutions. The vials were shaken at a speed of 165 rpm at 37 °C for 3 h in a shaker (C25, New Brunswick Scientific, USA). To evaluate the creatinine solutions' volume effect on zeolites' creatinine adsorption capacity; 0.025 g 840, P-87, and P-371 powders were added into 3 ml, 6 ml, 10 ml, and 18 ml 400 μmol L^{-1} creatinine solution and shaken for 3 h at the same conditions as above. Finally, the effect of adsorption time on zeolites' creatinine adsorption capacity was measured; 0.025 g 840, P-87, and P-371 powders were added into 10 ml 400 μmol L^{-1} creatinine solution and were shaken for 5 min, 10 min, 15 min, 20 min, 1 h, and 3 h at the same condition as above. All the experiments were repeated three times. A UV-Visible spectrophotometer (Ultraspec 2100 pro) was used to measure the absorbance of the creatinine solution. A UV calibration standard line for creatinine in ultrapure water was prepared based on the absorption value of creatinine solution at 234 nm. Solutions with concentration of 50, 100, 150, 200 and 250 μmol L^{-1} were tested for drawing the UV calibration standard line.

Adsorption studies of PAN-zeolite composite membranes

The creatinine adsorption capacity of different composite membranes were tested in a flow state according to the following procedure. First, circular composite membranes with a diameter of 10 mm were cut and positioned in a syringe filter cartridge (EMD Millipore, CA). Then, a 400 μmol L^{-1} creatinine solution was introduced into the inlet of the cartridge to flow through the membrane and exit through the outlet at a flow rate of 1 ml h^{-1} for 3 h. Finally, UV absorption spectra of solutions collected from the outlet were measured. Three samples of each type of membrane (30 wt% of 840, P-87 and P-371) were tested.

5.3 Results and discussion

5.3.1 Zeolite powder analysis

The SEM images and particle size distribution of the three zeolite particles used in this paper are shown in Figure 5.1. The framework is ZSM-5 and they all have relatively uniform particle sizes. 840 zeolite particles (Figure 5.1(a,d)) are relatively spherical with an average particle diameter of 1849 nm, while P-87 zeolite particles (Figure 5.1(b,d)) are also spherical with an average particle diameter of 578 nm. P-371 zeolite particles (Figure 5.1(c,d) are rods with particle size of 300 700 nm. Figure 5.1(d) shows the average particle size of the three zeolites, as measured by DLS. From Figure 5.1 we can confirm that 840 and P-87 zeolites have difference in particle size, while P-87 and P-371 zeolites have different shapes.

5.3.2 Fabrication of PAN and PAN-zeolite composite membranes

Electrospinning is a simple and effective way to make porous membranes which can be used in water treatment, bacterial and particle filtration and dialysis. In this paper, PAN nanofibrous membranes as well as PAN-zeolite composite membranes were fabricated by adjusting important influence factors such as voltage, feed rate, tip-to collector distance and humidity. The best electrospinning conditions were found to be voltage of 22.5 kV, feed rate at 1 ml h^{-1}, distance of 15 cm, and humidity of 10%, respectively. The

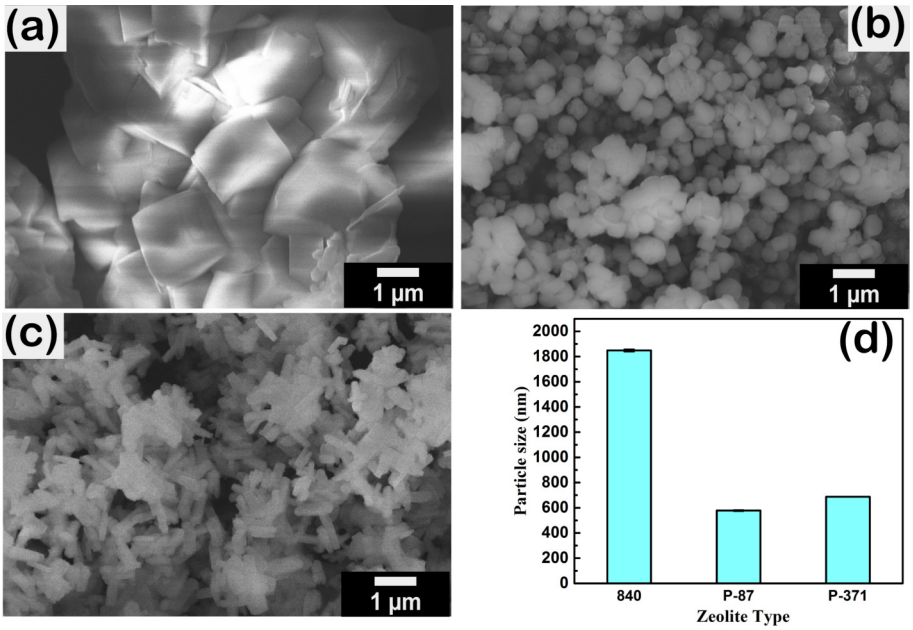


Figure 5.1: SEM images of zeolite particles and their average particle size. 840 (a), P-87 (b), P-371 (c) and particle size distribution.

morphology of PAN membranes and PAN-zeolite composite membranes are shown in Figure 5.2. Figure 5.2(a) shows a membrane with 10 wt% PAN. Smooth fibers with rare beading can be observed in the SEM image. The average diameter of the fibers is 9 nm (Figure 5.2(b)), which is the thinnest among the four samples. After zeolites were incorporated into the membrane, the edge of the fiber is coarser. We can see zeolite particles attached along with the fiber, as indicated by Figure 5.2(c,e,g). The reason is that zeolite particles can appear on the surface of the fiber, partially in the fiber or completely within the fiber, which disturbs the smooth fiber morphology. When we compare the average diameter of fibers with different zeolite particles, we observe that the composite membrane with microparticle 840 zeolite (Figure 5.2(c,d)) has the thickest fiber diameter, at 286 nm. The membrane with P-371 zeolite has an average diameter of 280 nm (Figure 5.2(h)) while the membrane with P-87 has an average diameter of 257 nm (Figure 5.2(f)). From Figure 5.2 we can see that the membrane presented an increased fiber diameter after zeolite was incorporated. The increase was relevant to zeolite particle size.

EDX test shows the atomic distribution in the image. Silicon (Si) atoms were chosen to represent zeolite distribution since in our samples it could only be found in zeolites.

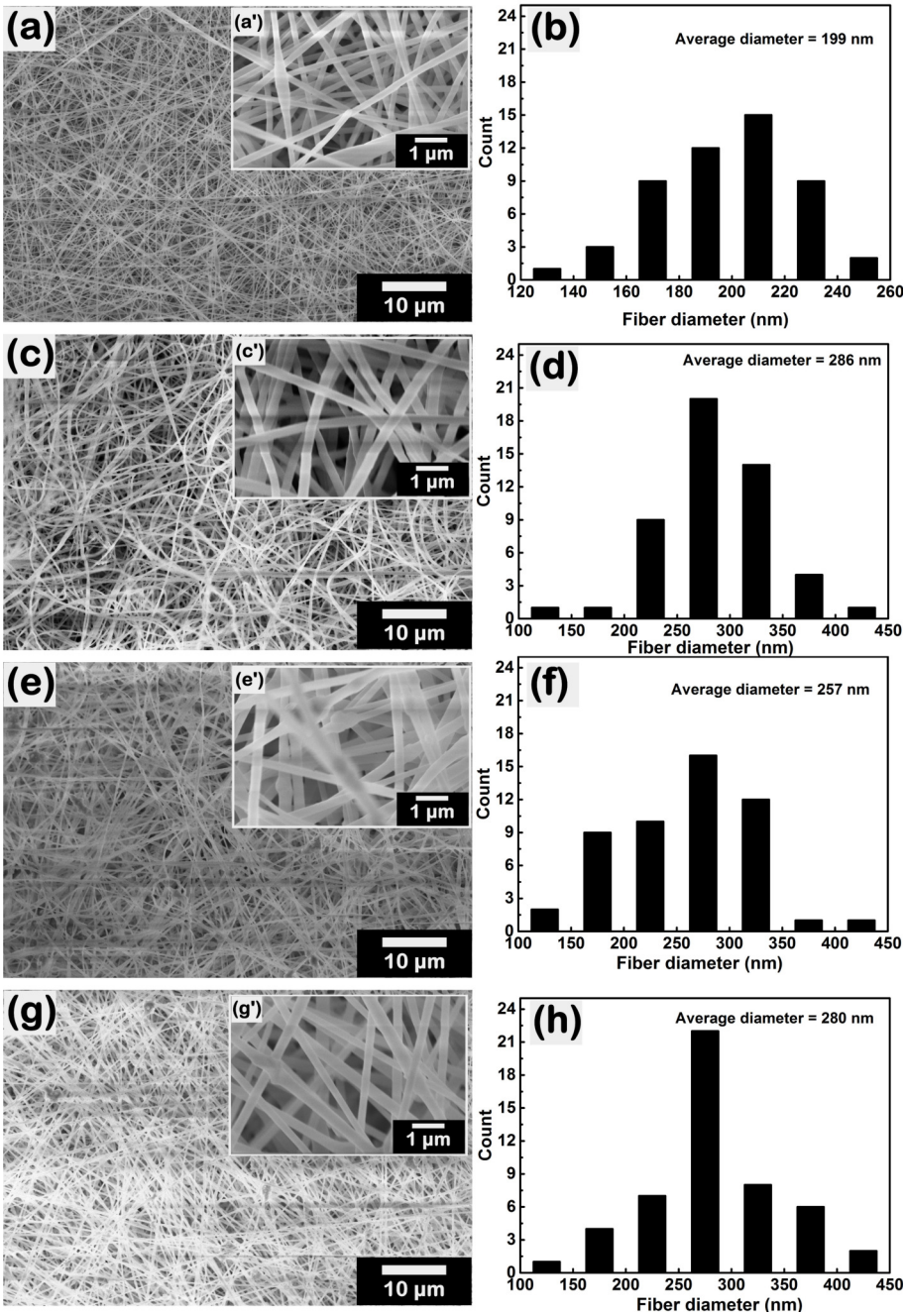


Figure 5.2: SEM images of electrospun PAN and PAN-zeolite membranes as well as their fiber diameter distributions. PAN (a,b), PAN-840 (c,d), PAN-P87 (e,f) and PAN-P371 (g,h). (PAN is 10 wt % and all the zeolites are 30 wt %)

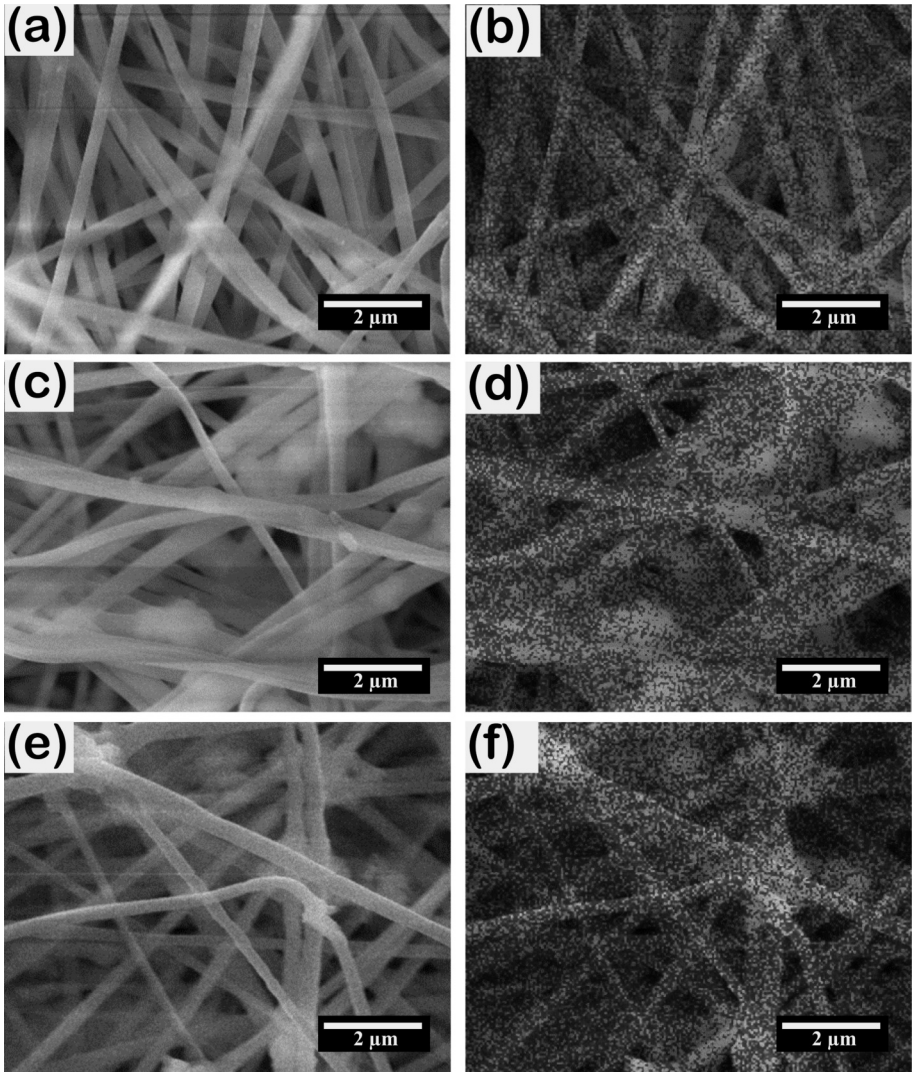


Figure 5.3: SEM and EDX mapping images of PAN-zeolite membranes: PAN-840 (a) with Si-mapping (b), PAN-P87 (c) with Si-mapping (d) and PAN-P371(e) with Si-mapping (f).

Figure 5.3 is the SEM/EDX mapping images of composite membranes with 840, P-87 and P-371 zeolites. Figure 5.3 (b,d,f) shows that the Si atoms are mostly distributed along the fiber, relatively uniform.. Some large areas of Si aggregation were observed in Figure 5.3(c) and mild aggregation also existed in Figure 5.3(e). We believe that aggregation occurs for particles that cannot be easily separated. Even though all three particles were stirred with the same process, we can see that nanoparticles are harder to distribute evenly when compared with micro-particles.

The TGA test further showed the precise weight percentage of zeolites inside the membranes, as indicated in Figure 5.4. The weights of the membranes are considered

as 100 wt% at room temperature and they gradually decreased due to the combustion of PAN polymers as the temperature goes up. We can see that all the PAN were fully combusted when the temperature reached 700 C. There is zero weight left in pure PAN membrane when the temperature was above 700 C, as indicated in Figure 5.4 (a). For the other three types of composite membranes fed with 30 wt% 840, P-87 and P-371 zeolites, they had respectively 22.5 wt%, 22.5 wt% and 22.5 wt% zeolites left, as shown in Figure 5.4(b, c, and d). The data indicates that the difference between the percentage of zeolite in feed and zeolite in membrane was 25%.

5.3.3 Creatinine adsorption capacity of zeolites

Investigating the adsorption behavior of zeolite powders provides guidance to maximize the creatinine uptake by zeolites. Here we studied how the creatinine concentration, creatinine solution volume, and adsorption time affected zeolites' creatinine adsorption ability.

All three types of zeolite showed gradually improved creatinine uptake in creatinine solutions with increased concentration from 50 μmol L^{-1} to 625 μmol L^{-1}. To be specific, the creatinine uptake level of 840, P-87 and P-371 zeolite powders were 1410, 1625, and 1853 μg g^{-1} in 50 μmol L^{-1} creatinine solution, and they improved to 10511, 10820, 10443 μg g^{-1} in 625 μmol L^{-1} creatinine solution, respectively (as shown in Figure 5.5 (a)). This indicated that all three zeolites had a higher creatinine uptake ability in creatinine solution with higher concentrations. When we compared the creatinine adsorption levels of 840, P-87 and P-371 at each concentration, they showed very similar result. Thus, the particle size and particle shape barely influences the creatinine adsorption level of the three zeolite powders if the creatinine concentrations is kept the same.

Figure 5.5(b) further shows creatinine uptake level of 840, P-87 and P-371 zeolite powders in 400 μmol L^{-1} creatinine solution with increased volume (3, 6, 10, 18 ml). All three zeolites showed improved creatinine uptake level with increased creatinine volume. However, they had different rates of increase. The creatinine uptake level of 840 zeolite in 18 ml creatinine solution was 2.8 times of that in 3 ml creatinine solution, with creatinine uptake levels maximized at 18 ml. The creatinine uptake level

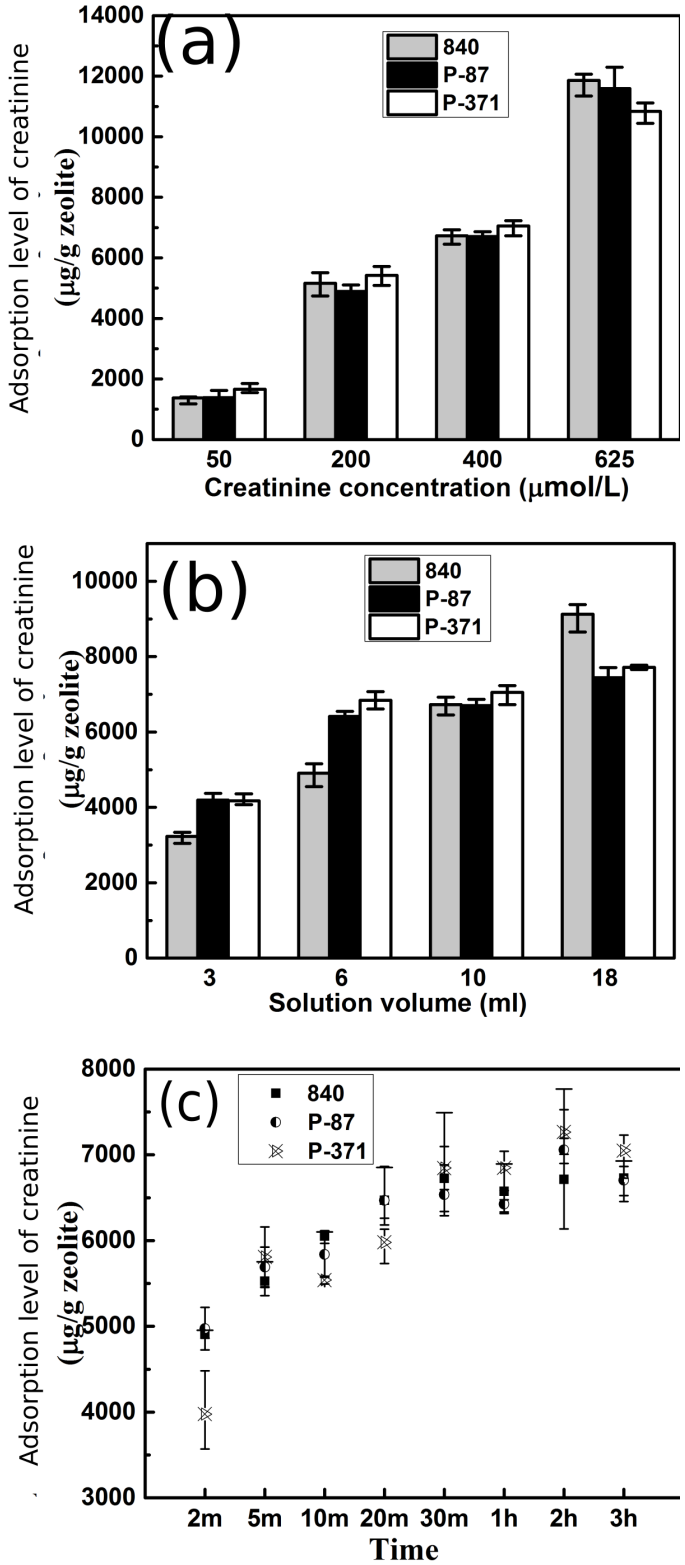


Figure 5.4: TGA analysis of membranes: pure PAN (a), PAN with 840 (b), PAN with P-87 (c) and PAN with P-371 (d).

of P-87 and P-371 zeolite powders improved 1.9 and 1.8 times respectively in an 18 ml creatinine solution compared to a 3 ml creatinine solution. However, they both reached maximum creatinine uptake in 6 ml creatinine solution. When we compared 840 with P-87 zeolite powders, 840, which has larger particle size, presented better performance on adsorbing creatinine. However, when we compared P-87 with P-371 zeolite powders, the performance was similar despite their different particle shapes. Thus, zeolite particles with larger particle size had higher creatinine adsorption, while particles with different shapes presented no difference along with increased creatinine volume.

Figure 5.5(c) shows the effects of adsorption time on the creatinine adsorption capacity of the zeolites in 10 ml 400 μmol L^{-1} creatinine solution. The figure showed that all three zeolites reached the maximum creatinine uptake level at 30 min. Besides, comparing the creatinine adsorption level of 840, P-87 and P-371 zeolite powders at each time interval (2 min-3 h), we saw very similar levels, except that of P-371, which was very low at 2 min. Thus, the particle size and particle shape barely influence the creatinine adsorption level of the three zeolite powders at different adsorption time. Furthermore, the figure shows that the three zeolites have a creatinine uptake of 5500 μg g^{-1} in 5 min, this indicates that the adsorption speed of zeolites is fast when comparing with hemodialysis membranes, which is normally 3 h [139].

5.3.4 Comparison of zeolite particle effects

The investigation of zeolite powders showed that zeolite shape had no effect on its creatinine adsorption level at various conditions. Similarly, the size had no effect on the adsorption level in creatinine solution with different concentrations or adsorption time except in solution with different volumes. However, the particle size and shape both had significant effects on zeolite's creatinine uptake level when they were incorporated inside membranes. Figure 5.6 shows the comparison of creatinine adsorption level of zeolites as filler in the membranes and as powders. Same amount of zeolite powder was measured for adsorption experiment after calculating the relative mass of zeolites inside their membranes. 840 in the membrane had a creatinine adsorption capacity as high as 8957 g g^{-1} , which is half of that of 840 as powders. P-87 inside the membrane had much lower creatinine adsorption capacity when compared with that of P-87 powders. On the

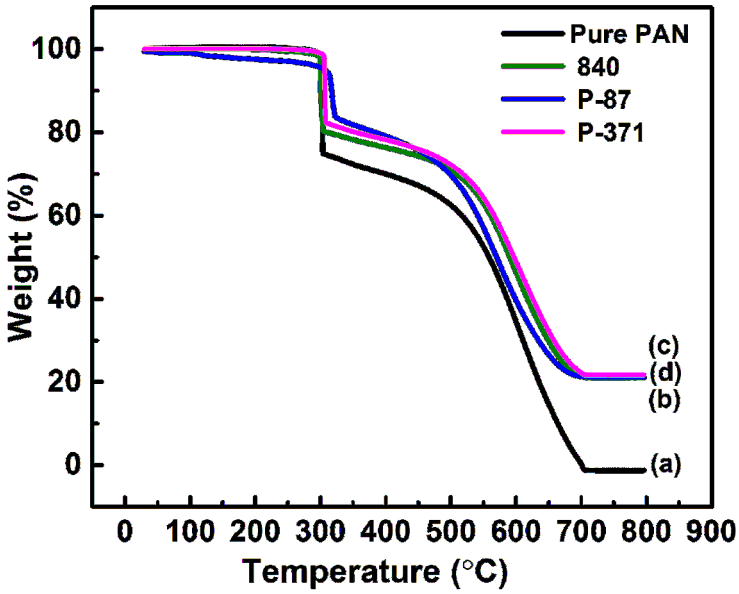


Figure 5.5: Study of the relationship of zeolite powders' adsorption capacity of creatinine with creatinine concentration (a), solution volume (b), and adsorption time (c).

other hand, P-371 showed the most decreased creatinine adsorption capacity inside the membrane when comparing with that of its powders. The adsorption capacity of zeolites showed various level of decreased inside the membranes because the fiber blocked parts of the surface of zeolites. However, the results showed that micro-840 in the membranes kept approximately half of its capacity as free powders, while nano-size P87 lost almost 3 quarters of its capacity compared with its powder and P-371 lost an even higher percentage of its capacity. The size and shape of zeolites has an important effect on their creatinine adsorption capacity when incorporated inside the membranes.

Micro-particle 840 in membranes had much higher creatinine adsorption level than that of nanoparticle P-87 in the membrane. The reason is that when zeolites were incorporated in the membranes, the PAN nanofibers which had an average diameter of 9 nm, tended to block parts of surface area of zeolites powders. The polymer fiber blocked a relatively smaller percentage of microparticle 840 since there is a nearly nine-fold size difference between particles and PAN fiber. So the unblocked functional surface area of microparticles was larger than nanoparticles, which had roughly threefold particle size difference with the diameter of PAN fibers. As a result, microparticle zeolite

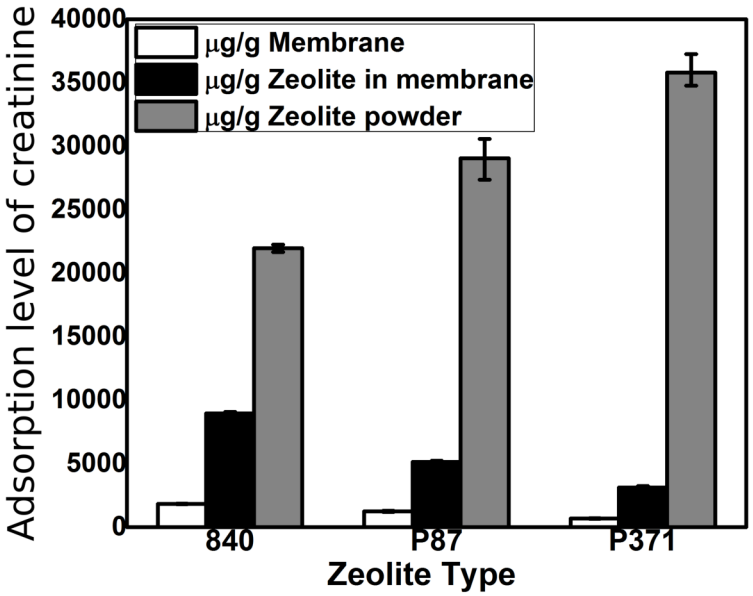


Figure 5.6: Comparison of creatinine adsorption capacity of 840, P-87 and P-371 zeolite in membranes (by membrane mass and zeolite mass) and as powders.

(840) in membranes showed higher creatinine adsorption capacity when compared with membranes with nanoparticle zeolites (P-87).

Spherical particle P-87 zeolite in membrane had higher creatinine adsorption level than rod particle P-371 zeolite in membrane. The possible reason is that when the composite fiber is formed in the electrical field, the rods tend to align with the fiber. The rod is 300 nm on one dimension, which is very similar to the fiber diameter, thus, it can easily get buried inside the fiber. As a result, a large percentage of its surface is blocked by PAN fiber.The unblocked functional particle area is relatively small when compared with spherical particles, which had particle sizes close to the fiber diameter.

5.4 Conclusion

In this chapter, we studied the influence of zeolite size and shape on the performance of PAN-zeolite membranes with respect of creatinine uptake level. We first measured spherical microparticle 840, spherical nanoparticle P-87 and rod-like nanoparticle P-371 zeolites as powders in creatinine solution with different concentrations, volumes

and adsorption time. These particles showed similar creatinine uptake ability. Then, nanofibrous membranes with these zeolites were electrospun and their ability to adsorb creatinine was measured and compared. Zeolites had significantly different creatinine uptake ability after being incorporated inside the membranes. Spherical microparticle 840 in the membrane presented the best creatinine uptake ability, at 8957 μg g^{-1}, which was half of its powders'. On the other hand, P-87 presented largely decreased, while P-371 presented even lower creatinine uptake ability in membranes when compared to respective powders'.

We proved that the size and shape of zeolites have a significant effect on their creatinine adsorption level in the membranes. Microparticles have better adsorption capacity than nanoparticles when incorporated inside the membranes although the size does not have any effect on zeolite powders. The spherical nanoparticle shape is a better choice than rod nanoparticles when incorporated in the polymer fiber made through electrospinning. This finding can provide guidance for choosing the right size and shape of zeolites to be incorporated in the fibrous membrane for adsorption usage.

Chapter 6

Creatinine adsorption by zeolite-polyethersulphone membranes

In the previous two chapters, we used an electrospinning method to fabricate composite membranes and we proved that these membranes are able to to adsorb water-soluble toxins. Dialysis membranes should have pore sizes larger than 5 nm in order to remove large molecular uremic toxins and smaller than 8 nm in order to prevent the leaking of albumin. SEM images of our electrospun membranes, however, showed that the pore size of our membranes is around 5 micrometers, making them unsuitable for hemodialysis. In this chapter, we adopt a spin-coating method with the goal of fabricating composite membranes that fulfil the requirements of hemodialysis. In order to understand the adsorption mechanism of zeolites we study pH and salts' effect on zeolite's adsorption and desorption.

6.1 Introduction

Current hemodialysis helps patients to clear uremic toxins mainly through a hollow fiber dialyzer. These toxins are cleared through diffusion due to the gradient difference in blood and dialyzate[140]. While diffusion methods are excellent at clearing water-soluble toxins, other types of important toxins, such as protein-bound toxins, are ignored. A more promising way to clear toxins is through adsorption of toxins by sorbents since they can both adsorb water-soluble toxins and protein-bound toxins [23, 141, 142].

Sorbents have been used in hemodialysis for the past three decades [142, 143]. They can be used to regenerate dialyzate [144, 145, 146, 147, 148, 149], which greatly reduces the amount of dialyzate needed during hemodialysis and makes portable hemodialysis

possible. Activated carbon [21], charcoal [141] and zeolites [136] are excellent adsorbents for uremic toxins. Zeolites in particular are the most promising adsorbents for hemodialysis because they can specifically adsorb uremic toxins without affecting other biological molecules in blood [53]. Wernert's [23, 139] research showed that zeolite particles can successfully remove water-soluble uremic toxins and p-cresol. Sorbent membranes [141, 142, 21, 150] also proved able to reduce uremic toxins and are promising membranes for hemodialysis.

In previous two chapters [136], we fabricated zeolite-polyacrylonitrile nanofiber membranes through an electrospinning method and these membranes presented fast and good creatinine adsorption ability. The drawback of our nanofiber membranes is that their pore size is too large for hemodialysis, making them unable to effectively prevent the leakage of albumin into dialyzate.

In order to fabricate composite membranes that are suitable for hemodialysis, a spin-coating method is proposed in this chapter. Spin-coating is an effective and easy method to make membranes. Nie [98] proved that spin-coating can be used to make hemodialysis membranes. Polyethersulfone (PES) polymer was chosen as the polymer to incorporate zeolite since it is commercially available and has been currently used as hemodialysis membranes in clinic [151]. Another advantage of PES polymer is that it can be used to make porous membranes through spin-coating in the lab. The spin-coating set-up is uncomplicated and the process is repeatable. It can also be used to make other composite membranes [98, 6].

In this chapter, we fabricate three types of zeolite membranes through a spin-coating process, then we test and compare their adsorption ability for creatinine. We also study the effect of pH and salt on P87 zeolite powders' creatinine adsorption properties in order to deduce the mechanism through which P87 adsorbs creatinine.

6.2 Sample preparation

6.2.1 Materials

Commercial Ultrason E 6020 PES was obtained from BASF, Co (U.S.) and used as received. Dimethylacetamide (DMAC) and creatinine were purchased from Sigma Aldrich,

Co. HSZ-series zeolites 840-NHA was purchased from Tosoh. P-87 and P-371 were purchased from ACS Materials, LLC. 1.5 inch by 1.5 inch glass slides were cut by laser from microscope slides, which is from Ted Pella, Inc. Ultrapure water was also used. NaCl, KCl and $CaCl_2$ were purchased from Fisher Scientific, Co.

6.2.2 Sample fabrication

Composite membranes of PES-zeolite were prepared through spin-coating followed by liquid-liquid phase separation in water. A typical process is as follows: an 18 wt% PES solution was first made by dissolving PES flakes in DMAC and it was stirred overnight at room temperature. Then, 0.48 g zeolite was added into 8 g of pre-made PES solution and stirred overnight to obtain a composite solution. The composite solution was then dripped on a glass substrate and spin-coated at 400 rpm with an acceleration of 4 for 60 s. The glass slides with flatted composite solutions were immersed in distilled water immediately and membranes were formed in the water shortly. By this method, PES membranes with 50 wt% of 840, P-87 and P-371 were synthesized. Pure PES membranes were also synthesized by the same procedure and used as control.

6.2.3 Measurements

Thermal gravimetric analysis (TGA)

A Q500 TGA instrument from TA Instruments was used to carry out thermal gravimetric analysis for all the samples. The temperature scans were taken from room temperature to 800 °C with a heating rate of 10 °C min^{-1} and at an ambient atmosphere with a flow of 20 ml min^{-1}.

Water flux

The water flux of the spin-coated composite membranes was measured using a 10 ml ultrafiltration cell from Millipore. The effective membrane area is 4.1 cm^2. The system was steadied with water for 20 min at 11 psi to compact the membranes. Then, the

water flux was measured at 10 psi for 20 min, and calculated by equation

$$\text{Flux} = \frac{m}{StP},$$

where m is the quality of the permeated water (g); S is the effective membrane area (m^2); P is the pressure (hmmHg) and t is the permeated time (h).

Creatinine adsorption study

The creatinine adsorption study of fabricated pure PES membranes and PES membranes with 50 wt% of 840, P371, P-87 zeolites was tested in 0.1 mg/mL creatinine solutions. All these membranes were spin-coated at a speed of 400 rpm with an acceleration of 4 for 1 min on the 1 inch by 1 inch glass substrates. A piece of each type of membranes was weighed and immersed in a 6 ml creatinine solution and stirred at 37 °C for 3 h. Accordingly, the actual amount of zeolite contained by each membrane was calculated by using the TGA data. Then, the corresponding weight of zeolite powders was measured and the creatinine adsorption rate of these powders was also studied through the same procedure as the membranes. All the experiments were repeated three times. The creatinine concentration was determined by a UV-visible spectrophotometer at 235 nm with a 1 mm quartz cuvette at room temperature. The adsorption level of the membrane was expressed as μg creatinine per g of membrane and μg creatinine per g zeolite in the membrane. Similarly, the adsorption level of zeolite powder was expressed as μg creatinine per g zeolite.

Effect of pH and salts on creatinine adsorption by zeolite

To evaluate whether pH and salt affect P87's adsorption level, the following experiments were carried out. The influence of salt and pH on creatinine's UV intensity were measured and set as control. First, a 0.1 mg ml^{-1} creatinine solution was made. Then, 500 μl 0.1 mg ml^{-1} creatinine solution were mixed with 500 μl water, NaCl , KCl $CaCl_2$ and pH 4 to pH 9 PBS buffer. We piped 500 μl of these mixed solutions and added each of them to 1.5 ml PBS before measuring their UV-vis intensity.

Adsorption tests in salt and pH medium were carried out by measuring 0.01 g P87 zeolite and placed them into centrifuge tubes with 500 μl 0.1 mg ml^{-1} l creatinine

solutions. Then, 500 μl water, NaCl , KCl, $CaCl_2$ and pH 4 to pH 9 PBS buffer were added into each centrifuge tube and incubated for 30 min. They were centrifuged at 15000 rpm and 500 μl supernatant was mixed with 1.5 ml PBS before measurement by UV-vis spectrometer.

Effect of pH and salts on creatinine desorption by zeolite

In order to evaluate how pH and salt affect P87's creatinine desorption, 0.01 g P87 zeolite was measured and placed into the centrifuge tubes with 1 ml of 0.1 mg ml^{-1} creatinine solutions. The mixture was centrifuged at 6000 rpm after 0.5 h incubation to get precipitant. The precipitant was washed with 1.5 ml water to remove non-adsorbed creatinine. Then, 1 ml water, NaCl , KCl, $CaCl_2$ and pH 4 to pH 9 PBS buffers were added into precipitant and mixed well. They were further incubated for 0.5 h before being centrifuged at 15000 rpm. Following this, 750 μl of supernatant was mixed with 1.25 ml PBS and UV-vis intensity was measured.

6.3 Results and discussion

6.3.1 Data presentation methods

In this chapter, the data related to water flux are presented in a table, the value is the average of three repeated test.

The data related to adsorption test are presented through bar figures. In these figures, the height of the bar is the average value and the error bar is the range of value. The data are presented in this way to show the value range of these data.

The data related to pH and salts effects on adsorption are presented by fluorescence images. In these images, C represents control groups, while the red line represents the experiments data under different conditions. The data are presented in this way to eliminate the potential pH/salts effects on indoxyl sulfate adsorption value.

The data related to pH and salts effects on adsorption are presented by fluorescence images. Each line indicates the experiments data under different conditions.

6.3.2 Properties of membranes

Figure 6.1 shows the cross-section of PES and PES-zeolite composite membranes. The figure presents the morphology and structure of the membranes as well as the distribution of zeolites. Clear and smooth channels were observed in pristine PES membranes, as Figure 6.1(a) shows. Large channels with diameter of 5 μm are present in the membranes. We can also observe 100-200 nm pores on the inner surface of membranes that consisted of membranes channels, as shown in Figure 6.1(b). Figure 6.1(a, b) indicated that PES membranes, while displaying a high internal porosity, presented smooth outer surfaces. As a result, it should be difficult for water to permeate through the membranes. Indeed, water flux experiments confirmed that the average water flux for pure PES membranes (shown in Table A.4) is merely 0.85 g/m^2 h mmHg.

Figure 6.1(c.d) shows PES membranes with 50 wt% of 840 zeolites. The smooth and clear channels observed in pristine PES membranes were clearly affected by incorporating of 840 zeolite. More irregular channels were observed caused by the coagulation of 840 particles. The surface of the membranes is coarse, as shown in Figure 6.1(d). Some round pores were formed with size below 100 nm due to the incorporation of 840 zeolites. Water flux of this membranes is 43.35 g/m^2 h mmHg, which indicates that the addition of zeolites into membranes can improve the pore connection.

Figure 6.1(e,f) shows PES membranes with 50 wt% of P87 zeolites. P87 are sphere nanoparticles with diameter of 550 nm. They are smaller than 840 microparticles, which have an average diameter of 1850 nm. As a result, They affect the inner structure of their membranes differently. The channels are still regular and clear though the inner-channel surface is no longer smooth when compared with that of pure PES. Similarly, pores with sizes around 500-1000 nm were observed on the inner surface of this type of membrane. Water flux of this membrane is 76.83 g/m^2 h mmHg, a result in accordance with the morphology and structure of P87 membranes, which have more small pores on the surface of the membranes as well as regular pore channels.

Figure 6.1(g,h) shows PES membranes with 50 wt% of P371 zeolites. Due to the rod-like shape of these zeolites, they tend to entangle among themselves. As such, smeared pore channels were observed in Figure 6.1(g). Zeolite rod clusters were also observed in Figure 6.1(h). Affected by these structural reasons, the water flux of this

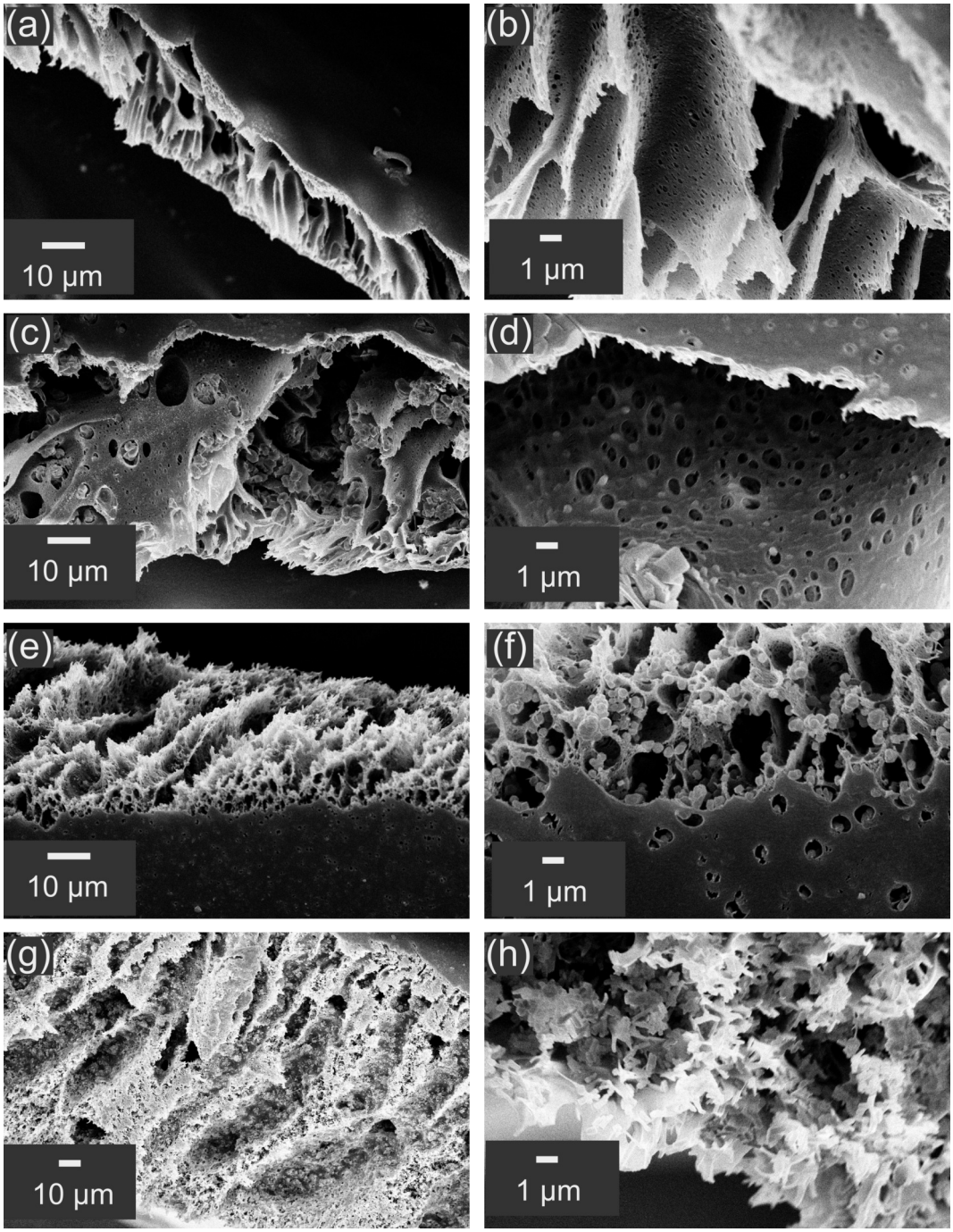


Figure 6.1: Cross-section SEM image of membranes: PES(a,b), PES-840(c,d), PES-P87(e,f) and PES-P371(g,h).

Table 6.1: Water flux of pure PES and composite PES-zeolite membranes.

Membrane Type	Water Flux(g/m^{2}h mmHg)
Pure membranes	0.85
840 membranes	43.35
P87 membranes	76.83
P371 membranes	58.15

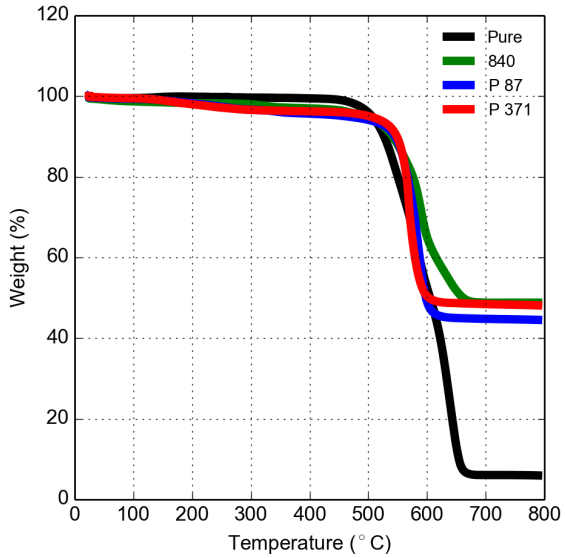


Figure 6.2: TGA data of pure PES and composite PES-zeolite membranes

type of composite membrane is 58.15 g/m^2 h mmHg.

Here, we know that the incorporating of zeolites into pristine membranes results to membranes with different inner and surface structures. Furthermore, the structural changes in the membranes are related to the size and shape of the zeolite, as also indicated by nanofibrous membranes with these zeolites[152]. Finally, changes to the membrane structure further affect membrane properties, such as water flux.

TGA data indicated (Figure 6.2) that membranes mass changed considerably as the temperature increased from room temperature to 800 °C. For pure PES membranes, around 5 wt% residual was left. For 840 and P87 and P371 membranes, around 50.8 wt%, 46.5 wt%, and 49.1 wt% residuals respectively were left. The result indicated that the majority of zeolites from the composite solutions were incorporated into the

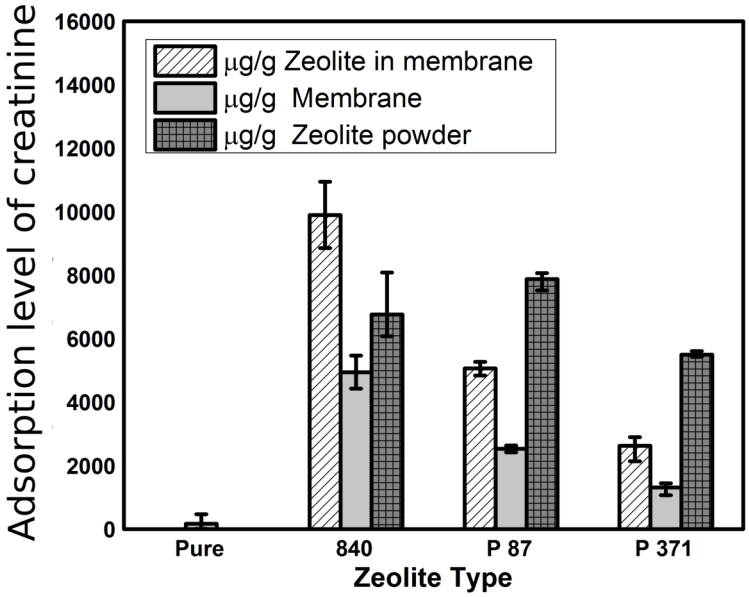


Figure 6.3: Creatinine study of PES/ PES-zeolite membranes and zeolite powders.

membranes.

6.3.3 Creatinine adsorption

Creatinine has previously been used as a representative of water-soluble uremic toxins [153, 133, 135], so it was also used in this paper. After we incorporated 50 wt% of these three zeolites into the PES membranes, the creatinine adsorption levels of the compoiste membranes were measured. Figure 6.4 shows that 840, P-87 and P-371 compoiste membranes' creatinine adsorption levels were 4948, 2532 and 1312.5 μg g^{-1} respectively. By calculating the incorporated amount of zeolite in each types of membrane, we measured the relative zeolites' creatinine adsorption level as free powders. The results were 6787, 7880 and 5500 μg g^{-1}. In general, the composite membranes had lower adsorption level when compared with that of free powders. This is easy to understand, each gram of composite membranes have around 0.5 g of PES and 0.5 g zeolite. PES has a very low creatinine adsorption level, at 171 μg g^{-1}. Even though all the membranes had lower creatinine adsorption levels when compared with same weight of their powders, 840 membranes had 0.73 times of its powders' adsorption ability, while P87 and P371

sustained only 0.32 and 0.24 times of their powders' adsorption levels. The difference is related to the particle size and shape, as well as the difference in the membranes' flow channel, as show in SEM image. 840 zeolite are sphere microparticles with an average diameters of 1840 nm. 87 zeolite are sphere nanoparticles with an average diameters of 550 nm. P371 are rod nanoparticles with average diameters of 300 $\times$700 nm. The larger the particle size, the smaller percentage of surface will be blocked by PES matrix. We observed similar result when we incorporated these three types of membranes within nanofibrous membranes [152].

However, the adsorption level of zeolites in the membranes with 840 is the highest, at 9896 μg g^{-1}. It is even higher than its free powders. Meanwhile, P87 and P371 in membranes had lower adsorption levels when compared with their free powders. Two possible factors contributed to the phenomenon. One factor is that PES matrix blocks parts of zeolites surface. This prevents creatinine from entering some of the pore channels. Another factor is that dispersing zeolites in membranes actually breaks soft aggrations of zeolite powders and enables more surface exposed. The adsorption level is the comprehensive result of these two forces. For 840 zeolite, microparticles, dispersing factor plays a major role while for P87 and P371, nanoparticles, blocking factor plays a major role.

6.3.4 pH and salts effect on adsorption

Figure 6.4 shows the pH effect on P87's creatinine adsorption level. We tested the adsorpton of 0.01 g of P87 in 0.25 mg ml^{-1} water based creatinine solution with pH adjusted PBS buffer(pH 4 to 9). The control groups are the corresponding solutions without zeolites. As the figure shows, acidic environments (pH 4 to 6) enhance P87 powders' creatinine adsorption level while alkaline environments (pH 8 to 9) weaken it. This difference happens because creatinine is already protonated at low pH. Since the pKa value of creatinine is 5.02 [110], it is adsorbed into zeolite through ion exchange. However, creatinine is neutral at pH 7 [154]. At this condition, it needs to diffuse to the zeolite channels before being protonated in-site. When pH $>$ 7, the alkaline environment hinders the protonation of creatinine. Thus as the pH increases from 4 to 9, a gradual decrease in creatinine adsorption level is observed.

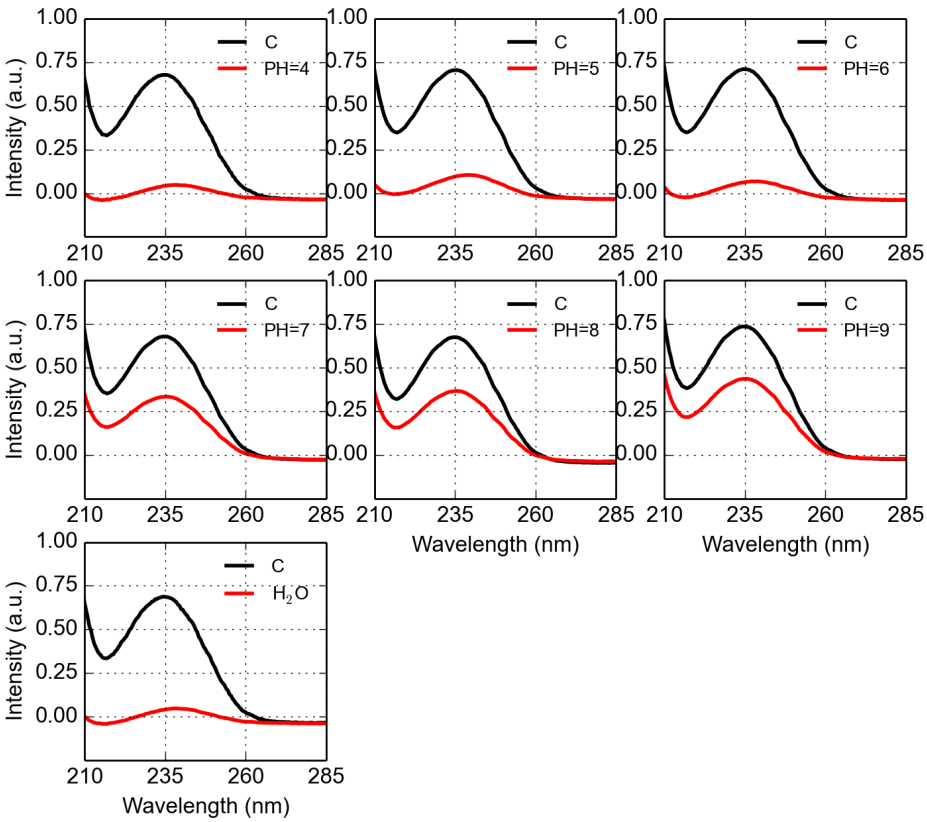


Figure 6.4: The effect of pH on P87's adsorption level of creatinine.

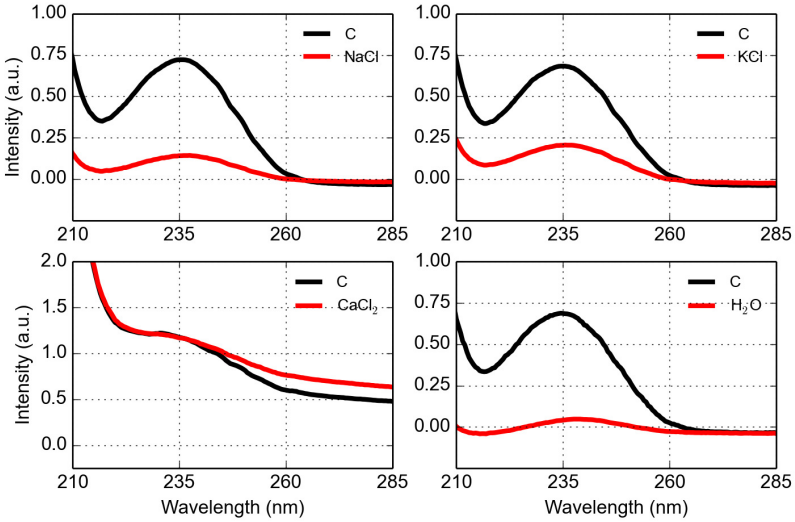


Figure 6.5: The effect of salts on P87's adsorption level of creatinine.

When we compare the adsorption of creatinine in water and in PBS at neutral pH, we observe that it has a higher adsorption level in water. With the presence of PBS, P87 had a decreased adsorption level. This phenomena was also confirmed by Schäf [110]. The reason is that PBS contains cations that will compete with the creatinine for adsorption sites.

Figure 6.5 indicates how various salt solutions affect the adsorption of creatinine for P87 zeolite particles. The slightly increased intensities of solution with the presence of NaCl and KCl show that Na^+ and K^+ compete with the creatinine for adsorption sites. However, in the presence of Ca^{2+} , P87 did not adsorb any creatinine. We can predict that all the adsorption sites are occupied by Ca^{2+} cations, since it has double the electric charge than protonated creatinine.

6.3.5 pH and salts effect on desorption

After the creatinine was absorbed onto zeolites formed as conjugates, PBS buffer with pH from 4 to 9 and different salt solutions (NaCl, KCl and $CaCl_2$) were added to the conjugates in order to study the desorption of creatinine under these mediums. Figure 6.6 further confirms that the presence of Ca^{2+} will replace all the protonated creatinine in the zeolite channels. K^+ and Na^+ only partially replace adsorbed creatinine. At the

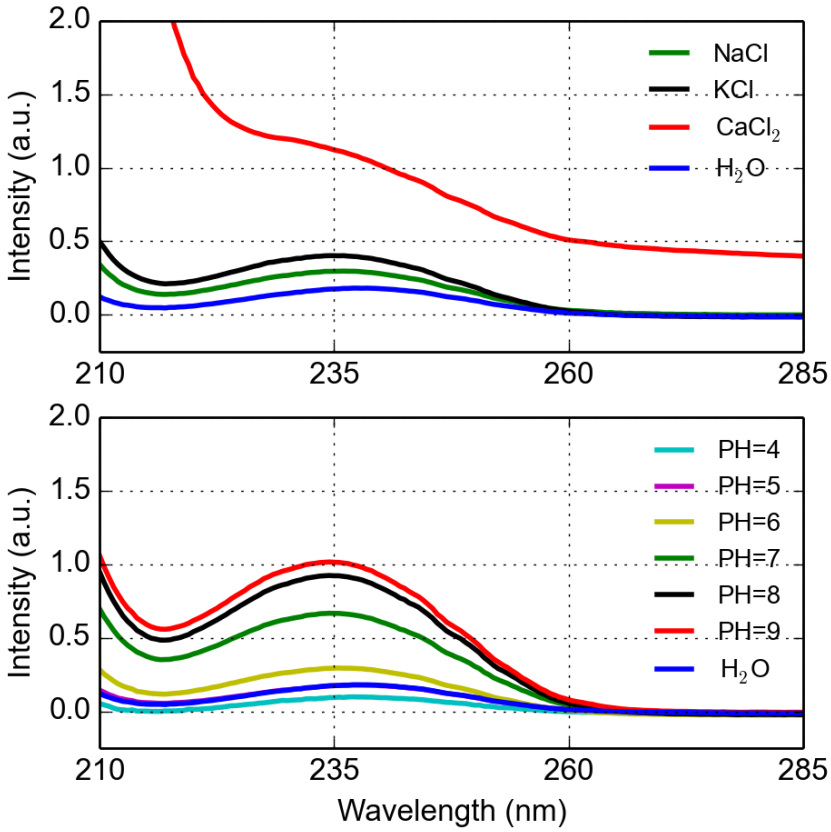


Figure 6.6: Salt's and pH effect on P87's desorption of creatinine.

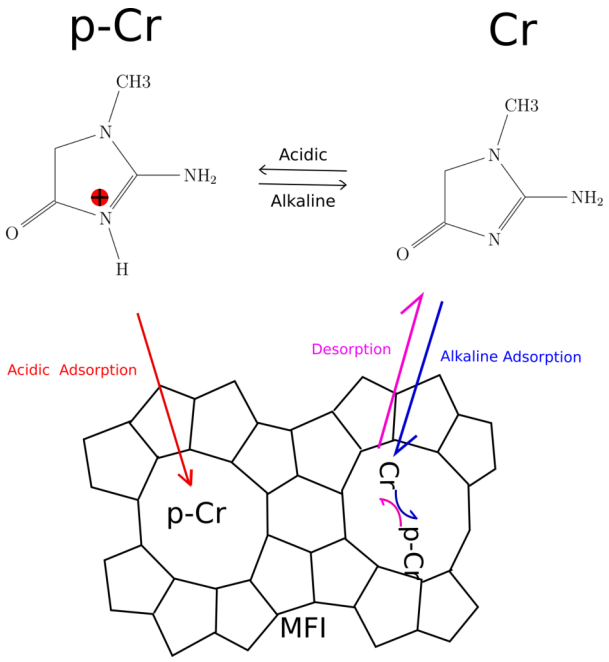


Figure 6.7: Illustration of P87 adsorbs creatinine in acidic and alkaline environment

same time, we can see that the adsorbed creatinine is quite stable in water since only a very small portion of them desorbed.

Figure 6.6 clearly shows that at lower pH (4-6), the protonated creatinine is stable inside the zeolite, while neutral and alkaline environment will reverse creatinine's protonated process, thus it will be desorbed from the adsorption site in the zeolite. The more alkaline, the higher percentage of creatinine was desorbed from the zeolite. The mechanism is illustrated in Figure 6.7.

6.4 Conclusion

Spin-coating is a simple and effective method to fabricate membranes. In this chapter, polyethersulphone-zeolite membranes were made through a simple spin-coating process and evaluated for creatinine adsorption. SEM images showed that the incorporation of zeolite into the membranes affected their pore channels. The water flux was also affected. Creatinine adsorption tests showed that the membranes with 840 could adsorb 4948 μg creatinine per g membranes.

In order to infer the membranes' adsorption mechanism, we also studied the effects

of pH and salts on zeolite's adsorption and desorption of creatinine. We found that acidic environments enhance zeolite's creatinine adsorption while alkaline environments weaken it. We predict that creatinine needs to be protonated before adsorbed onto porous zeolites. The acidic environment helps to protonate creatinine, while alkaline environment hinders this process. The existence of various cations also decreases zeolite's creatinine adsorption. The reason is that cations will compete with creatinine for the adsorption sites in zeolites. The study of the effects of pH and salts on zeolites adsorption of creatinine provided insights into its adsorption mechanism.

In summary, we successfully fabricated a membrane with suitable pore size that can be used for hemodialysis. We also proved that these membranes can adsorb water-soluble toxins.

Chapter 7

Indoxyl sulfate adsorption by zeolite and zeolite-polyethersulfone membranes

In the previous chapter, we fabricated PES-zeolite membranes with suitable pore size for hemohemodialysis. We also studied their ability and mechanism to eliminate water-soluble toxins. It was still unclear, however, whether they could adsorb protein-bond toxins, and through which mechanism. In this chapter we answer both of these questions.

7.1 Introduction

Kidney function impairment leads to a progressive retention of a large number of compounds which are normally excreted via the urinary tract [155, 156]. These compounds are called uremic toxins and they can be classified into three groups according to their molecular weight and protein-bonding ability[157]: (1) small molecular weight water-soluble compounds; (2) protein-bound compounds and (3) middle molecules [158]. Protein-bound solutes are generally ignored, as hemodialysis adequacy is traditionally measured by urea removal. Hemodialysis can only eliminate 30% of protein-bound toxins due to their binding to albumin, while it can clear 60% of urea and creatinine [159]. In modern dialyzers and hemodialysis prescription, protein-bound solutes are poorly cleared [160].

Toxic effects appear to be caused by compounds that are difficult to be removed through hemodialysis. This is particularly true for protein-bound compounds. Increasing experimental and clinical evidence [161] support the hypothesis that uremic toxins, especially protein-bound toxins, are not only related in the progression of chronic

kidney disease(CKD) [162, 163], but also in the advancement of cardiovascular disease [164, 163]. Two protein-bound compounds, indoxyl sulfate and p-cresyl sulfate, are normally chosen as protein-bound toxin prototypes in research. These two proteins have shown to exert toxin effects in vitro [165]. Results with CKD patients also identified these two proteins as emerging mortality risk factors [164, 166, 161].

Vanhoder[167] performed a systematic review on biologic effects of protein-bound uremic retention solutes. The studies showed that most functional deterioration were linked to uremic cardiovascular disease and kidney damage, and it seems to confirm the toxicity of indoxyl and p-cresyl sulfate and support their roles in vascular and renal disease progression.

Clinical studies also showed that individuals with chronic kidney disease are at an extremely high risk of cardiovascular disease [168] and this is caused by protein-bound toxins. In hemodialysis patients, serum concentrations of indoxyl sulfate and p-cresyl sulfate are approximately 54 and 17 times higher, respectively, than the corresponding concentrations in healthy subjects. Serum indoxyl sulfate levels have been shown to associate with vascular calcifications [169]. P-cresyl sulfate also seems to be associated with cardiovascular mortality in patients with chronic kidney disease [170, 28, 164, 166]. More than 50% of deaths in CKD stage 5 are due to cardiovascular disease [171]. Hemodialysis patients with chronic kidney disease had approximately 10-20 times more frequent cardiovascular death than healthy individuals [172].

Methods are developed to reduce the level of protein-bound solutes include modifying the hemodialysis procedures (increase K_oA and Q_d) to enhance their clearance [173], using sorbents [149], or limiting their production [15]. Among these method, adsorption of protein bound toxins onto porous particles is promising [6, 135, 21, 23, 139]. By incorporating adsorbents into hemodialysis membranes, we seek to clear protein-bound toxins through adsorption.

In this chapter, we propose a new generation of innovative hemodialysis membranes that have a high clearance level for protein-bound toxins. In order to achieve this, we fabricated PES-P87 membranes through spin-coating. We also studied the mechanism through which P87 adsorbs protein-bound toxins by measuring the ζ-potential, and the effects of pH and salts on P87' adsorption and desorption.

7.2 Materials and methods

7.2.1 Materials

Indoxyl sulfate was purchased from Sigma Aldrich, Co. All the other materials are same as Chapter 6. That is, commercial Ultrason E 6020 PES was obtained from BASF, Co (U.S.) and used as received. Dimethylacetamide (DMAC) and creatinine were purchased from Sigma Aldrich, Co. P-87 was purchased from ACS Materials, LLC. 1.5 inch by 1.5 inch glass slides were cut by laser from microscope slides, which is from Ted Pella, Inc. Ultrapure water was also used. NaCl, KCl and $CaCl_2$ were purchased from Fisher Scientific, Co.

7.2.2 Measurements

Dynamic light scattering (DLS)

A dynamic light scattering device, Zetasizer Nano ZS (Malvern), was used to analyze the particle size distribution of zeolite powders. The powders were dissolved in water at a concentration of 8.6 g L^{-1} and all samples were tested three times. ζ-potential of samples was also measured with the same instrument, with a folded capillary zeta cell (Malvern).

Indoxyl sulfate (IS) adsorption

The indoxyl sulfate adsorption level of PES-zeolite and pristine PES was determined by an adsorption experiment. Known amounts of dry membranes were put in an indoxyl sulfate solution (with a concentration of 3.5 mg dL^{-1}) and stirred at 37 °C for 0.5, 1 and 3 h. Based on thermal gravimetric analysis (TGA) of PES-zeolite membranes, the corresponding weight of P87 powders was measured and its indoxyl sulfate adsorption level was also tested by the same process. All the experiments were repeated three times. The florescence data of solutions were tested using 1 mm quartz cuvette at room temperature with excitation of 278 nm and emission of 399 nm. The adsorption level of each membrane was expressed as μg adsorbed indoxyl sulfate per g of adsorptive membrane and per g of adsorptive zeolite in membranes. Similarly, the adsorption level

of indoxyl sulfate by zeolite powder was expressed as μg indoxyl sulfate per g zeolite. The screening of zeolites through adsorption of IS also carried out as follows: 0.01 g zeolites were measured and added to tubes. Then, 1 ml indoxyl sulfate solution was added to the tubes and incubated for 0.5 h. The tubes were centrifuged at 12000 rpm to precipitate the zeolites. 200 μl supernatants were piped into 1 ml PBS buffer and mixed well before fluorescence tests.

Effect of pH and salts on IS adsorption by zeolite

To evaluate how pH and salt affect P87's IS adsorption level, the following experiments were carried out. The intensities of IS in salts and pH were set as control and measured through the following procedures. First, a 7.5 mg dL^{-1} IS solution was made. Then, 500 μl 7.5 mg dL^{-1} IS solution was mixed with 500 μl water, NaCl , KCl, $CaCl_2$ and PBS buffer with pH adjusted from 4 to 10. Finally, 200 μl of these mixed solutions were each added to 1 ml PBS (pH=7.4) and the fluorescence intensity were measured.

Adsorption tests with salt and pH mediums were carried out by measuring 0.01 g P87 zeolite and placing them into centrifuge tubes with 500 μl 7.5 mg dL^{-1} IS solutions. Then, 500 μl water, NaCl, KCl, $CaCl_2$ and PBS buffer (pH 4 to 10) were added into each centrifuge tube and mixed well. They were centrifuged at 15000 rpm after incubating for 0.5 h. Finally, 200 μl supernatant from each tube was mixed with 1 ml PBS (pH=7.4) and the fluorescence intensity was measured.

Effect of pH and salts on IS desorption by zeolite

To evaluate whether pH and salts affect P87's IS desorption, 0.01 g P87 zeolite was measured and placed into centrifuge tubes with 1 ml of 7.5 mg dL^{-1} IS solutions. The mixture was centrifuged at 6000 rpm after 0.5 h incubation to obtain precipitant. The precipitant was washed with 1.5 ml water to remove non-adsorbed IS. Then, 1 ml water, NaCl , KCl, $CaCl_2$ and PBS (pH from 4 to 9) were added into precipitant and mixed well. They were further incubated for 0.5 h before being centrifuged at 15000 rpm. Following this, 200 μl supernatant was mixed with 200 μl PBS before measuring the fluorescence intensity.

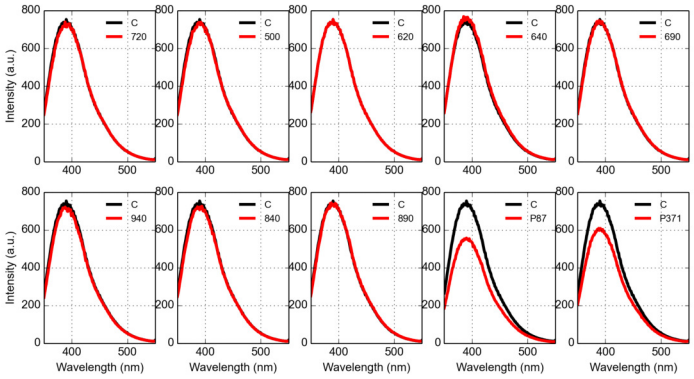


Figure 7.1: The screening of zeolites.

7.3 Results and discussion

7.3.1 Screening of zeolites

The adsorption of indoxyl sulfate by 10 types of zeolite with 5 different frameworks was tested and compared. Figure 7.1 shows that only P87 and P371 adsorb indoxyl sulfate while P87 has a lightly higher adsorption level. As a result, P87 is chosen in the following studies.

7.3.2 Properties of membranes

Figure 7.2(a) shows the morphology of P87 zeolite powders. They are spherical particles with grain sizes of 200-400 nm. The images also show that these particles congregated together. DLS tests in Figure 7.2(b) presented that the average particle size of P87 powder is 1056 nm. The test further confirmed that P87 particles tend to congregate. Figure 7.2(c, d) presents the cross-section of P87-PES membranes while Figure 7.2(e,f) shows that of pristine PES membranes. When we compare the morphologies of P87 incorporated membranes with that of pristine PES membranes, three differences are present: (1) in pristine membranes, the surface is smooth and solid-like, while in P87 composite membranes, the surface is rough and has pores. (2) The channels observed in the cross section of pristine membranes are clear and with smooth channel surfaces, while the channels observed in composite membranes have zeolite particles embedded

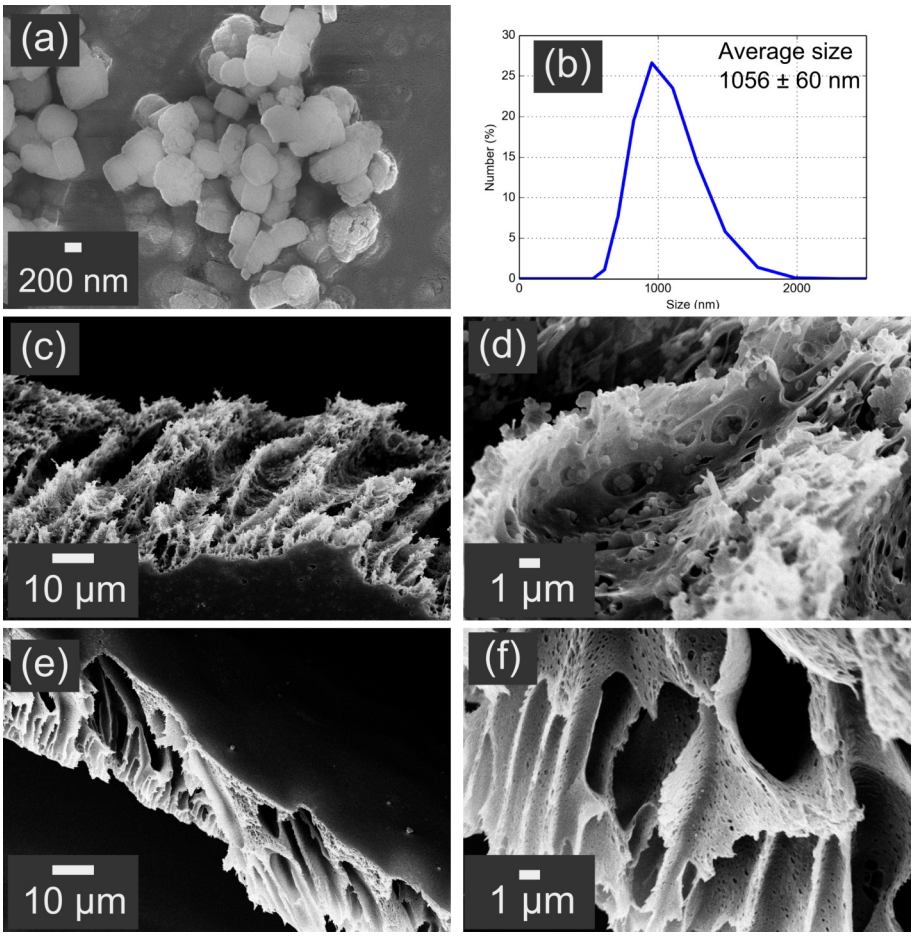


Figure 7.2: SEM and DLS of zeolite powders and cross-section of membranes: (a,b) P87 powder, (c,d) PES-P87 membranes, and (e,f) PES membranes.

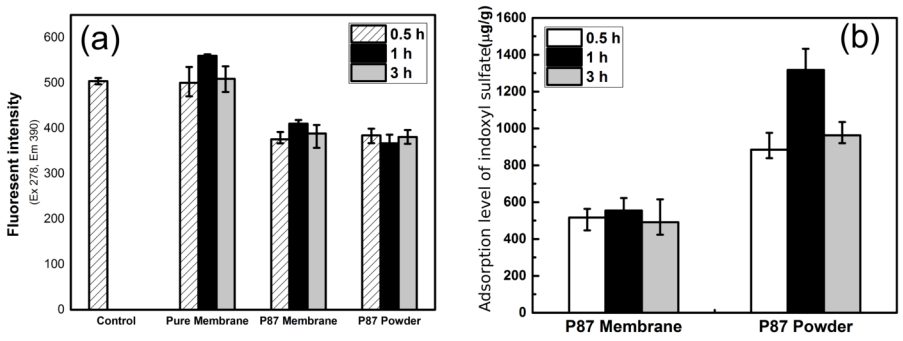


Figure 7.3: Adsorption of indoxyl sulfate by P87 powders and membranes at different time: adsorption level of P87 powder and membranes (a), the fluorescent intensity difference (b).

on the surface. (3) When compared to composite membranes, the pristine membranes are thinner.

We can tell that the addition of P87 powders in PES membranes resulted in their morphology and structure changes. As a result, we can expect PES-zeolite membranes have much higher water flux because of the nanopores on their surface. Water flux experiments were carried out through the procedure described in Appendix A.6 using the system illustrated in Figure A.4. The water flux test data in Table A.3 shows greatly improved water flux for PES-P87 composite membranes when compare to that of pristine membranes. It is on average 112 g/m^2 h mmHg for PES composite membranes and 0.52 g/m^2 h mmHg for pristine membranes. The major reason is that the surface pore existed on P87-PES membranes connect the inner channels and formed a water flow route.

Thermal gravimetric analysis(TGA) tests were also carried out to evaluate the actual percentage of P87 powders in the membranes. The tests result (shown in Figure A.5) showed that 46.5 wt% of P87 were incorporated in the membranes, and it is close to the theoretical data of 50 wt%. The difference between the percentage of zeolite in precursor solution and in the final membrane was small. This indicates that spin-coating is a reliable method for fabricating composite membranes with a high percentage of particles.

7.3.3 Indoxyl sulfate adsorption

It is important to quantify P87 zeolite's and its membranes' indoxyl sulfate adsorption levels. Figure 7.3(a) compares the indoxyl sulfate adsorption level between P87 as pow-

ders and membranes. Overall, the P87 powders had a higher indoxyl sulfate adsorption level than its membranes. The reason is that PES matrix tends to block parts of P87 surface, resulting in reduced effective particle adsorption surface. With the adsorption time increased from 0.5 h to 3 h, the membranes showed similar indoxyl sulfate adsorption levels. However, the zeolite powders had the highest adsorption values in 1 h. A possible explanation is that the adsorption equilibrium process is an adsorption and desorption process, and the adsorption process takes more than 0.5 h to reach a balance.

Figure 7.3(b) shows the indoxyl sulfate intensity after being adsorbed by various materials (pure membranes, PES-zeolite membranes and zeolite powders). It shows that pristine PES membranes do not adsorb indoxyl sulfate, since the intensity is as strong as the control group. P87 membranes and P87 powders both partially lowered 25% of the intensity of indoxyl sulfate. It indicates that the membranes and P87 could partially adsorb indoxyl sulfate in water. However, the adsorption force is weak. We conjecture that the adsorption happens because of electrostatic attraction between the particles and indoxyl sulfate.

7.3.4 Mechanism studies of indoxyl sulfate adsorbed by P87 powders

To study the adsorption mechanism through which P87 zeolites adsorbs indoxyl sulfate, the ζ-potentials of P87-indoxyl sulfate systems were tested and results were showed in Table 7.1. The ζ-potential of P87 is 44.0 mV, while that of indoxyl sulfate is -8.0 mV. Since they have opposite charges on the surface of zeolite and indoxyl sulfate, we expect that indoxyl sulfate will be adsorbed onto zeolite particles through electrostatic attraction. After we incubated the zeolite particles with indoxyl sulfate, the potential for zeolite conjugate became 35.6 mV. We then washed the conjugate to eliminate extra free indoxyl sulfate in the system. After washing, the zeolite potential of the system became 39.1. The data indicates IS lowered the ζ- potential of the zeolite because IS was adsorbed onto zeolite. Here we infer that indoxyl sulfate could be adsorbed into zeolites through molecular sieve or onto the surface of zeolites through electrostatic attraction, more tests are needed to determine the exact mechanism.

Table 7.1: ζ-potential studies of P87 powder and indoxyl sulfate.

Sample	**ζ-potential(mV)(Average)**
P87 in water	44.0
IS in water	-8.0
P87 + IS conjugate washed	39.1
P87 + IS conjugate unwashed	35.6

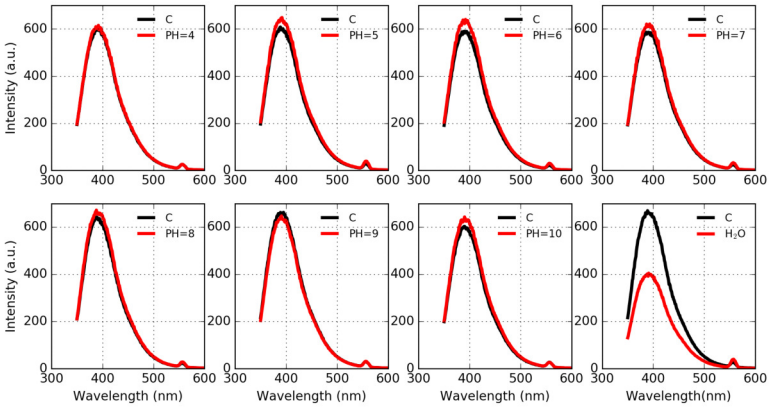


Figure 7.4: pH's effect on indoxyl sulfate adsorption by zeolite.

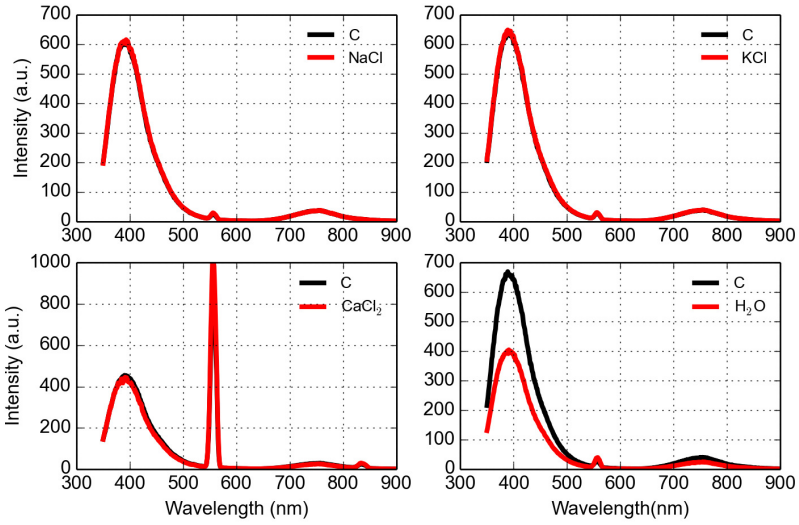


Figure 7.5: Salt's effect on indoxyl sulfate adsorption by zeolite.

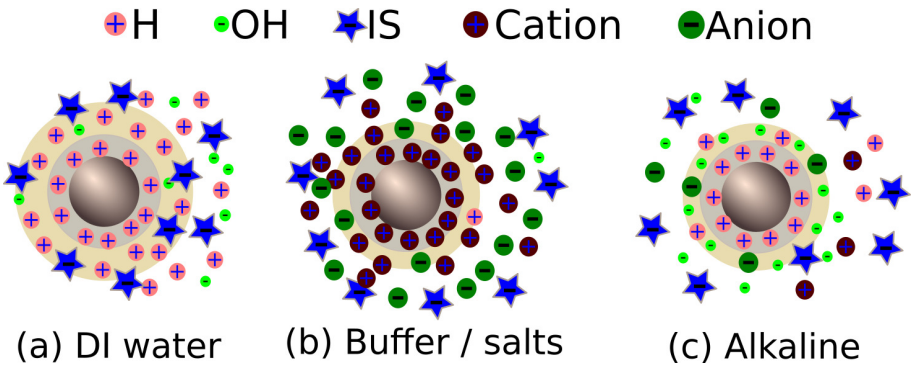


Figure 7.6: Illustration of electrostatic attraction and electric blocking of indoxyl sulfate.

In order to determine the adsorption mechanism, experiments were carried out to measure the effects of pH and salts on the adsorption rate of the zeolite. Figure 7.4 and Figure 7.5 show that in the presence of salt and pH adjusted PBS, P87 zeolite no longer adsorb indoxyl sulfate anymore. However, the zeolites adsorb around 42 wt% of indoxyl sulfate in deionized water. In the environment of deionized water, negatively charged P87 particles attract H^+ and form electric double layers (Appendix A.8). They adsorb indoxyl sulfate through electrostatic attraction. However, the introduction of pH adjusted PBS buffer and 1M salts solutions bring excessive ions (0.5 mole/L) to the systems, and the increased ionic strength largely decrease Debye length. The ions also screen the electrostatic attraction between the zeolite particles and indoxyl sulfate. As a result, indoxyl sulfate is not adsorbed onto zeolites. Another phenomenon might also occur with PBS buffer at high pH. Because of the superabundant OH^- ions, the Debye length layer is mainly occupied by OH^- ions, thus the zeta potential of the system is negative. As a result, negatively charged OH^- could repulse indoxyl sulfate molecules away from the surface of P87 zeolites [174]. All these three phenomena are illustrated in Figure 7.6.

Experiments to determine the effect of pH and salts on zeolite desorption were carried out to further confirm the interaction between zeolite and indoxyl sulfate. Figure 7.7 shows that in the presence of salt and pH adjusted PBS, P87 adsorbed indoxyl sulfate is eluted into solution. The introduction of PBS with adjusted pH totally interrupted the attraction between zeolite particles and indoxyl sulfate. The excessive cations and anions from the salt also replaced the majority part of adsorbed indoxyl sulfate on the zeolite because electrostatic attraction is a weak force and excessive ions lead to elec-

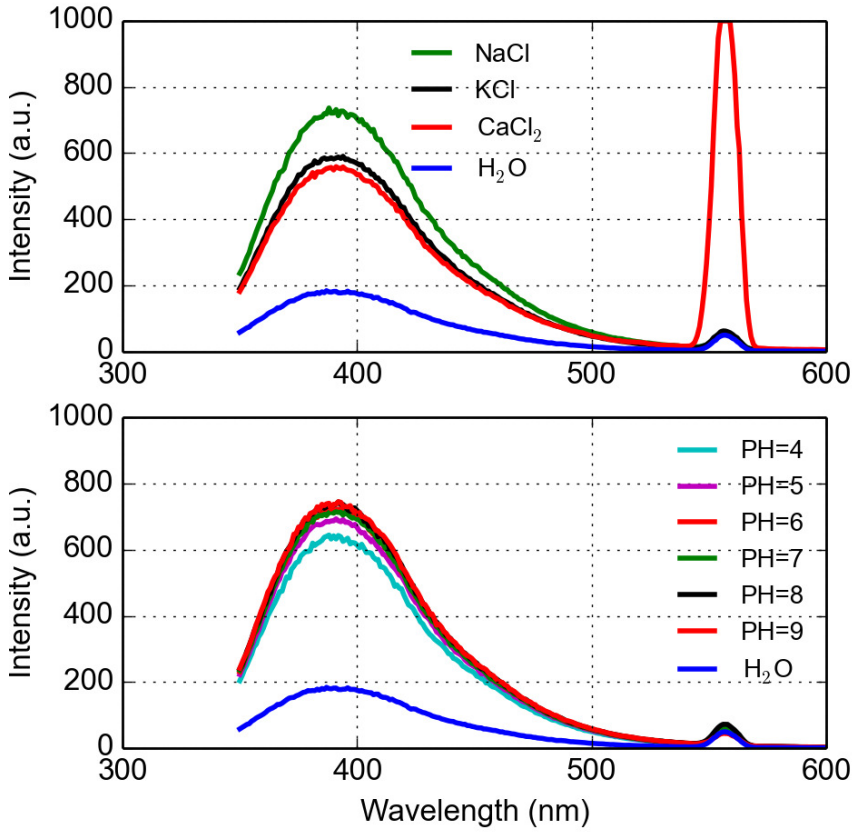


Figure 7.7: pH and salt's effect on indoxyl sulfate desorption from zeolite.

tric adsorption screening effects for indoxyl sulfate. In Figure 7.7 (a), we see that the replacement strength is $Na^+ > K^+$. We believe this is related to the size and weight of the cations. Na^+, which has smaller size and lighter weight, moves faster and easier in the medium, thus exerts more influence on the zeolite-IS conjugates. As a result, in the NaCl medium, a higher percentage of zeolite-IS conjugate is disrupted. However, in deionized water, merely a small percentage of indoxyl sulfate was desorbed from zeolite particles because of the electric double layer generated by negatively charged P87 attracts indoxyl sulfate.

7.4 Conclusion

Currently, hemodialysis can clear around 70% of urea, but only 30% of protein-bound toxins. Protein-bound solutes are routinely ignored, as hemodialysis adequacy is typically benchmarked by urea removal. Increasingly, studies have shown that protein-bound toxins are related to the progression of chronic kidney disease (CKD), and in the generation and aggravation of cardiovascular disease. Indoxyl sulfate is usually chosen as a representative of protein-bound toxins since it plays an important role in causing reno-cardiovascular syndromes.

In this chapter, we first screened types of zeolite that adsorb indoxyl sulfate. Then we fabricated polymer-zeolite composite membranes to evaluate whether they can remove protein-bound toxins through adsorption. We observed that zeolite-PES membranes can adsorb 550 μg indoxyl sulfate per g membrane in deionized water. We further studied the mechanism through which P87 zeolite adsorb indoxyl sulfate by measuring the ζ-potential, and the adsorption effects of pH and salts. We concluded that electrostatic attraction is likely the mechanism through which P87 adsorbs indoxyl sulfate.

Chapter 8

Conclusion and future work

The main goal of this thesis was to fabricate hemodialysis membranes that could quickly eliminate both water-soluble and protein-bond toxins. In Chapter 4, we fabricated a membrane through electrospinning technology that could adsorb creatinine, a representative of water-soluble toxins, at high capacity and fast speed. These composite membranes had the potential to reduce the duration of hemodialysis, since they can clear toxins through diffusion, adsorption and convection. Their pore size, however, was too large for the purpose of hemodialysis. Therefore, in Chapter 6 and Chapter 7, we proposed spin-coating as a better method to synthesize potential hemodialysis membranes. We conducted experiments that proved that membranes fabricated through spin-coating can adsorb both water soluble toxins and protein-bond toxins through adsorption. Furthermore, these membranes have suitable pore-size for hemodialysis. In Chapter 5, we evaluated the choice of different zeolites in order to maximize the adsorption effect.

The key research findings from each chapter are summarized below.

- Chapter 4 (Toxin adsorption by PAN-zeolite electrospun membranes):
  - Novel fibrous membranes using PAN and zeolite particles were fabricated through electrospinning with the average fiber diameter of 673 nm.
  - The creatinine adsorption of 940-zeolite powders increased from 2234 μg/g in 50 μmol/L creatinine solution to 25423 μg/g in 625 μmol/L creatinine solution.
  - The speed of adsorption was very quick; 0.025 g of 940-zeolite powders could eliminate 91% of 2 μmol creatinine in 5 min.
- Chapter 5 (Effect of size and shape on zeolite adsorption):
  - Size and shape of zeolites had significant effect on their creatinine adsorption ability when added into membranes.

  - Microparticles presented better adsorption capacity than nanoparticles when incorporated inside the membranes, although the size does not have any effect on zeolite powders' creatinine adsorption.
  - The spherical nanoparticle shape proved a better choice than rod nanoparticles when incorporated in the polymer fiber made through electrospinning.

- Chapter 6 (Creatinine adsorption by zeolite-polyethersulfone membranes):
  - Polyethersulfone-zeolite membranes were made through a simple spin-coating process.
  - Membranes with 840 could adsorb 4948 μg creatinine per g membranes.
  - The incorporation of zeolite into membranes affected the membranes' pore channels, thus also affecting the water flux.
  - pH and salts effect on zeolites' creatinine adsorption indicate that the process is chemical adsorption.

- Chapter 7 (Indoxyl sulfate adsorption by zeolite and zeolite-polyethersulfone membranes):
  - Zeolite-PES membranes could adsorb 550 μg indoxyl sulfate per g membranes.
  - Electrostatic attraction probably is the mechanism for P87 to adsorb indoxyl sulfate.

Future work

In this thesis, we found that many types of zeolites (Appendix A.1) are excellent at adsorbing creatinine. However, only P87 and P371 could adsorb indoxyl sulfate through electrostatic attraction. A zeolite that can adsorb protein-bound toxin at a high level remains to be found. Based on the research from Wernert[23], we can see that silicalite type of zeolite has excellent indoxyl sulfate adsorption capacity. It would be interesting to test its protein-bound toxin adsorption ability. The adsorption test procedure can similar to the one used in Chapter 7.

Based on the results and conclusion from this thesis and Figure 7.1, it is clear that P87 and P371 can adsorb indoxyl sulfate. They are particles with crystal size 300 and 300 by 700 nm. We conjecture that the mechanism is likely to be electrostatic attraction, formed due to zeta potential layer. However, it is unclear whether reducing the particle size can improve the adsorption of indoxyl sulfate. To verify this, mordenite zeolites with particle size smaller than 50 nm are needed. Then, indoxyl sulfate adsorption tests, as well as mechanism tests, can be performed as in Chapter 7.

The initial study on the urea acid adsorbing capability of zeolites is shown in in Appendix A.2 showed that they do not adsorb urea acid. This proved that zeolites have specific adsorption for uremic toxins. In order to find toxins that could specifically adsorb uric acid, the following directions could be considered. Based on the research from Wernert[23], we can see that stilbite type of zeolite have excellent uric acid adsorption capacity. It would be a good start to purchase or synthesis stilbite zeolite and then test its uric acid toxin adsorption ability referring to the adsorption test procedure in Chapter 4.

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Appendices

Chapter A

A.1 Adsorption of creatinine by various zeolites

During our experiments for this thesis, we tested 6 types of zeolite to adsorb creatinine. In this section, we compare all of them through the following procedure.

The creatinine adsorption test was carried out as follow: 0.01 g zeolites were measured and added to tubes, and then 1 ml creatinine solution was added to these tubes and incubated for 0.5 h. These tubes were centrifuged at 12000 rpm to precipitate the zeolites. 500 μl supernatant was piped into 1.5 ml PBS buffer and mixed well before ultraviolet spectrum tests.

The testing results are shown in Figure A.1. As we mentioned in the background, the molecular size of creatinine is 0.71 x 0.81 x 0.3. Zeolites need to have comparable pore channel size with creatinine in order to adsorb it. We can see that 720 type zeolite, which is ferrite, barely adsorbs creatinine. The pore channel of ferrite is 0.42 x 0.54 and 0.35 x 0.48, which is smaller that the size of creatinine.

500-type zeolite does not adsorb any creatinine, even though the pore size is comparable. The reason is that 500 is K^+ cation type. H-protonated creatinine cannot replace K^+.

620, 640 and 690, which are H-morderite type zeolites, all adsorbed creatinine, but in various levels. The relation between the adsorption levels was 640 = 690 > 620. The pore channel sizes of H-morderite zeolites are 0.65 x 0.7 and 0.34 x 0.48, which are comparable to that of creatinine. As H-morderite has H^+ site in the channel, it can be replace by H-protonated creatinine.

940, which is H-Beta type zeolite, adsorbed zeolite at the highest levels. Two reasons contribute to this. The pore channel of this zeolite is 0.66 x 0.67 and 0.56 x 0.56 nm, which is comparable to creatinine. 940 is H^+ type zeolite and it have sites that can be

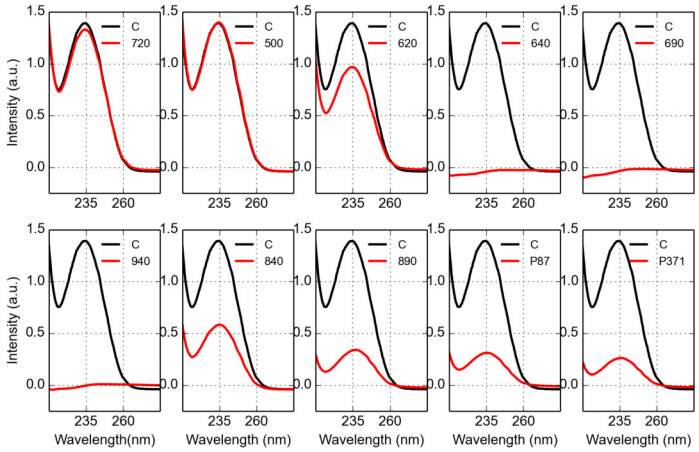

Figure A.1: The adsorption of creatinine by zeolites.

replaced by protonated creatinine.

For the zeolites from ZSM group, the adsorption level of creatinine was $P87 > P371 = 890 > 840$. This happens since P87 and P371 are nanoparticles; they have smaller grain size and higher surface area. Therefore, their adsorption levels are higher than that of microparticles (840,890).

A.2 Adsorption of uric acid by various zeolites

In some preliminaries experiments for this thesis, we tried to use zeolite to adsorb uric acid. The results are shown in Figure A.2.

The uric acid adsorption test was carried out as follow: 0.01 g zeolites were measured and added to tubes. Then, 1 ml uric acid with concentration of 0.2 mmol and 0.05 mmol was added to these tubes and incubated for 0.5 h. These tubes were centrifuged at 12000 rpm to precipitate the zeolites. The supernatants were tested by ultraviolet spectrum test. From the result we can see that 4 types of zeolite did not adsorb any uric acid. A possible explanation is that the uric acid does not protonate, so they cannot replace the adsorption site in zeolite. As such, zeolites do not adsorb uric acid.

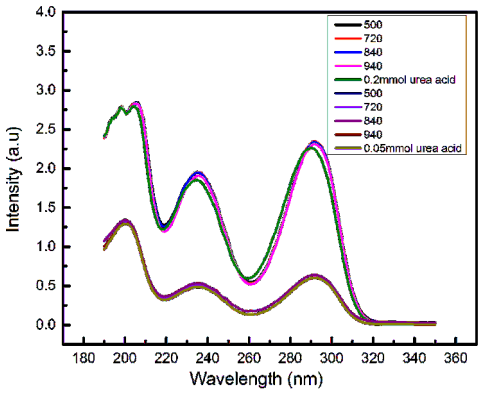

Figure A.2: The adsorption of uric acid by zeolites.

Name	Structure	Pore Size	SiO_2/AlO_3	BET(m^2/g)	Crystal size	DLS
720	K-FER	0.42×0.54, 0.35×0.48	17.7	170	1000	4097
500	K-LTL	0.71×0.71	6	290	400	702.2
620	H-MOR	0.65×0.7,0.34×0.48	15.7	400	1000-3000	2106
640	H-MOR	0.65×0.7,0.34×0.48	18	380	100×500	1995
690	H-MOR	0.65×0.7,0.34×0.48	240	450	100×500	2315
940	H-Beta	0.66×0.67,0.56×0.56	40	530	500×1000	645
840	NH_4-ZSM-5	0.51×0.55,0.53×0.56	40	330	2000×4000	1849
890	ZSM-5	0.51×0.55,0.53×0.56	1500	310	2000×5000	5560
P87	ZSM-5	0.51×0.55,0.53×0.56	87	362	300	578
P371	ZSM-5	0.51×0.55,0.53×0.56	371	362	300×700	687

Table A.1: Zeolites properties (all sizes in nm)

A.3 Zeolite comparison data

10 types of zeolites are purchased, with P87 and P371 from ACS Materials, LLC. and the rest of them from Tosoh Corporation. Their properties incluing structure, pore size, the ratio of SiO_2/Al_2O_3, BET, crystal size and particles size mearused throuhg dynamic light scattering are presented in Table A.1.

A.4 Creatinine standard

The creatinine standard is calculated by linear regressionA.3.

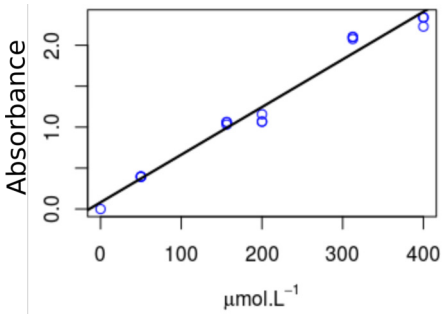

Figure A.3: Creatinine standard

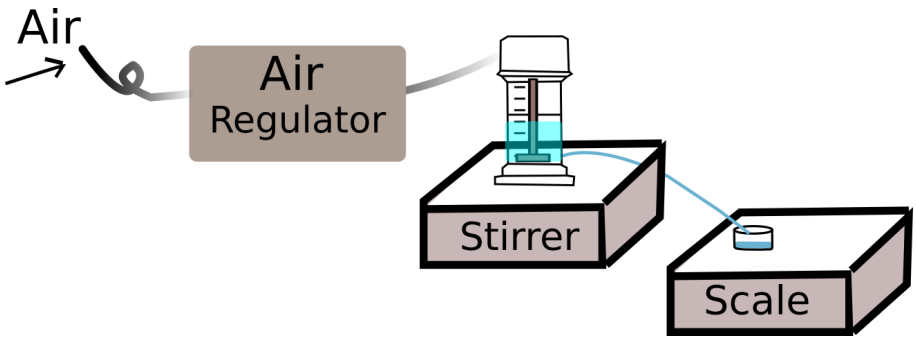

Figure A.4: Illustration of water flux testing system

A.5 Raw data for PES-zeolite

PES-zeolite adsorption raw data related to chapter 6 is presented in table. A.2

A.6 Water flux

The water flux of the spin-coated composite membranes was measured using a 10 ml ultrafiltration cell from Millipore, the system is illustrated in Figure A.4. The effective membrane area is 4.1 cm^2. The system was first steadied with water for 20 min at 11 psi to compact the membranes. Then, the water flux was measured at 10 psi for 20 min, and calculated by equation

$$Flux = \frac{m}{StP}, \tag{A.1}$$

where m is the quality of the permeated water (g); S is the effective membrane area (m^2); P is the pressure (hmmHg) and t is the permeated time (h).

The tested data is shown in Table A.3.

	Weight(g)	Creatinine(mg/ml)	Volume(ml)	UV 235(nm)
0-PES	0.0348	0.1	6	1.371
0-PES	0.02998	0.1	6	1.339
0-PES	0.0334	0.1	6	1.368
50-840-PES	0.0822	0.1	6	0.439
50-840-PES	0.0794	0.1	6	0.375
50-840-PES	0.0767	0.1	6	0.59
50-P87-PES	0.1	0.1	6	0.784
50-P87-PES	0.104	0.1	6	0.738
50-P87-PES	0.097	0.1	6	0.828
50-P371-PES	0.1941	0.1	6	0.736
50-P371-PES	0.1797	0.1	6	0.924
50-P371-PES	0.1877	0.1	6	0.743
840 Powders	0.0406	0.1	6	0.8
840 Powders	0.0401	0.1	6	0.625
840 Powders	0.044	0.1	6	0.748
P87 Powders	0.05	0.1	6	0.445
P87 Powders	0.0513	0.1	6	0.485
P87 Powders	0.0505	0.1	6	0.439
P371 Powders	0.0919	0.1	6	0.224
P371 Powders	0.0906	0.1	6	0.224
P371 Powders	0.0925	0.1	6	0.184
Creatinine	-	0.1	-	1.330
Creatinine	-	0.1	-	1.369
Creatinine	-	0.1	-	1.330

Table A.2: Creatinine adsorption by zeolites and their PES membranes.

Tests	Membranes	Waterflux(g/m^2 h mmHg)
1	PES	0.85
2	PES	0.41
3	PES	0.31
1	PES-P87	77
2	PES-P87	136
3	PES-P87	124

Table A.3: Water flux

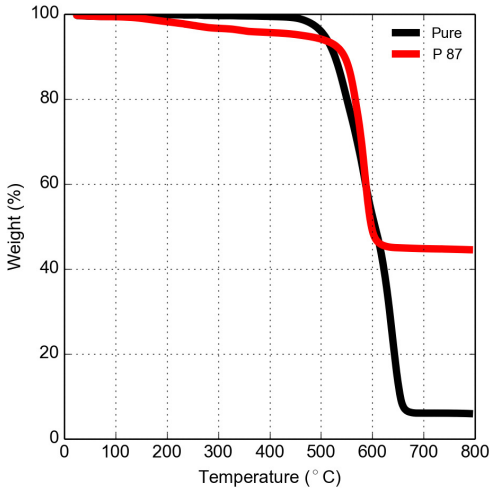

Figure A.5: TGA data of pure PES and 50-P87-PES composite membranes

A.7 Thermal gravimetric analysis (TGA)

A Q500 TGA instrument from TA Instruments was used to carry out thermal gravimetric analysis for pristine polyethersulfone and polyethersulfone-zeolite membranes. The temperature scans were taken from room temperature to 800 °C with a heating rate of 10 °C min^{-1} and at an ambient atmosphere with a flow of 20 ml min^{-1}. The results is shown in Figure A.5.

A.8 Electric double layer for spherical particles

A sphere particle's electric double layer is illustrated in Figure A.6. Debye length(λ_D) is a measure of a charge charrier's net electrostatic effect in solution, and it can be expressed by the following equation in monovalent(1-1) electrolyte:

$$\lambda_D = \sqrt{\frac{\epsilon_0 \epsilon_r k_B T}{2 N_A e^2 I}} \tag{A.2}$$

where, I is the ionic strength of the electrolyte, and here the unit is mole/L, ϵ_0 is the permittivity of free space, ϵ_r is the dielectric constant, k_B is the Boltzmann constant, T is the absolute temperature in kelvins, N_A is the Avogadro number, e is the elementary

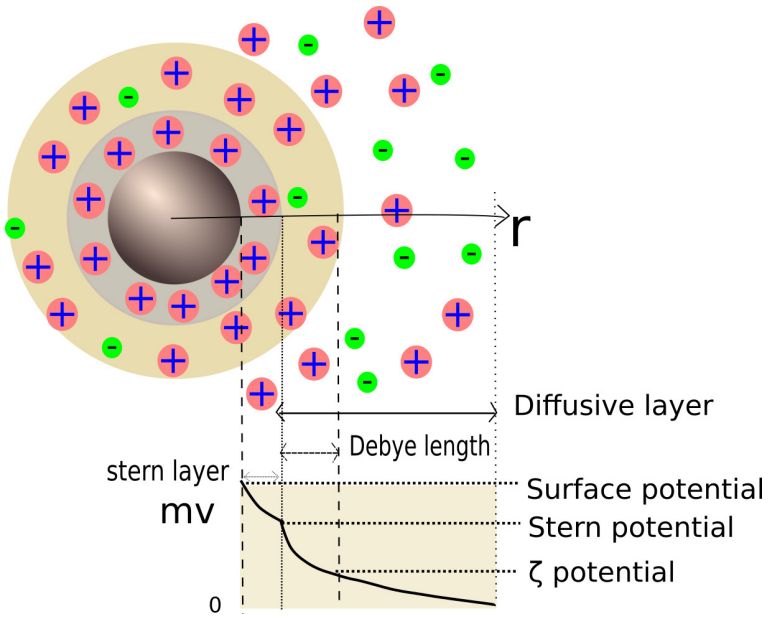

Figure A.6: Illustration of a sphere particle's electric double layer

charge.

$$I = \frac{1}{2}\sum_{i=1}^{n} c_i(z_i)^2 \tag{A.3}$$

where, c_i is the molar concentration of ion i (M, mol/L), z_i is the charge number of that ion.

We know that Debye length is proportionally related to ionic strength of solution through the following relation,

$$\lambda_D \propto \sqrt{\frac{1}{I}}$$

A.9 Adsorption raw data

PES-zeolite indoxyl sulfate adsoprtion raw data is presented in table. A.4

	Weight(g)	IS(mg/100ml)	Volume(ml)	0.5 h	1 h	3 h
0-PES	0.0347	3.5	6	471	561	480
0-PES	0.03348	3.5	6	535	563	511
0-PES	0.0329	3.5	6	495	555	536
50-P87-PES	0.102	3.5	6	392	417	357
50-P87-PES	0.0993	3.5	6	366	395	407
50-P87-PES	0.01026	3.5	6	368	418	401
P87 Powders	0.0572	3.5	6	367	341	366
P87 Powders	0.0569	3.5	6	386	373	380
P87 Powders	0.0506	3.5	6	399	385	396
-	-	3.5	-	511		
-	-	3.5	-	504		
-	-	3.5	-	497		
0-PES	0.0345	14	6	884	801	847
0-PES	0.03378	14	6	915	872	816
0-PES	0.0335	14	6	930	869	940
50-P87-PES	0.1013	14	6	808	789	814
50-P87-PES	0.1082	14	6	831	817	752
50-P87-PES	0.01023	14	6	844	795	877
P87 Powders	0.0534	14	6	787	767	797
P87 Powders	0.0526	14	6	786	781	797
P87 Powders	0.0563	14	6	796	776	813
-	-	14	-	874		
-	-	14	-	881		
-	-	14	-	903		

Table A.4: Indoxyl sulfate adsorption by P87 and its membranes.(EX 278 nm,EM 390 nm)