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RESPONSE SURFACE METHODOLOGY APPROACH TO STUDY THE INFLUENCE OF PEG AND WATER IN CELLULOSE ACETATE DIALYSIS MEMBRANES

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Abstrak. Flat sheet asymmetric dialysis membranes were fabricated using phase inversion method from polymer solution consisting of cellulose acetate, acetic acid, polyethylene glycol (PEG) and distilled water. The effect of acetic acid/PEG ratio and the distilled water content in the dialysis membrane were being investigated with respect to the urea clearance performance. Response surface methodology (RSM) was used to design the experiments and analysed the results obtained. The analysis revealed that the significant factor that affects the cellulose acetate dialysis membrane performance in terms of urea clearance is the ratio of acetic acid/PEG. Dialysis membrane with higher ratio of acetic acid/PEG gives higher urea clearance percentage due to the formation of finger like macrovoids. The relation between the urea clearance and the ratio of acetic acid/PEG in the given range of 4 – 14, was a quadratic model and the mathematical model suggested could adequately describe the performance indicators within the limits mentioned.

Keywords: Dialysis membrane; RSM; water content; acetic acid/PEG ratio; urea clearance

Abstract. Membran kepingan nipis dihasilkan dengan menggunakan larutan polimer yang mengandungi sellulose asetat, asid asetik, PEG dan air suling melalui cara *phase inversion*. Kesan nisbah asid asetik/PEG dan kandungan air suling dalam membran terhadap prestasi penyingkiran urea telah dikaji. Metodologi permukaan respons digunakan untuk membentuk eksperimen dan analisis keputusan yang diperolehi. Analisis menunjukkan faktor utama yang mempengaruhi prestasi sellulose asetat dialisis membran dari segi penyingkiran urea ialah nisbah asid asetic/PEG. Dialisis membran dengan nisbah asid asetic/PEG yang tinggi mencapai penyingkiran urea yang tinggi akibat terbentuknya struktur *finger like macrovoids*. Hubungan antara penyingkiran urea dan nisbah asid asetik/PEG dalam julat 4-14 ialah model kuadratik dan model matematik yang dicadangkan menjelaskan prestasi penunjuk dalam had yang ditentukan.

Kata kunci: Membran dialisis; RSM; kandungan air; nisbah asid asetik/PEG; penyingkiran urea

1.0 INTRODUCTION

Dialysis membranes are no longer seen as simple semi-permeable barriers for solutes and water, but are considered an important interface between patients blood and

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subsequently, as an outcome predictor [1]. There were many attempts to improve the efficiency of dialysis process, not only to the dialysis system but to the properties of the dialysis membrane itself.

Numerous parameters can be investigated in order to improve the efficiency of membrane separation process such as membrane composition, membrane properties and the membrane fabrication process. The effect of adding additives and non-solvent into the dope solution is one of the most popular issues being discussed. Lai *et al.* reported that the addition of non-solvent in casting solutions elevated the porosity of TPX (poly(4-methyl-1-pentene)) membranes and thus drastically influence the membrane morphology [2]. Tan and Matsuura also revealed that different non-solvent additives, which consist of branched and linear alcohols ranging from C_3 to C_{10} gave different surface morphologies that yielded different pure gas permeation value [3]. Studies by Xu and Qusay stated that different amount of additives added to the casting solutions using polyethersulfone (PES) as the polymers strongly influenced the performance and the morphology of the membrane produced. In their studies, lower concentration of ethanol (less than 10 wt%) would increase the rejection of PEG 10,000, lysozyme and chicken egg albumin for PES hollow fiber membranes [4]. In contrast, higher concentration of non-solvent additive would increase the molecular weight cut off (MWCO) and the permeation flux of the membrane [5]. Also, additions of additives were reported to increase the hydrophilicity and the diffusive transport properties of solute through the polysulfone hollow fiber membrane [6]. However, most of these investigations mentioned involved reverse osmosis, ultrafiltration and gas membranes. The effect of additives and non-solvent on the performance of the dialysis membrane had not been systematically investigated. Also, the conclusions reached by various studies are also far from unanimous and were often markedly discordant [7]. Therefore, the investigations on the effect of dialysis membrane composition to the membrane performance are urgently important.

Previous studies carried out were mostly based on one-factor-at-a-time experimental approach, which is time consuming, exorbitant in cost and only useful in identifying trends between a single factor and a single response. The use of statistical design of experiments such as factorial design, response surface methodology and Taguchi methods enable various factors to be analyzed simultaneously in order to ease the research process. Therefore, in this study, the influence of additives, particularly PEG and water, on the performance of cellulose acetate dialysis membrane were being studied using the response surface methodology.

2.0 MATERIALS AND METHODS

2.1 Material

Cellulose acetate with an average molecular weight of 30,000 Dalton (Sigma-Aldrich) was used as the membrane-forming polymer. The solvent used was acetic acid (Acc) with an analytical purity of 99% (Merck Co.) and distilled water was used as a non-solvent agent. Polyethylene glycol (PEG) 400 (Merck Co.) was used as the additive. Experiments were performed using urea (60.02 MW) obtained from Sigma-Aldrich.

2.2 Preparation Process

Cellulose acetate of 20 wt% concentration was dissolved in mixtures of acetic acid, PEG 400 of various ratios. The dissolution process was clearly described by Idris *et al.,* [9]. Previous study showed that the ratio of acetic acid/PEG lies between 4 and 14 [8] and therefore the lower level and upper level for the ratio of acetic acid/PEG were 4 to 14. Dunweg *et al.* [10] has used 5 to 15 wt% of water in his work, thus the levels chosen for water are 5 % wt for the lower level and 15 wt% for the upper level. The lower and upper levels for both factors are shown in Table 1, where the ratio factor is denoted by A and the water factor is denoted by B. The details of the 13 experiments generated by the Design Expert Software are summarized in Table 2.

Table 1 Dialysis membrane formulation factors

Factor	Units	Low Level (−1)	High Level (+1)
Ratio Acetic acid/PEG (A)	–	4	14
Water content (B)	% wt	5	15

Table 2 Complete design layout and results

Std. run no.	Run	Block	Factor		Urea Clearance, –%
			Water, %wt	Ratio of acetic acid/PEG	
1	10	1	5	4	23.64
2	13	1	5	14	36.68
3	9	1	15	4	26.03
4	3	1	15	14	34.12
5	2	1	10	4	23.17
6	6	1	10	14	37.49
7	8	1	5	9	23.06
8	12	1	15	9	23.99
9	1	1	10	9	21.64
10	4	1	10	9	21.67
11	11	1	10	9	23.56
12	5	1	10	9	19.48
13	7	1	10	9	21.64

2.3 Membrane Casting and Testing

Membrane with thickness of 200 μm was casted using casting knife and the performance of the dialysis membrane in terms of clearance is evaluated using the testing system as described in Idris *et al.* [9].

2.3.1 Testing Using Urea

The concentration of urea used in this experiment is 1 mg/mL, which is close to the urea concentration level of kidney failure patients. The concentration of urea was evaluated using a commercial diacetyl method obtained from Eagle-Diagnostics, as described in Idris *et al.* [9].

2.3.2 Scanning Electron Microscopy (SEM)

The membranes were snapped under liquid nitrogen to give a generally consistent and clean break. Images of cross sections of the membranes were obtained using Phillip SEM Model XL-40 microscope.

3.0 RESULTS AND DISCUSSION

The membrane performance results in terms of urea clearance as per the experimental trials generated are shown in Table 2. The response variable, which is the urea clearance obtained from the experimental trials were input into the Design Expert software for further analysis. Without performing any transformation on the response, examination of the Fit Summary output revealed that the quadratic model is statistically significant and therefore will de used for further analysis.

3.1 ANOVA Analysis

Table 3 shows the ANOVA table for response surface quadratic model for urea clearance. It summarizes the results of the tests for significance of the regression model, individual model coefficients and the lack-of-fit need. It can be seen from Table 3 that the value of "Prob>F" for the model , the main and 2^{nd} order effect the ratio of acetic acid/PEG (A) are less than 0.05 indicating the model and the main and 2^{nd} order effect of factor A are significant. In contrast, the values of "Prob>F" for all terms involving factor B (water content) are greater than 0.05 indicating that these terms are insignificant. In order to eliminate the insignificant terms in the model generated, a backward analysis was performed.

The terms that are not significant will be automatically eliminated in the model and the correlation between the responses and the factors is then clarified. The ANOVA result for the reduced quadratic model is shown in Table 4. Results from

Table 3 ANOVA table (partial sum of square) for response surface quadratic model

Source	Sum of Square	DF	Mean Square	F	Prob>F	Remarks
Model	426.71	5	85.34	36.11	< 0.0001	significant
A	209.445	1	209.45	88.62	< 0.0001	
B	0.096	1	0.096	0.041	0.8458	
A^2	163.72	1	163.72	69.27	< 0.0001	
B^2	2.21	1	2.21	0.93	0.3660	
AB	6.13	1	6.13	2.59	0.1515	
Residual	16.54	7	2.36			
Lack of Fit	8.20	3	2.73	1.31	0.3871	insignificant
Pure Error	8.34	4	2.09			
Cor. Total	443.25	12				
S.D	1.54		**R^2**	0.9627		
Mean	25.86		**Adj. R^2**	0.9360		
C.V.	5.95		**Pred. R^2**	0.8081		
PRESS	85.05		**Adeq. Precision**	14.948		

Table 4 indicate that the quadratic model and the previous significant terms are still significant, with the “Prob>F” value less than 0.0500.

The “Prob>F” for the lack of fit test of the model is 0.4088 and the F-value is 1.33, which both indicate insignificant lack of fit. This is desirable, as we want the model that fits. The R^2 value is 0.9437, which is desirable as it is close to 1. The predicted R^2 of 0.9015 is in reasonable agreement with the adjusted R^2. Moreover, the adequate precision is a tool that compares the range of the predicted values at the design points to the average prediction error. A ratio greater than 4 is desirable as it indicates adequate model discrimination. In this particular case, the value of 18.373 is well above 4.

Table 4 ANOVA table (partial sum of square) for reduced quadratic model

Source	Sum of Square	DF	Mean Square	F	Prob>F	Remarks
Model	418.28	2	209.14	83.74	< 0.0001	significant
A	209.45	1	209.45	83.87	< 0.0001	
A^2	208.83	1	208.83	83.62	< 0.0001	
Residual	24.97	10	2.50			
Lack of Fit	16.63	6	2.77	1.33	0.4088	insignificant
Pure Error	8.34	4	2.09			
Cor. Total	443.25	12				
S.D	1.58		**R^2**	0.9437		
Mean	25.86		**Adj. R^2**	0.9324		
C.V.	6.11		**Pred. R^2**	0.9015		
PRESS	43.68		**Adeq. Precision**	18.373		

As mentioned previously, conventional approach is only useful in identifying trends between a single factor and a single response. The relationship between them are normally qualitatively described. By using the response surface methodology, the actual relationships between the factor and response can be correlated using the empirical equation. The empirical model in terms of coded factors for urea clearance is shown in Equation 2.

$$\text{Urea clearance} = 22.15 + 5.91\ A + 8.04\ A^2 \quad (2)$$

In terms of actual factors, the following equation is used.

$$\text{Urea clearance} = 37.56 - 4.61 * \text{Ratio of acetic acid/PEG} + 0.32 * (\text{Ratio of acetic acid/PEG})^2 \quad (3)$$

The normal probability plots of the residuals and the plots of the residuals versus the predicted value of urea clearance are shown in Figure 1. The graphics in Figure 1(a) revealed that the residuals generally fall on a straight line implying that the errors are distributed normally. There are no obvious residuals, which are out of the acceptable range that can cause unpredictable response. Also, from Figure 1(b), it is apparent that they have no observable pattern and unusual structure. This shows that the model proposed by RSM analysis is adequate. There is no reason to suspect any violation of the independence or constant variance assumption.

The 3D surface graph for the urea clearance due to the water content and ratio of acetic acid/PEG is plotted in Figure 2. The plot has a profile in accordance to the

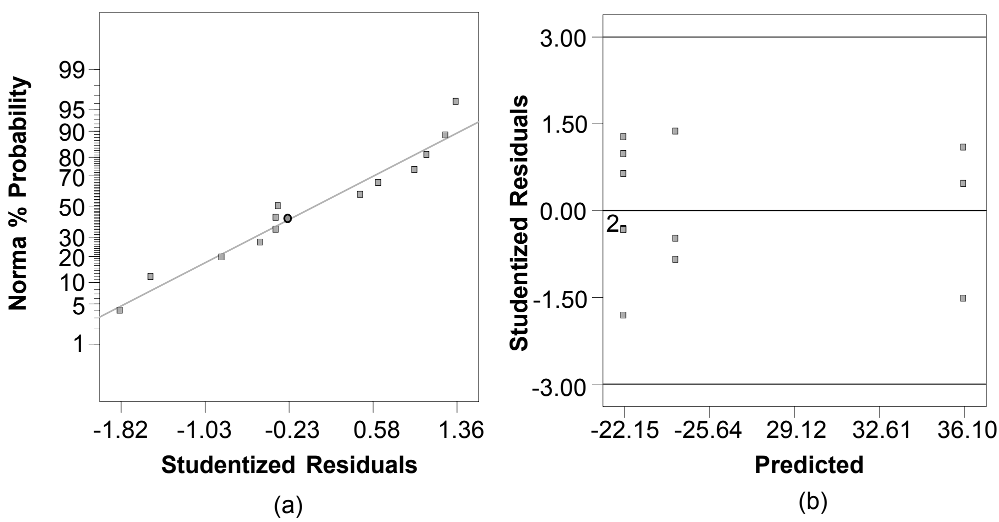

Figure 1 ANOVA analysis plot; (a) Normal probability plot of residuals (b) Plot of residuals vs predicted urea clearance

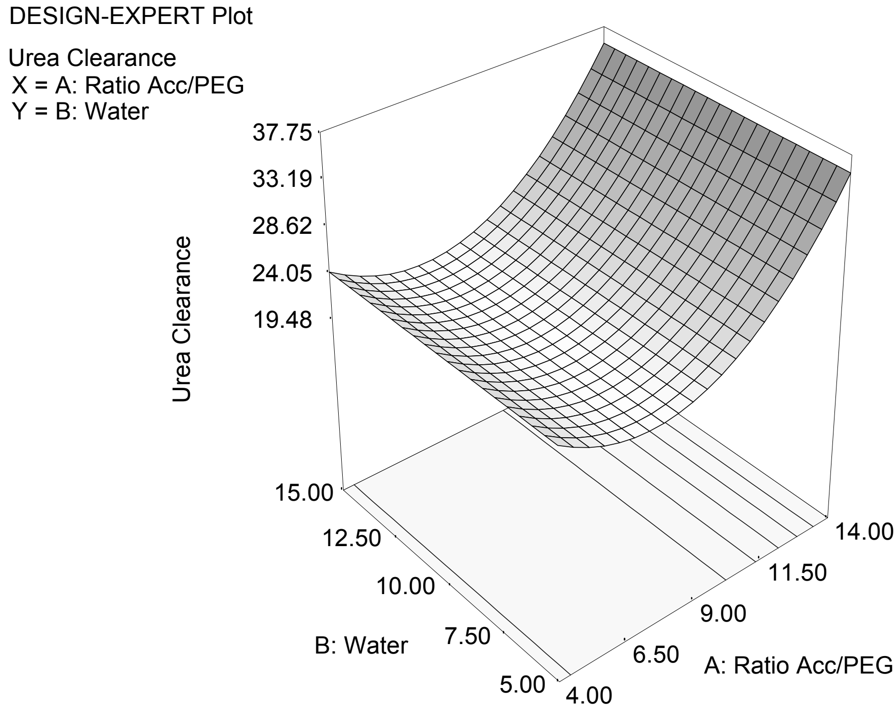

Figure 2 3D surface graph for urea clearance

quadratic model fitted. At any point of the water content in the dope formulation, the urea clearance is not affected. However, increasing the ratio of acetic acid/PEG beyond 7 will give a significant increment of urea clearance performance. In contrast, the clearance was not desirable when the ratio is increased from 4 to 7. The correlation is much more obvious when looking at the one factor plot of urea clearance versus ratio of acetic acid/PEG in Figure 3.

Figure 4 depicts the morphology of the dialysis membranes produced at various acetic acid/PEG ratio and water content. It is observed that the morphology of the membranes is very much influenced by the acetic acid/PEG ratio. Dialysis membranes with the lowest acetic acid/PEG ratio, membrane 1, 3 and 5, exhibits a dense sponge structure while formation of finger-like structure was found as the acetic acid/PEG ratio increase.

Lower acetic acid/PEG ratio indicates higher amount of additives, PEG, was added in the dope formulations. Frommer and Massalem had revealed that the presence of higher amount of additives would reduce the rate of precipitation and favor a more dense sponge structure. In addition, lower amount of solvent (acetic acid) in the formulations with lower acetic acid/PEG increase the viscosity of the dope solution.

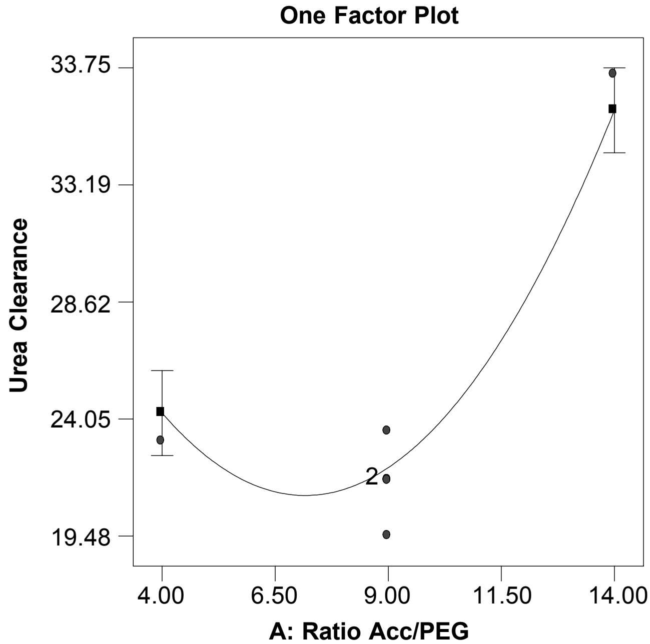

Figure 3 Correlation between urea clearance and the ratio of acetic acid (■ is the actual point, • is the design points)

Increasing the viscosity of the dope solutions suppress the formation of macrovoids as reported by several authors [6, 11 - 14]. The results seemed to be in line with the results obtained as depicted in membrane 1, 3 and 5, which have the lowest acetic acid/PEG ratio.

Finger like structure macrovoids are often observed in the asymmetric membranes made by phase inversion method. Smolders *et al.* [15] reported that finger-like structure is formed during instantaneous demixing and it has been proven that appropriate amount of additives can shift the phase inversion system from delayed to instantaneous demixing [15, 16]. As can be seen in Figure 4, increasing the acetic acid/PEG ratio encourages the formation of finger-like structure (membrane 3, 6 and 9) and this observation seems to be similar to the findings mentioned.

Finger-like structures are known to be suitable for ultrafiltration process [15], improving the water flux and lower the solute rejection [17]. Kim and Lee [18] in their latest findings also showed that at higher amount of PEG used in membrane preparation, the flux will decrease and the solute rejection will increase. The purpose of the dialysis process is to remove uremic toxic out from human blood and therefore higher solute removal are desirable. The formation of finger-like structure enable the solute to pass through the membrane easily whilst diminishing of the internodular void space would lead to an increase in solute rejection [19]. Thus, the finger like structure seems to be favorable with respect to urea clearance performance. It can be seen from Figure 4, membrane 3 and 6, which has the most finger-like structure, exhibits higher urea clearance of approximately 37% and 38%, respectively.

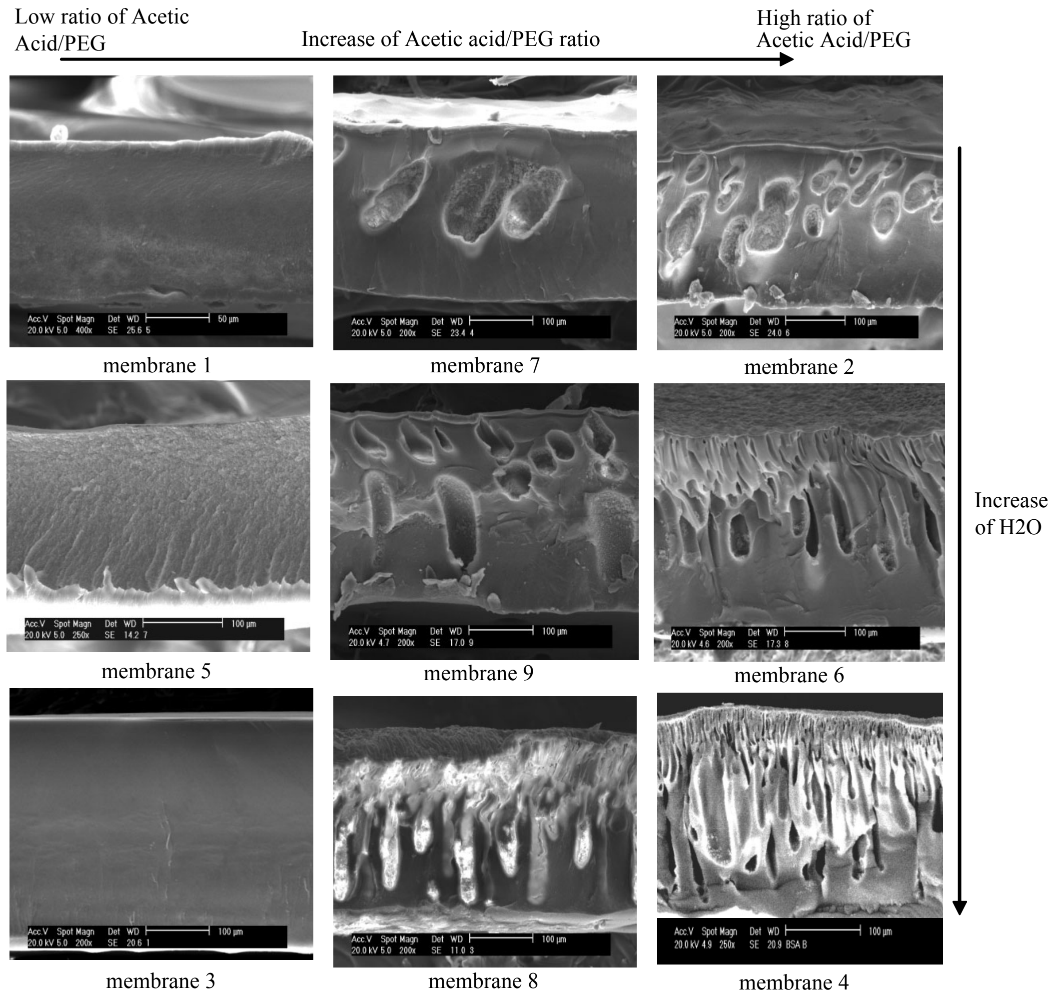

Figure 4 SEM cross section images of dialysis membrane produced: membranes 1, 7 and 2 at water content of 5 wt%; membrane 5, 9 and 6 at water content of 10 wt% and membrane 3, 8 and 4 at water content of 15 wt%. From left to right for each category, the acetic acid/PEG ratio is 4, 9, 14, respectively

Nevertheless, the finger-like structure is transform to cellular wound shape structure as the amount water is increased from 5 wt% to 15 wt%. In other words, the macrovoids was being suppressed as the amount of non-solvent increased. It was reported that too much of non-solvent would reduced or readjusts the dissolving power of the solvent for the polymer [20] and promotes the delayed demixing that reduce the formation of macrovoids [15, 16]. Consequently, the morphology of dialysis membranes was also influenced by the amount of water added in the formulations. However, water content is not a significant factor that affects the urea clearance performance as given by the RSM analysis results and this may due to the dissolving power of water to polymer are lower compared to the acetic acid and PEG.

Table 5 Confirmation experiments

Ratio Acetic acid/PEG	Calculated value	Actual value, –%	Errors, %
4	24.28	23.17	–4.79
6.5	21.20	20.38	–4.04
9	22.15	21.64	–2.35
11.5	27.11	28.47	4.77
14	36.10	37.49	3.72

3.2 Confirmation Runs

In order to verify the adequacy of the model developed using RSM, five confirmation run experiments are performed and the results achieved are tabulated in Table 5. Three of the confirmation runs were performed using the previous conditions, where the acetic acid/PEG ratio were 4, 9 and 14 whilst the remaining two confirmation runs were conditions that have not been used previously but are within the range of the levels defined previously, using the acetic acid/PEG ratio of 6.5 and 11.5. The predicted values and the associated predicted prediction interval are calculated according to model developed previously. All these values are presented in Table 5. It was found that the quadratic model generated by RSM analysis is very accurate with less than 5 % error.

4.0 CONCLUSIONS

This paper presents the findings of an experimental investigation into the effect of acetic acid/PEG ratio and water content on the urea clearance performance of cellulose acetate dialysis membranes. The ANOVA results revealed that the main and the 2^{nd} order effect of acetic acid/PEG ratio are the significant terms while the terms involving water are not significant in affecting the urea clearance performance. Higher ratio of acetic acid/PEG gives higher urea clearance percentage and promotes the finger-like macrovoids formation in the dialysis membrane produced. Dialysis membranes with lower acetic acid/PEG ratio give a dense spongy structure macrovoids and are not favorable in terms of urea clearance performance. Although the amount of water does not affect the urea clearance result, it does affect the morphology of the dialysis membrane. The most desirable dialysis membrane for urea clearance performance in this study is the one with the lowest PEG content. Additionally, the reduced quadratic models developed using RSM were reasonably accurate and can be used for prediction within the limits of the factors investigated.

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