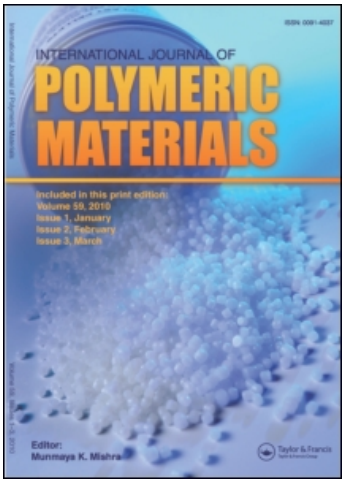

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Monosodium Glutamate Influence on Cellulose Acetate Hemodialysis Membranes

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The influence of monosodium glutamate (MSG) additive and its concentration on the performance of hemodialysis membrane were investigated. Concentration of MSG was varied from 1 wt% to 8 wt% and the performance of the hemodialysis membrane was evaluated in terms of urea clearance and bovine serum albumin (BSA) rejection. Results revealed that membrane with 6 wt% of MSG, which was fabricated from 64 wt% formic acid and 10 wt% distilled water, achieved the best urea clearance of 53.20% and BSA rejection of 94%. SEM images illustrated that the increment of MSG concentration in the casting solution tends to promote macrovoids formation. However, when the amount of MSG was further increased beyond 6 wt%, the urea clearance was reduced and the macrovoids structure disappeared. FTIR spectra indicated that both N–H and C–N bonds from MSG were absent indicating that the MSG was removed during phase inversion.

Keywords: cellulose acetate, dialysis membrane, formic acid, monosodium glutamate, urea clearance performance

INTRODUCTION

During the past few years, hemodialysis treatment proved to be more favorable compared to peritoneal dialysis among end-stage renal disease (ESRD) patients [1]. With the increment of ESRD patients undergoing hemodialysis treatment, the requirement of dialysis

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membrane escalating in the future is a matter of conjecture. Despite the availability of commercial hemodialysis hollow fiber membrane, the membrane formulation has always been treated as a trade secret.

The use of cellulose acetate membrane in the medical field is a matter of controversy among the researchers. Averbukh et al. [2] found that cellulose acetate dialyzer caused red eye syndrome on 22 of 24 patients. However, there are reports [3,4] regarding the undesired severe adverse reaction on patients such as conjunctivitis caused by the use of aged cellulose acetate membranes due to the polymer degradation. According to the National Kidney Foundation Inc. K/DOQI Clinical Practice Guidelines [5], the occurrence of red eye syndrome is common for hemodialysis patients and is believed to be triggered by chronic inflammation and metastatic calcification [6]. This syndrome is frequently observed when the serum calcium concentration is high and it subsides when the serum calcium concentration returns to a normal level [7].

Although the use of cellulose acetate in the medical field was refused in the United States [8], Echanova et al. [8] still believe that cellulose acetate is suitable for biomedical applications and the use of this starch-based polymer in medical device membranes is increasing. In addition, several researchers [9–11] have elucidated the suitability of cellulose acetate (CA) as the main material to fabricate hemodialysis membranes. According to Vazquez et al. [9], cellulose acetate-based membrane allows the diffusion of ions and low molecular weight solutes, whereas Kesting [10] emphasized that cellulose acetate membranes possess maximum uniformity, permselectivity, and optimum physical properties such as strength and flexibility. Besides, it has convincing characteristics, which includes good toughness, deep gloss and high transparency, good desalting, high flux and relatively low cost [11].

In the biomedical field, biocompatibility of membranes has always been a major concern. Ye et al. [12] has used acetone and 2-propanol as additives and PMB80 as internal coagulant to improve the cellulose acetate biocompatibility. The membranes produced were reported to have good permeability and low protein absorption. Idris et al. [13] studied the influence of various molecular weights polyethyleneglycol (PEG) additive for hemodialysis cellulose acetate membranes. It was revealed that PEG 200 is a better additive compares to PEG 400 and PEG 600 and the membrane fabricated was able to achieve 40.37% urea clearance. When the membrane performance was evaluated using human blood, there was an insignificant change of white blood cell and platelet count during the pre- and post-dialysis.

Cellulose acetate is also widely used by researchers especially in producing ultrafiltration membranes. Arthanareeswaran et al. [14] fabricated cellulose acetate ultrafiltration membrane with PEG 600 as additive. The result indicates that when PEG 600 concentration increased from 2.5% to 6.5%, pure water flux increased from 13.5 to 98.7 L m^{-2} h^{-1}. The addition of PEG 600 also tends to increase the thermal stability of cellulose acetate membranes. An attempt has been made to blend cellulose acetate with polysulfone [15] for ultrafiltration application. High pure water flux was achieved at high concentration of polysulfone and polyvidylpyrrolidone (PVP). Qin et al. [16] investigated the effect of air gap length and hypochlorite treatment on cellulose acetate ultrafiltration membrane. In this particular study, PVP with molecular weight of 360,000 was used as additive. The hypochlorite-treated membrane exhibited a higher flux (three times more) compared to the untreated membrane. This proved that hypochlorite treatment is an essential step to improve the flux of the membrane.

Cellulose acetate membrane with good adsorptive property was fabricated by Liu et al. [17] using wet spinning method. The presence of chitosan was observed to reduce hydrophilicity of the membrane and thus results in reduced flux but improved Cu^{2+} ion adsorption performance. Membrane which consists of 1 g chitosan was able to adsorb 1.093 mg Cu^{2+} ion/g of hollow fibers compared to membrane without chitosan, where 0.0367 mg Cu^{2+} ion/g of hollow fibers was adsorbed at pH 6.

Formic acid, also known as methanoic acid, with molecular formula H−COOH is an organic solvent that is not widely studied by membrane researchers. According to Wade [18], low molecular weight carboxylic acids (less than five carbons in the molecular structure) are miscible with water and very soluble in alcohol. This is because acids form hydrogen bonds with hydroxyl groups (–OH) in both water and alcohol. However, if the hydrocarbon chain increases, the solubility of carboxylic acid is decreased. CA is an acetylated cellulosic where the hydroxyl groups along the cellulose chain are fully or partially acetylated in highly polar aprotic solvents, such as N,N-dimethylacetamine DMAc and N-methylpyrrolidone NMP [19]. When formic acid (the shortest hydrocarbon chain) is used as a solvent for CA, hydrogen bond is formed between formic acid and –OH groups from CA, hence, formic acid can be considered as a good solvent for CA. In addition, food-grade formic acid is used in this study.

Barzin et al. [20] have produced hemodialysis membrane from polyvinyl alcohol (PVA) and distilled water as solvent and investigated the influence of various additives: PEG 400, PEG 600 and acetic acid on

urea clearance and morphologies. The results revealed that acetic acid is a better additive compared to PEG 400 and PEG 600 due to its higher ionization strength. In another study, Barzin et al. [21], prepared hemodialysis membrane by dissolving polystyrene PS and PVP in N,N-dimethylacetamide DMAC and the surface was analyzed using the atomic force microscope (AFM). The membrane morphology was analyzed using scanning electron microscope (SEM) and ultrafiltration test was performed. From the enumerations given above [13–16, 20–21], it is observed that PVP and PEG are the common additives used by researchers in order to enhance the membrane performance.

Monosodium glutamate (MSG) is a well-known food additive, nontoxic and highly hydrophilic. It is easy to obtain and cheap. Nevertheless, the use and effect of MSG as an additive on membrane performance has never been explored. Thus, the objective of this study is to investigate the influence of MSG additive on membrane's morphology and performance. The membranes were further analyzed using Fourier transform infrared (FTIR) so as to determine the formation of any new bonds.

EXPERIMENTAL

Materials

Cellulose acetate with the average molecular weight of 30 kDa (degree of acetylation = 39.8%), purchased from Sigma–Aldrich, was used as the membrane-forming polymer. Food-grade formic acid with 98–100% purity (AppliChem) was employed as solvent and distilled water was used as coagulation bath. Monosodium glutamate (MSG) was used as the additive. Urea with molecular weight of 60.02 Da and BSA molecular weight 66 kDa were obtained from Sigma–Aldrich and were used as feed solutions for the dialysis process. Urea Nitrogen Rate Reagent Set (Eagle Diagnostics) was used to analyze the urea concentration. Biuret reagent was used to evaluate the bovine serum albumin concentration.

Methods

Membrane Preparation

Casting solutions as shown in Table 1 were prepared by dissolving the polymer and additives in formic acid with continuous stirring for 4 h at 70°C. After complete dissolution, the air bubbles which were trapped in the casting solution were removed by placing the solution

TABLE 1 Composition of Prepared Casting Solutions

Membrane	Cellulose acetate (wt%)	Formic acid (wt%)	MSG (wt%)	Distilled water (wt%)
CA0	20	70	0	10
CA1	20	69	1	10
CA2	20	68	2	10
CA3	20	67	3	10
CA4	20	66	4	10
CA5	20	65	5	10
CA6	20	64	6	10
CA7	20	63	7	10
CA8	20	62	8	10

bottle in an ultrasonic bath. Casting process was done by using a casting knife of 200 μm thickness on a glass plate as support. The polymer solution film was then immersed immediately in distilled water bath at room temperature (25°C) for complete phase separation. Finally, post treatment was performed by immersing the nascent membrane into hot water at 90°C, followed by immersion in methanol to remove excess formic acid. The membranes were then ready for use.

Dialysis Experiment

The dialysis experiment set-up used is similar to the one reported by Idris et al. [13]. Solute reservoir containing either 1 mg/mL of urea or 1 mg/mL of BSA while dialysate reservoir was filled with distilled water. The total effective area of the membrane is 30 cm^2. The flow configuration applied during the dialysis experiment is counter-current flow where solute and dialysate flow in opposite directions. This flow configuration maintains an optimal solute-dialysate concentration gradient throughout the dialyzer. Maximum efficiency can be achieved by setting the dialysate flow 2 to 2.5 times higher than solute flow [22]. In order to ensure a complete contact between the solutions flow and the dialysis membrane [23], the maximum flow rate for the dialysis cell design is limited to 100 mL/min. The flow rate for the solutes and dialysate side were maintained at 50 mL/min and 100 mL/min, respectively. The operating temperature was maintained at 37 ± 2°C by using a Digi-sense temperature controller. Samples were collected at both solutes and dialysate reservoirs every 30 min for a period of 3.5 h. Then, the urea concentrations of the samples were measured by Urea Nitrogen Rate Reagent Set (Eagle Diagnostics) [24]. The membrane which achieved the best urea clearance was then tested with BSA and the related samples were tested using Biuret

reagent [25]. This dialysis experiment was repeated 3 times for each membrane with different compositions to ensure repeatability. Solute clearance (%) was calculated as follows:

$$\text{Solute clearance}(\%) = \left(\frac{C_t - C_0}{C_0}\right) \times 100\% \quad (1)$$

where

C_0 = Sample concentration at time t = 0
C_t = Sample concentration at time t

Scanning Electron Microscope (SEM)

The morphologies of membranes were inspected using SEM Model SUPRA 35VP. The samples were snapped in liquid nitrogen so as to obtain a clean and constant break. The samples were sputter-coated with gold and mounted onto brass plates using double-sided cellophane tapes in a lateral position, ready for imaging in SEM.

Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectroscopy was performed on the surface of sufficiently thin films, using Perkin Elmer Spectrum One FTIR Spectrometer, and FTIR spectra were recorded. In addition, the spectrum for the pure cellulose acetate in powder form was also recorded and used as a reference. All spectra were scanned at room temperature, with 16 scans/min. Each sample was scanned three times in order to obtain more accurate results. Each spectrum was recorded in the mid IR region between 370 cm^{-1} and 4000 cm^{-1}.

RESULTS AND DISCUSSION

Effect of Monosodium Glutamate on the Performance and Morphology of Cellulose Acetate Membrane

Figure 1 illustrates the influence of MSG concentration on the urea performance. As can be observed, small amounts of MSG do not seem to drastically increase the urea clearance. Highest urea clearance of 53.2% was achieved by CA6 membrane, exceeding the 48% urea clearance when no MSG was used. Further increase in MSG beyond 6 wt%, CA8 membrane resulted in a decline in urea clearance. Compared to previous work done by Idris et al. [13] and Barzin et al. [20], where urea clearance achieved was 40.37% and 48%, respectively, the result

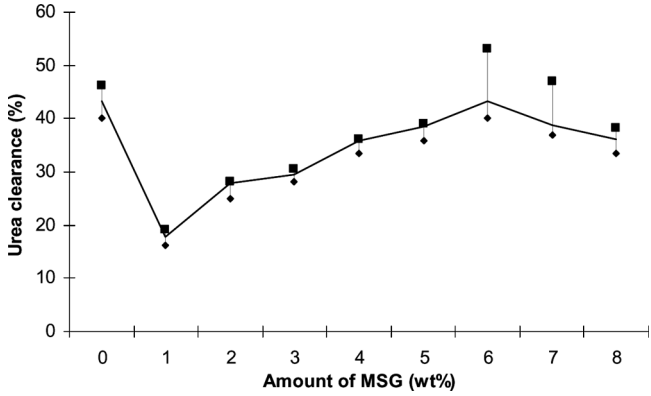


FIGURE 1 The effect of MSG on the performance of dialysis membrane in terms of urea clearance.

achieved is good; hence, the use of MSG as an additive seems convincing. This result was consistent with qualitative observation of SEM images in Figures 2 and 3. It appears that the skin layer of the CA2 membrane has a thick dense structure and the sublayer appears to be less porous than the CA4 membrane, which explains the low urea clearance. Compared to the SEM image in Figure 3, the skin layer of the CA6 membrane was much thinner than the CA4 membrane, thus explaining the higher urea clearance. However, when the amount of MSG was further increased to 8wt%, urea clearance decreased due to the thick and dense structure as depicted in Figure 2(e).

The miscibility between the added additives and coagulant is a significant factor in determining the formation of macrovoids [26]. Formation of macrovoids and finger-like pores can be suppressed or promoted by the addition of suitable additives depending on their miscibility with the coagulant. The hydrophilic MSG in small amounts of 2–6 wt% tend to dissolve very well in the formic acid thus enhancing the solvent power of formic acid. In addition, this results in a rapid movement of the solvent out due to the miscibility between the added MSG and coagulant and thus enhances the formation of finger-like pores and macrovoids. The hydrophilic MSG additive promotes instantaneous demixing, and consequently promotes the formation of macrovoids or finger-like structure. This can be clearly seen in Figure 2. A dense spongy structure with a thick asymmetric skin is observed in the CA0 membrane. The addition of small amounts of MSG (2 wt%) clearly promotes the formation of macrovoids under the skin layer.

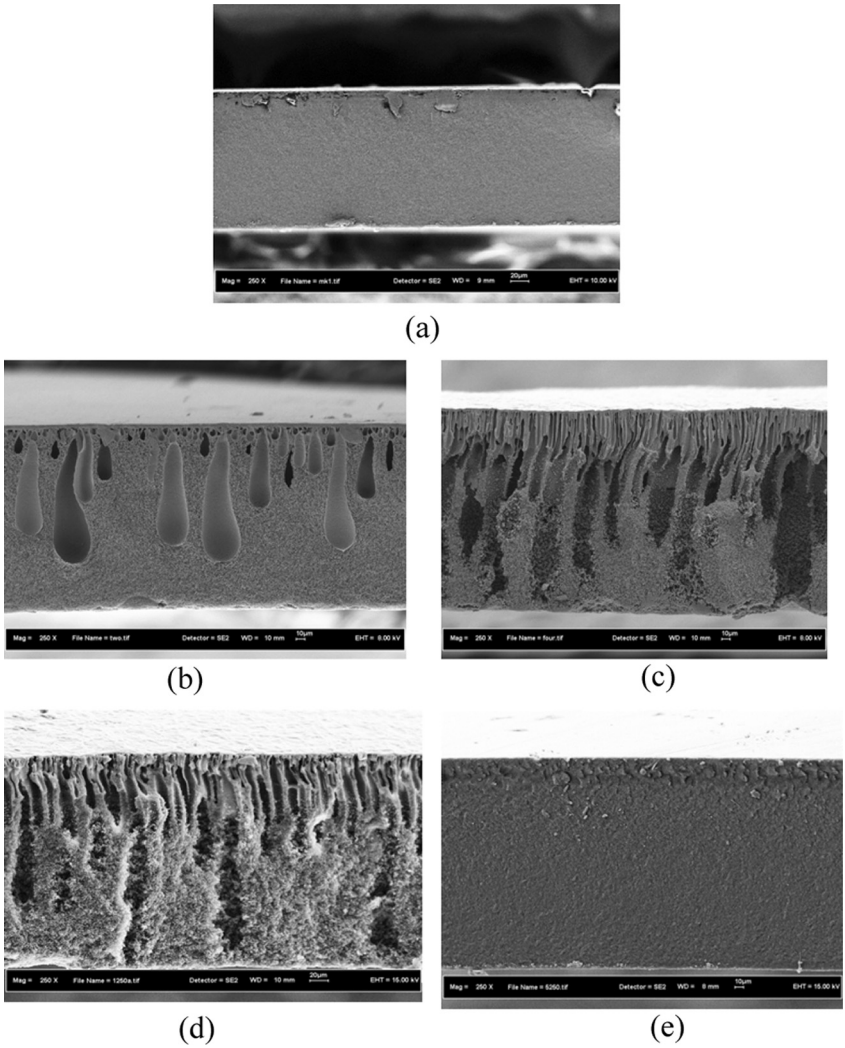
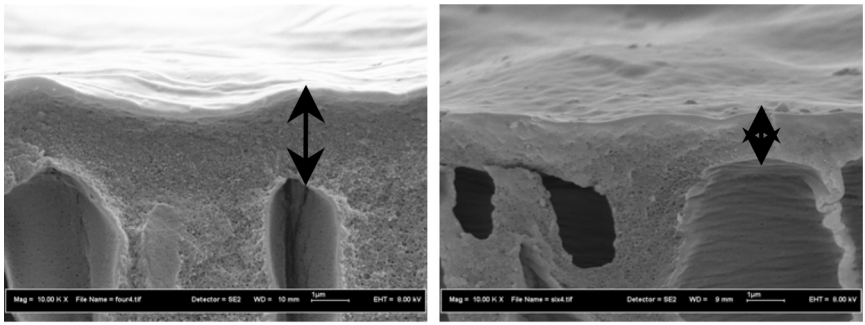


FIGURE 2 SEM cross-section images of (a) CA0; (b) CA2; (c) CA4; (d) CA6; and (e) CA8 membranes.

However, when the amount of MSG increases beyond 6 wt%, the formic acid can no longer dissolve the MSG. Instead, it tends to form complexes with MSG, thus reducing its solvent power. This results in a higher viscosity solution, which contributes to the dense and spongy structures as illustrated in membrane CA8. As described by



(a) (b)

FIGURE 3 SEM images on the skin layer of (a) CA4 and (b) CA6 membranes.

Smolders et al. [27], macrovoids formation is dominated by the ratio of influx of the coagulant liquid (nonsolvent) and the influx of solvent from casting solution into the nonsolvent droplet in the casting solution. Casting solution with high viscosity will reduce the influx of solvent from the surrounding casting solution into the nonsolvent droplet and thus macrovoids-free structure is obtained.

A study reported by Chaturvedi et al. [28] showed that there was a difference between the membrane thickness before and after phase inversion process. This is due to the densification of the polymer network during the phase inversion process. This indicates that the final membrane thickness is very much dependent on the polymer densification. Figure 2 shows that there is a difference in membrane thickness, especially when comparing the membrane without MSG and the one with MSG. This may be attributed to the presence of MSG which influences the polymer densification process, thus resulting in the membrane becoming porous, less dense but thicker compared to the membrane without MSG.

In order to determine the suitability of this MSG membrane for dialysis purpose, CA6 membranes which achieved the best urea clearance, were evaluated in terms of bovine serum albumin. Result revealed that 94% of BSA was rejected. Thus, the occurrence of albumin loss syndrome can be avoided and is minimized.

FTIR Studies

As illustrated in Table 2, cellulose acetate membranes contain O–H, C–H, and C=O stretching modes, located at regions 3400–3700 cm^{-1},

TABLE 2 Characteristic IR Peaks of Cellulose Acetate (CA)/Formic Acid (FA) Membrane

Wave number (cm-1)	Assignment
3400–3700	O–H stretching; contributed by cellulose
2925	C–H stretching (present in CH_2OH group); contributed by cellulose
1739	C=O stretching; contributed by acetate group
1370	C–H symmetric deformation vibration of acetate group; contributed by acetate group
1232	C–O stretching; contributed by acetate group
1048	C–O stretching; contributed by cellulose

$2925\,cm^{-1}$, and $1739\,cm^{-1}$ respectively. In addition, frequencies at $1232\,cm^{-1}$, and $1048\,cm^{-1}$ are referred to as the C–O stretching mode; the former frequency was due to the acetate group while the latter frequency was contributed by cellulose [29]. This spectrum is in qualitative agreement with cellulose acetate membrane FTIR spectra studied by several researchers [30–32], despite the different solvents used. However, compared to these previous works [30–32], C–H symmetric deformation vibration of acetate group [29], located at $1370\,cm^{-1}$ is absent. This is probably due to the different solvents used, for instance acetone [32] and 1,4-dioxane [30] which might have reacted with this C–H bond.

Based on the MSG molecular structure in Figure 4, MSG contains C–N bond and N–H bond. It is interesting to note that there are no new N–H ($2500–3100\,cm^{-1}$) and C–N bonding ($1350–1000\,cm^{-1}$) observed in all the FTIR spectra in Figure 5. This probably indicates that the MSG was washed away during phase inversion.

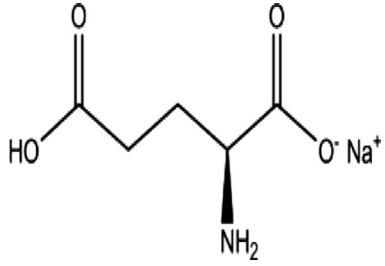


FIGURE 4 Molecular structure of monosodium glutamate.

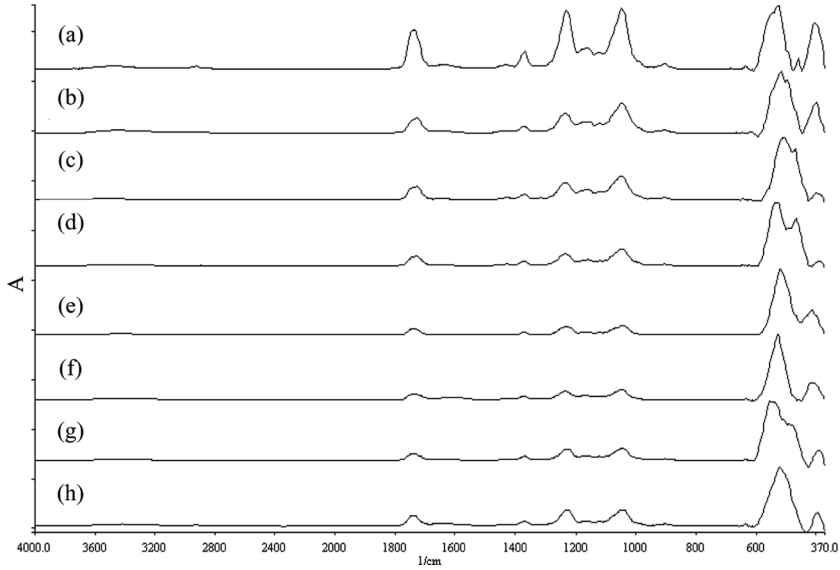


FIGURE 5 IR frequencies (cm^{-1}) for (a) CA0; (b) CA1; (c) CA2; (d) CA3; (e) CA4; (f) CA6; (g) CA7; and (h) CA8 membranes.

CONCLUSION

Cellulose acetate-based membrane achieved the best urea clearance of 53.20% when 6 wt% of MSG was used. The membrane performance deteriorated when the MSG was further increased beyond 6 wt%. FTIR spectra revealed the absence of C−N and N−H bonds indicating that the MSG was washed away during phase inversion. Based on the results of urea clearance and BSA rejection, MSG can be considered a good additive for dialysis membrane. Thus, further research on the use of MSG as an additive for other polymers, such as PES and PS, can be considered.

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