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Synthesis of eugenol-based selective membrane for hemodialysis

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Abstract. Research on the synthesis of eugenol-based imprinted hemodialysis membranes has been undertaken. This study aims to produce eugenol-based urea selective membrane for hemodialysis. Eugenol containing functional groups of N and S tied with urea mixed with Poly Vinyl Acetate (PVA), Poly Ethylene Glycol Diglicidyl Ether (PEGDE) crosslinker and 1 Methyl 2 Pyrrolidone (NMP) solvent was heated at 110° to form hydrogel. The hydrogel was then reconstituted in the NMP and fed into the petridisc to form the membrane. The membrane was released the urea bonded with distilled water to obtain Molecularly Imprinted Membrane (MIM)-urea. The resulting MIM urea was characterized using FTIR, SEM. MIM urea was used to transport urea, creatinine and vitamin B-12. The research variables were thickness of membrane and comparison of transport result with NIM (Non Imprinted Membrane). The results obtained were MIM urea transported urea better than NIM. The result obtained was the thinner the membrane the better the urea transport. Membrane was also capable of transporting creatinine but not of transporting vitamin B-12.

Keywords: MIM urea, Eugenol, membrane for hemodialysis, urea

1. Introduction

Currently hemodialysis is one of the important applications of biomaterials that come into contact with blood. The central role of the hemodialysis is the semi-permeable membrane. A good semipermeable membrane must have the property of not passing proteins or cells, but passing urea and creatinine molecules in the blood, having high mechanical strength and resistance and biocompatibility. Balance of hydrophilicity and hydrophobicity of membranes is also expected [1]. Due to the limitation of cellulose and its derivatives studies on haemodialysis membranes develop. Cellulose, chitosan and polysulfone-based hemodialysis membranes have the disadvantage, that is, the blood protein is adsorbed onto the surface, therefore, in order to overcome this limitation, heparin is added which enable to damage blood cells [2, 3].

Indonesia has abundant natural resources, rich in natural ingredients; however, all these resources have not been utilized optimally. As a major producer of essential oils in the world, one of them is clove leaf oil, Indonesia fulfils almost half of the world's clove leaf oil needs in the early eighties [4]. Clove leaf oil contains eugenol of about 80-90% by weight [5]. Eugenol can be used as a starting material for the synthesis of a compound because of the three functional groups attached to it, namely the allyl, hydroxy and methoxy groups. Eugenol derivatives have been proven to be used for liquid membrane carriers with selectivity which can be adjusted depending on the functional group that was inserted [6-



9]. Djunaidi and Ulumudin [6] and Djunaidi [7] has proven that if N and S are included in polyeugenol, borderline and soft metal ions will be extracted more than other Pearson metal ions.

In addition, eugenol with its three functional groups also has the potential as functional monomer for selective adsorption process such as molecular imprinting polymers (MIP). Djunaidi *et al.* [10] used polyeugenol as a functional polymer with Polyethylene Glycol diglycidyl ether (PEGDE) for the synthesis of Fe MIP (Fe IIP), the selectivity of Fe IIP was proved by adsorbing Fe (III)>Pb (II)>Cr (III) >>Cd (II). Djunaidi *et al.* [11] used polyeugenol as a functional polymer for phenol and vanillin MIP, Phenol MIP proved to be much more adsorbing phenols than compounds with vanillin-like structures. Djunaidi *et al.* [12] and Djunaidi [13] also used polyeugenol as a functional polymer for MIM synthesize for selective transport of Fe, the membrane that was non-porous, elastic and selective to Fe (III). This membrane was synthesized in two ways, namely, in situ and particles. Combination of selectivity of Imprinted Molecules and polyeugenol functional groups, N- and S- produced a carrier surface selective against urea and creatinine. In this study we will synthesize MIM with polyeugenol which functions N and S for transport of urea and creatinine as the basis for haemodialysis membranes. Urea and creatinine have N and O atoms which allow interacting with N and S atoms of polydugol, so that this research will succeed.

2. Experimental Section

2.1. Materials

The materials used in this research purchased from SIGMA-Aldrich were Eugenol, BF₃-diethylether while other reagents purchased from E Merck, Germany were SOCl₂, 4-methyl-5-thiazoleethanol, NaOH, chloroacetic acid, chloroform, methanol, Polyvinyl alcohol (PVA), urea, creatinine, vitamin B-12,. Diethylether and demineralized water were purchased from Bratachem.

2.2. Instruments

The instruments used to characterization of PMTEEA in this study were FTIR Spectrophotometer (Shimadzu 8201PC), analytical balance (Mettler Tolendo AB54-S), UV Vis (Shimadzu), pH meter (HACH E C20) and SEM EDX (JSM-6510).

2.3. Polyeugenol Synthesis

5 gram of eugenol was put in a three-neck flask and then 1 mL of BF₃-diethyleter was added. The mixture had been stirred using a stirrer for 4 hours and every 1 hour was added 0.25 mL BF₃-diethyleter. After for 4 hours, the polymerization was stopped by adding 1 mL methanol. The gel formed was then dissolved in diethyl ether and washed with distilled water till a neutral pH was achieved. The solution was then dried by adding anhydrous Na₂SO₄. After being completely free from water, the solution was evaporated at room temperature. The precipitate formed was then dissolved in distilled water, dried and weighed. The result obtained was analysed using FTIR.

2.4. Synthesis of Polyeugenoxo Acetic Acid

5 gram polyeugenol was put into a 100 mL boiling flask, then added 33% NaOH solution (33 gram NaOH in 100 mL) of 17.5 mL. Then the mixture was stirred for approximately 30 minutes, and 12.5 mL of 50% chloroacetic acid solution (50 grams in 100 mL of water) was added little by little with a pipette while continuing to stir. The mixture had been heated in a water bath with temperature of 80-90°C for 2 hours, then it was cooled and acidified using 6 M HCl till pH 1 was obtained. Then it was extracted using diethyleter 3 times with 50 mL in each extraction. The ether extract was combined and extracted with sodium bicarbonate 5% b/v 3 times with 30 mL in each extraction. The water layer was then acidified with 6 M HCl till pH=1 was achieved. Afterward, filtering, drying and weighing of the result was conducted. The results obtained were analysed using FTIR.

2.5. *Synthesis of Poly (Methyl Thiazoleethyl Eugenoxy Acetate, PMTEEA)*

3 gram of *Polyeugenox Acetic Acid* was put into boiling flask and then added with 3 ml of thionyl chloride, refluxed for 240 minutes (40°C) and allowed to cool. Afterward, 2.5 ml of thiazoethanol was added (drop by drop) and refluxed back for 240 minutes (40°C). After getting cool, it was dissolved in chloroform and washed with water, dried with anhydrous Na₂SO₄, filtered and finally, the solvent was evaporated. The result obtained was analysed by FTIR.

2.6. *Making MIM urea in situ.*

0.5 g PMTEE was contacted with 10 mL of 100 ppm urea. The result was dried and analysed using FTIR. PMTEEA which was contacted with urea and added with 0.5 g PVA was dissolved in 5 mL NMP which was also added with sodium hydroxide as catalyst and PEGDE and heated at temperature of 100-110°C for 4 hours and allowed to stand overnight to form a gel. The gel was then added with NMP solvent and heated so that the desired viscosity was obtained for the casting process. The membrane layer from the casting had been then heated at 80°C overnight. The obtained membrane had been coagulated in 1.5 M NaCl solution for two days. The membrane sheet was then cut according to the size of the diffusion cell. The membrane sheets were then washed using demineralized water. Subsequently, the release of urea with distilled water for 24 hours was conducted to produce the MIM urea. Then the obtained membrane was installed in the ring of the diffusion cell device.

2.7. *Synthesis of Non Imprinting Membrane (NIM)*

NIM was synthesized in the same way as MIM urea synthesis but without the urea binding in the first stage. PMTEEA was used without being contacted with urea.

2.8. *Urea transport*

The transport of urea using membrane produced was undertaken using the diffusion cell device, where in the feed phase (feed, urea) was 100 mg/L urea and in the receiving phase was buffer phosphate (pH 6.5); each of the chemicals was 50 mL. After that, it had been stirred for 24 hours and every 2, 4, 6, 8 and 24 hours, sampling was conducted.

2.9. *Comparison of the performance of MIM and NIM in transporting urea.*

Membrane performance was undertaken by comparing 0.35 g MIM and 0.35 g NIM for 100 ppm urea transport.

2.10. *MIM urea performance test*

2.10.1. *Variation in gel weight (membrane thickness).* Performance of membrane related to the membrane thickness was tested to transport 100 ppm urea by varying the gel weights that were 0.35, 0.5 and 1 g.

2.10.2. *Variations in Urea concentration.* The concentration of urea in the feed phase (feed/urea) was varied by 100, 300 and 600 ppm. Urea transport was carried out using MIM 0.35 g.

2.11. *Creatinine transport*

Creatinine transport using membranes produced was conducted using a diffusion cell device; the feed phase (feed, creatinine) contained 25 mg/L creatinine and the receiving phase contained phosphate buffer (pH 6.5); each of the chemicals was 50 mL. This had been then stirred for 8 hours using 0.35 g MIM urea.

2.12. *Vitamin B-12 transport*

Vitamin B-12 transport with membranes produced was undertaken using a diffusion cell tool, in the feed phase (feed, urea) was 20 mg/L vitamin B-12 and in the receiving phase was 50 mL phosphate buffer and the mixture was stirred for 6 hours using 0.35 g MIM urea.

3. Results and Discussion

3.1. PMTEEA Synthesis

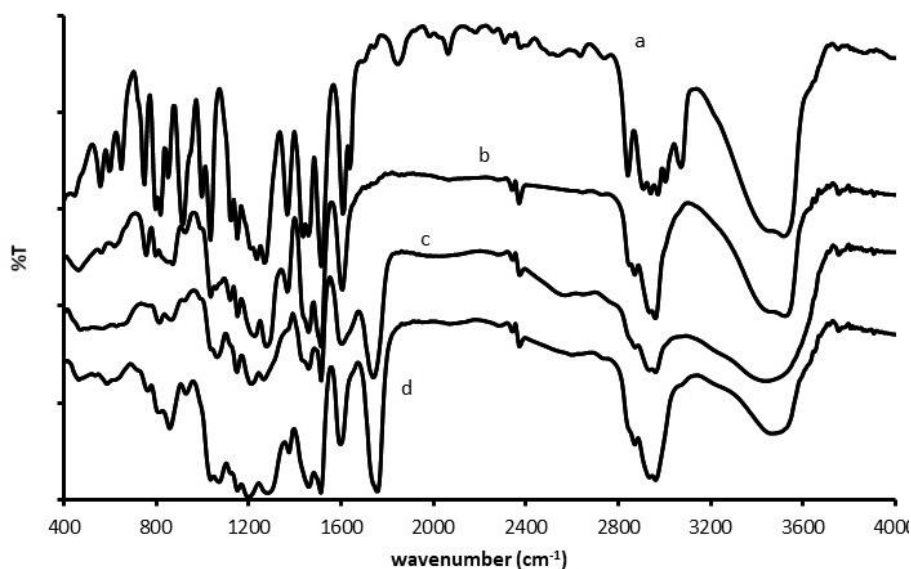


Figure 1. IR spectra of eugenol and its derivatives a. eugenol b. polyeugenol c. polyeugenol acetate d. PMTEEA.

It was seen in FTIR spectra (Fig. 1) that the loss of vinyl eugenol vibration modes at wavenumber of 915 cm^{-1} , 997 cm^{-1} and also $1648\text{--}1638\text{ cm}^{-1}$ indicated that polymerization of eugenol became polyeugenol occurred. A carbonyl group of alcohol (1600 cm^{-1}) changes to the carbonyl group of acid represented by absorption at 1720 cm^{-1} and shifts to a carbonyl group of ester (1743 cm^{-1}) after the esterification reaction with thiazole. Eugenol's and polyeugenol's hydroxyl (O-H) groups turn into hydroxyl groups of PMTEEA acid and ester around at 3400 cm^{-1} .

3.2. Urea Membrane Synthesis

PMTEEA which was successfully synthesized was then contacted with 100 ppm urea. The result obtained was then analysed using FTIR, as shown in Fig. 2. In Fig. 2 it shows the appearance of 1627 and 1643 cm^{-1} peaks (in the circle) attributed to the N-H bending vibration [14] which does not appear in PMTEEA.

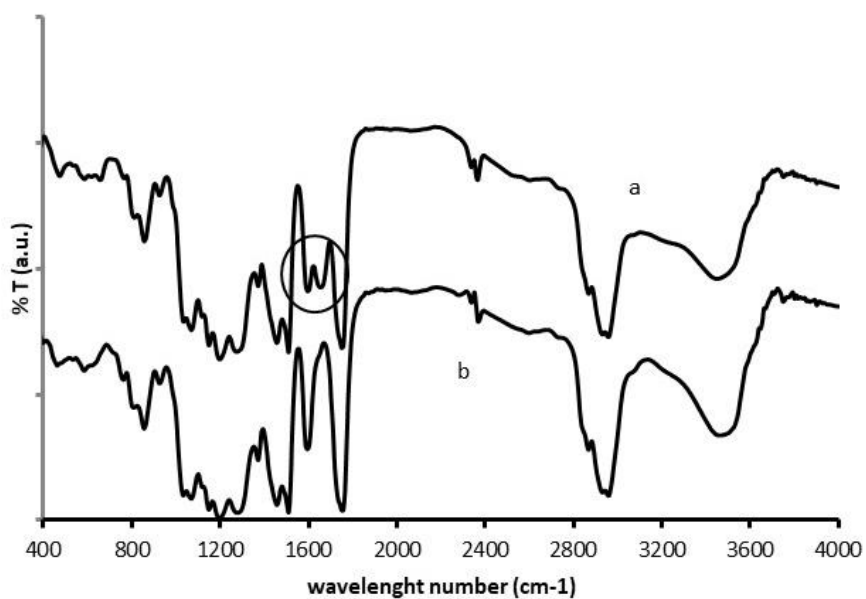


Figure 2. FTIR spectra of a. PMTEEA and b. PMTEEA-urea.

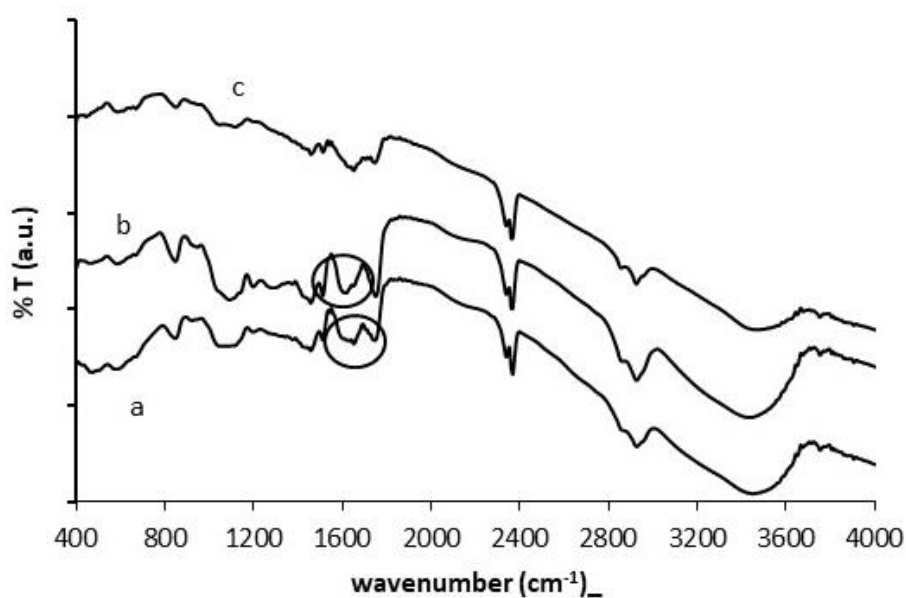


Figure 3. IR spectra of MIM urea a. MIM after urea transport b. NIM after urea transport c. MIM without urea transport.

3.3. Synthesis of NIM and MIM urea

Fig. 3 shows that urea gives the appearance of 1627 and 1643 cm^{-1} peaks (in the circle) attributed to the N-H bending vibration [14] which does not appear or just weak in MIM without transport. NIM and MIM urea show shift on carbonyl vibration mode to a greater wavenumber which indicates the presence of hydrogen bonds with urea.

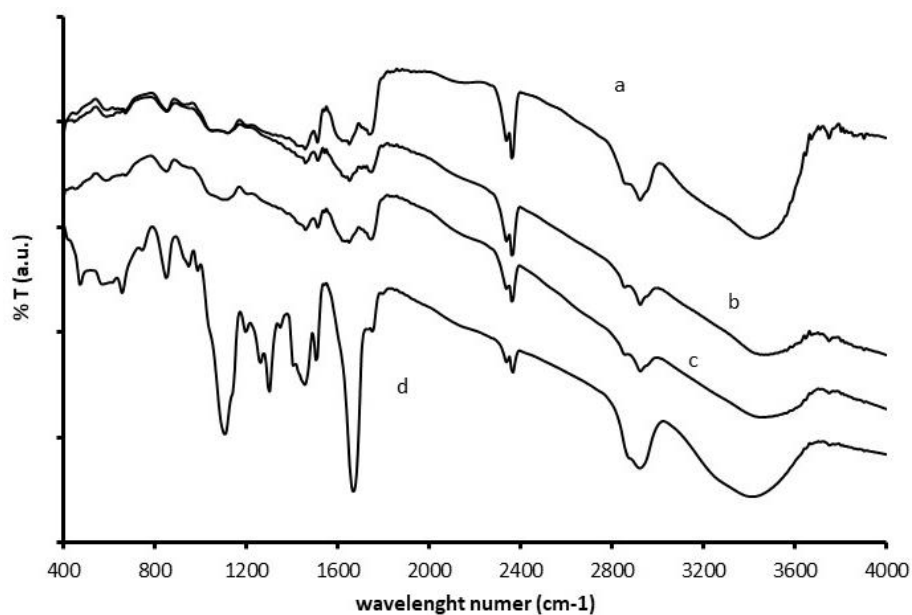


Figure 4. FTIR spectra of MIM urea from (a) 0.75 g (b) 0.35 g (c) 1 g gel and (d) PMTEEA-urea gel.

Fig. 4d shows that vibration modes of NMP solvent present around at 1670 cm^{-1} is lost by heating and C-O functional groups of glutaraldehyde and PVA are present around at 1100 cm^{-1} [10-13]. MIM urea produced from 0.35, 0.75 and 1 g of gel weights do not show a different spectrum.

3.4. Transport of 300 ppm urea

To see the performance of the membranes, they were used to transport 300 ppm urea. It can be seen in Fig. 5 that the MIM urea shows good transport, especially at the beginning of transport (up to 8 hours of transport), after 24 hours MIP and NIM show the same results on urea transport. This results indicated the effect of imprint on the membrane [6, 7].

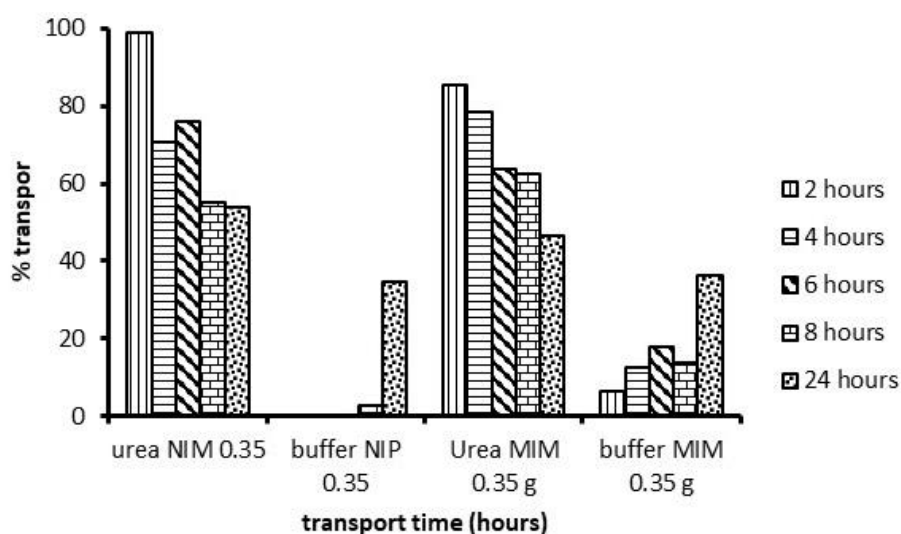


Figure 5. Comparison of urea transport between NIM and MIM urea.

3.5. Urea transport with membrane thickness variation

The thickness of the membranes also affect transport [8, 9]. This is proved by urea transport shown in Fig. 6. Membrane with a gel weight of 0.35 g is abler to produce thin membrane and shows better performance on urea transport than membranes produced with 0.5 and 1 g of gel weight.

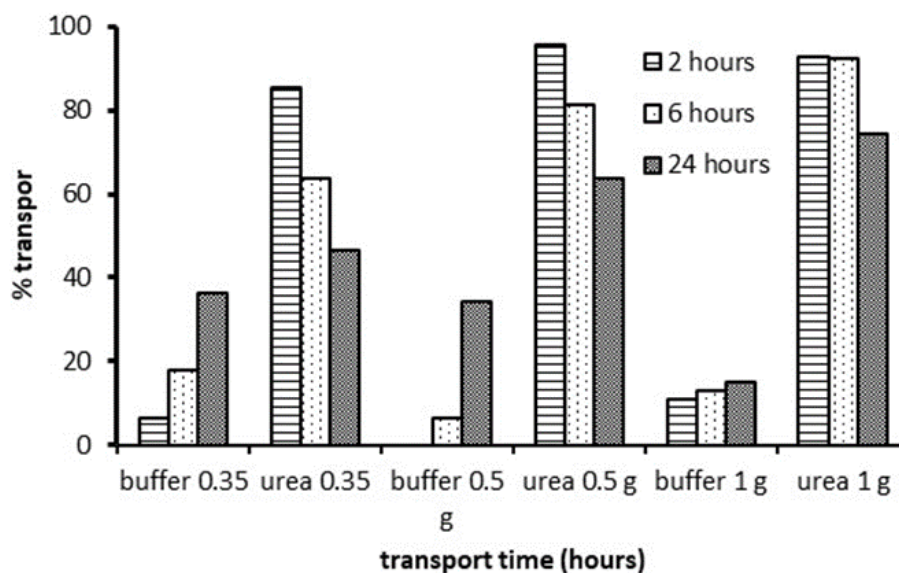


Figure 6. Comparison of the gel weight in the production of membranes for urea transport.

3.6. Transport of urea in different concentration

The concentration of urea also determines the rate of urea transport through the membrane. This is shown in Fig. 7. The greater the concentration of urea the greater the concentration of urea being transported. This is because transport occurs when there is a difference in concentration between the buffer phase (receiving phase) and the urea phase (feed/feed phase).

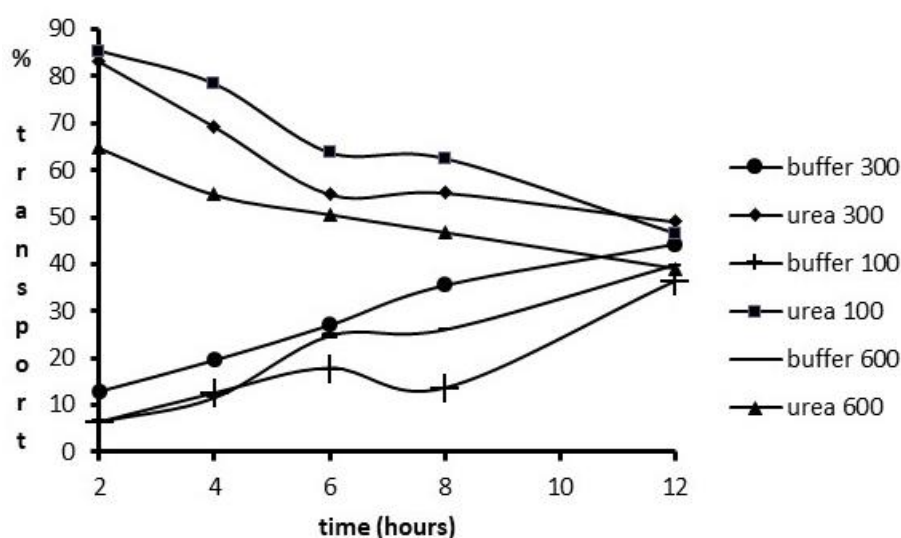


Figure 7. Comparison of urea transport in the variation of urea concentration.

3.7. Transport of creatinine and Vitamin B-12

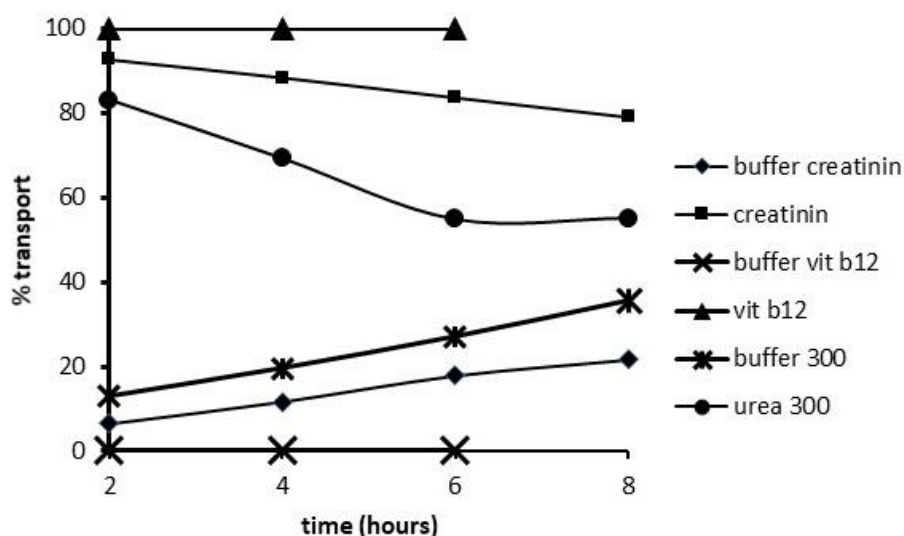


Figure 8. Creatinine, vitamin B-12 and urea transports by MIM urea.

It can be seen in Fig. 8 that the MIM urea is also capable of transporting creatinine even though it is not as large as urea, but it is unable to transport vitamin B-12. This is due to creatinine and Vitamin B-12 sizes which are greater than urea. Urea and creatinine sizes are 60 and 113 Daltons, respectively [15]; while vitamin B-12 has a size of 8.5 Å or 1.35 kDa [16]. Creatinine transport only had occurred for 6 hours because after this time creatinine became damaged.

3.8. Membrane Characterization using SEM EDX

3.8.1. Membrane washing. Table 1 shows washing of MIM urea for either 1 or 24 hour distilled water reduced NaCl level but not reduced urea level. This indicates that urea transport is caused due to hydrogen bonds between membranes with urea instead of imprint. Soaking the membrane in the buffer solution for 3 days did not reduce urea and N levels in the membrane, so that the urea level in the feed and receiving phases did not come from urea template leaching in the membrane but came from urea transport from the feed phase.

Table 1. Comparison of EDX of MIM urea washed for 1 and 24 hours with distilled water

Element			Weight Concentration			
			Washing for 1 hour		Washing for 24 hour	
Number	Symbol	Name	Before soaking in buffer solution*)	After soaking in buffer solution *)	Before soaking in buffer solution*)	After soaking in buffer solution*)
6	C	Carbon	51.3	47.2	46.6	45.0
17	Cl	Chlorine	13.6		2.8	-
8	O	Oxygen	16.9	25.8	24.9	26.7
7	N	Nitrogen	12.4	27.1	24.2	28.3
11	Na	Sodium	5.9		1.4	-

*) After soaking in buffer solution for 3 days

3.8.2. SEM Analysis. Fig. 9 shows the obtained membrane is porous with a size of about 1-5 μm . The membrane pore size is suitable for haemodialysis membranes.

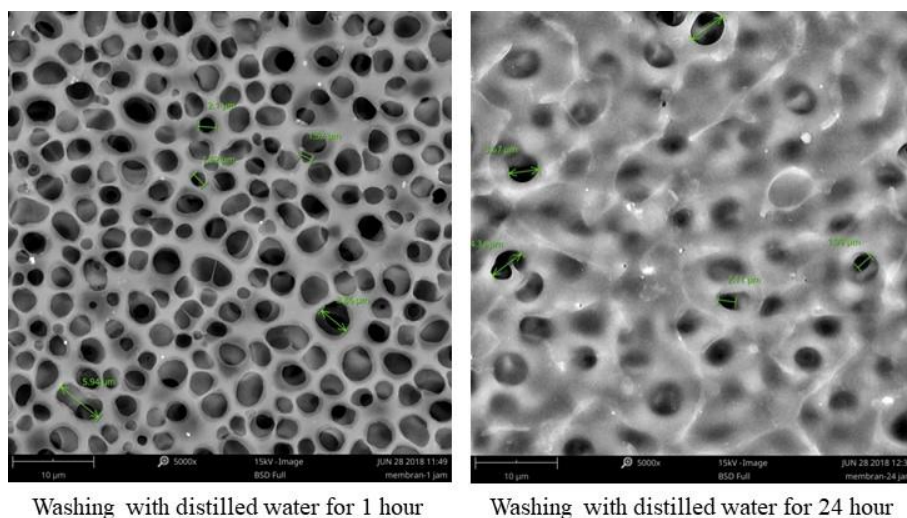


Figure 9. Comparison of SEM images of membranes after washing for 1 and 24 hours.

3.9. Analysis of MIM and NIM transport using EDX

Table 2. Comparison of MIM urea constituents before and after urea transport.

Number	Symbol	Element Name	Weight Concentration	
			Before transport	After transport for 24 hour
6	C	Carbon	44.8	44.6
8	O	Oxygen	34.3	31.8
7	N	Nitrogen	20.9	23.6

Table 3. Comparison of NIM constituents before and after urea transport.

Number	Symbol	Element Name	Weight Concentration	
			Before transport	After transport
6	C	Carbon	52.4	44.6
8	O	Oxygen	25.9	31.8
7	N	Nitrogen	21.7	23.6

It can be seen in tables 2 and 3 that the N content in both MIP and NIM membranes rises after transport. This means that there is still urea trapped in the membrane after 24 hours of transport.

4. Conclusion

Synthesis of membranes using active compounds from polyeugenol derivatives containing N and S functional groups was successfully undertaken. MIM urea show better transport compared to NIM, especially at the beginning of transport. The thinner the membrane, the greater the urea transport. The more urea concentration, the greater the urea transport. The urea membrane enabled to transport creatinine but not for vitamin B-12.

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