Hemodialysis Membrane Prepared from Cellulose/*N*-Methylmorpholine-*N*-oxide Solution. I. Effect of Membrane Preparation Conditions on Its Permeation Characteristics

YOSHIHIKO ABE,[1] AKIRA MOCHIZUKI[2]

[1] Research & Development Center, Terumo Corporation, 1500 Inokuchi, Nakai-machi, Ashigarakami-gun, Kanagawa 259-0151, Japan

[2] Kofu East Factory, Terumo Corporation, 1727-1 Tsuijiarai, Showa-cho, Nakakoma-gun, Yamanashi 409-3853, Japan

Received 21 May 2001; Accepted 15 August 2001

ABSTRACT: Flat hemodialysis membranes were prepared from cellulose/*N*-methylmorpholine-*N*-oxide (NMMO) solutions (dope) with different cellulose concentrations (6–8 wt %) by using a phase-inversion method. The coagulant used was NMMO aqueous solution, of which the NMMO concentration and its temperature were varied in the range of 0 to 50 wt % and 5 to 60°C, respectively. The effects of these preparation conditions on the permeation characteristics, the ultrafiltration rate (UFR) of pure water, and sieving coefficient (SC) of dextran, were investigated. The decrease in cellulose concentration of the dope and the increases in both temperature and NMMO concentration of the coagulant gave a membrane with high UFR. Concerning the SC, the increase of the cellulose concentration and the decreases in both temperature and NMMO concentration gave a good result. Consequently, the membrane having the preferable UFR and SC as a hemodialysis membrane was obtained when the 8 wt % cellulose dope was coagulated in water at 5°C. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 2302–2307, 2002

Key words: cellulose; hemodialysis membrane; *N*-methylmorpholine-*N*-oxide; ultrafiltration rate; sieving performance

INTRODUCTION

Today, various polymeric materials are widely applied to the preparation of hemodialysis membranes, such as regenerated cellulose, cellulose acetate, polysulfone, polyacrylonitrile, nylon, polymethylmethacrylate, and ethylene–vinyl alcohol copolymer, among which the most popular material is regenerated cellulose. The regenerated cellulose membrane, made by the cuprammonium rayon method, has found wide clinical use because of its excellent performance in the removal of the low molecular weight toxic substances such as urea and creatinine from patients' blood. However, the membrane has demonstrated weaknesses, such as in insufficiently removing the low molecular weight proteins and in blood compatibility. The molecular weights of the proteins, which are considered to cause various chronic side reactions, are in the range of 10,000 to 55,000 Da. In particular, it is well known that the accumulation of β_2-microglobulin (β_2-MG, 11,800 Da) in the body causes amyloidosis.[1] To solve these problems in the regenerated cellulose membrane, a number of synthetic polymer membranes were investigated, some of which have been in practical use, such as polysulfone

Correspondence to: Y. Abe (yoshihiko_abe@terumo.co.jp).

Journal of Applied Polymer Science, Vol. 84, 2302–2307 (2002)

and cellulose triacetate membranes. Of course, many attempts to improve the performance of the regenerated cellulose membrane have also been carried out by investigating the coagulation/regeneration conditions.[2–4] Almost all of the studies were based on the cuprammonium rayon method, given that a satisfactory solvent for cellulose was limited to cuprammonium hydroxide solution. In this method very complicated coagulation/regeneration processes such as aqueous alkaline-coagulation/acid-regeneration are adopted to make a hemodialysis membrane. Therefore, the controls of the morphology and performance of the membrane were restricted. In those investigations, however, some produced satisfactory results and were subsequently commercialized.[5,6]

From the viewpoint of the cellulose industry, the cuprammonium rayon method is neither economical nor ecologically friendly because it needs the cuprammonium solution and the complicated manufacturing processes as mentioned above. To simplify the dissolution/regeneration processes of cellulose, many attempts to dissolve cellulose in organic solvents were made. The solvents investigated by many researchers are dimethylacetamide/lithium chloride,[7] dimethylsulfoxide/formalin,[8] and alkyl amine-*N*-oxide.[9,10] It was known that amine oxide was the one of the most powerful solvents for cellulose, but it was not available. Because regenerated cellulose fiber prepared from *N*-methylmorpholine-*N*-oxide (NMMO) solution has recently been commercialized,[11] the solvent is now available. NMMO dissolves cellulose directly without the formation of the cellulose complex or its derivatives, whereas the cuprammonium hydroxide makes a complex with cellulose. When this solvent is applied to the preparation of the cellulose membrane, it is expected that the membrane morphologies and permeation characteristics can be comprehensively controlled by varying the coagulation conditions as in the preparation of the synthetic polymer membranes. Thus, we investigated the effectiveness of this solvent in preparing the regenerated cellulose membrane for hemodialysis.

In this study we report the relationship between the membrane preparation conditions and the permeation characteristics of the membranes.

EXPERIMENTAL

Materials

NMMO monohydrate containing 13.3 wt % of water (melting point: 72°C) was supplied from Nippon Nyukazai Co., Ltd. (Tokyo, Japan). The cellulose used, cotton linter containing over 98% of cellulose, was purchased from Taihei Paper Manufacture Co. (Tokyo, Japan). *N*-Propyl gallate and sodium *n*-dodecyl sulfate were purchased from Kanto Kagaku Co. (Tokyo, Japan).

Preparation of Membrane

Cellulose Solution (Dope)

Flat membranes were prepared from the cellulose/NMMO solutions (dopes) according to the method described below. Into a 500-mL separable flask, an adequate amount of NMMO monohydrate, 0.25 wt % of *n*-propyl gallate as an antioxidant, and 0.25 wt % of sodium *n*-dodecyl sulfate as a surfactant, which were based on the weight of cellulose, were added and the mixture was heated to 90°C with stirring in an oil bath. After the mixture turned transparent, cotton linter was added into the solution. Stirring the mixture for 15 h at 90°C dissolved the cellulose. Thus, the dopes containing 6, 7, and 8 wt % of cellulose were prepared.

Membrane

The cellulose dope, filtrated through a stainless filter (10 μm aperture), was cast onto a glass plate controlled at 90°C by using a doctor blade, with a clearance of 150 μm. The glass plate was immersed immediately into 1 L of the coagulant, in which it was maintained for 1 h. The coagulants used were ultrapure water and NMMO aqueous solutions, the NMMO concentration and the temperature of which were varied from 0 to 50 wt % and from 5 to 60°C, respectively. After the coagulation, the membrane was taken out of the coagulant and washed with ultrapure water to remove the solvent. The membrane thus obtained was kept in ultrapure water to maintain the membrane structure. The thickness of the water-swelled membrane was in the range of 40 to 70 μm. During the course of the experiment, membranes were never allowed to dry out.

Evaluation of Permeability Characteristics of Membranes

Membrane performances were investigated with respect to the ultrafiltration rate (UFR) for pure water and the sieving coefficient (SC) for dextran. The measurement methods of these performances are described below.

Ultrafiltration Rate (UFR)

TheUFR was measured at 37°C using a membrane holder (UHP-43K; Advantec Toyo Co., Tokyo, Japan), and was calculated from eq. (1):

$$\text{UFR [mL/(m}^2 \cdot \text{h} \cdot \text{mmHg)]} = V/SP \qquad (1)$$

where V is the measured water flux (mL/h), S is the effective membrane area (1.15×10^{-3} m^2), and P is the operation pressure (250 mmHg).

Sieving Coefficient (SC)

The membrane holder used was the same one used in the measurement of UFR. The dextran used was a mixture of Dextran T10 (weight-average molecular weight M_w = 10,000 by the light-scattering method) and Dextran T40 (M_w = 40,000) (Amersham Pharmacia Biotech, Piscataway, NJ) and its composition (T10 : T40) was 50 : 50 w/w. The test solution used was 1 wt % dextran saline solution. To avoid the concentration of the solute on the membrane during the measurement, the dextran solution was circulated at the rate of 25 mL/min; also, the solution in the membrane holder was stirred magnetically. After the test solution had been circulated at 37°C for over 30 min under 250 mmHg of pressure, the solution permeated through the membrane (permeate solution) and the test solution (permeant solution) were sampled. The molecular weight and concentration of dextran in the permeate and permeant solutions were measured by gel-permeation chromatography (GPC) (Shodex GPC system-21; Showa Denko Co., Tokyo, Japan) using two connecting columns (Shodex OHpak, KB-803; Showa Denko). In the GPC measurement, monodisperse pullulan supplied from Showa Denko (Shodex Standard P82) was used as a standard of molecular weight. The SC for each molecular weight of dextran was calculated according to eq. (2):

$$\text{SC} = C_1/C_2 \qquad (2)$$

where C_1 and C_2 are the dextran concentrations for each molecular weight (M_w = 1000 to 100,000 Da) in the permeate and permeant solutions, respectively.

RESULTS AND DISCUSSION

UFR Performance

In recent hemodialysis therapy a higher-flux membrane has been required because it can easily remove the excess water from the patient's body. Therefore, UFR is one of the most important membrane performances. The effect of the coagulant temperature on the UFR was first investigated, where the coagulant used was pure water, and its temperature was varied from 5 to 60°C. The results are shown in Figure 1. With an increase in the coagulant temperature, the increase of the UFR was observed in all series of membranes prepared from the dopes with the different cellulose concentrations. In particular, the membrane prepared from the 6 wt % cellulose dope exhibited the most drastic increase. Such behavior is observed in synthetic polymer membranes.[12,13] In general, the diffusion rate of low molecular weight solvent increases with an increase of temperature. When a coagulation process in a membrane preparation is considered on the basis of this fact, a solvent in a cast-solution film and a nonsolvent in a coagulant will exchange each other more rapidly with an increase of the coagulation temperature. Thus, the high temperature of the coagulant will cause the rapid coagulation of the polymer molecule. This phenomenon applies to the coagulation of the cellulose dope in this study. The temperature dependency of the UFR suggests that the rapid coagulation brings about the rough network structure of the membrane. The decrease in the cellulose concentration in the dope also brings about the loose structure of the membrane, resulting in the increase of UFR. These results of the UFR indicate that the cellulose membrane prepared from NMMO solution has the potential of having a

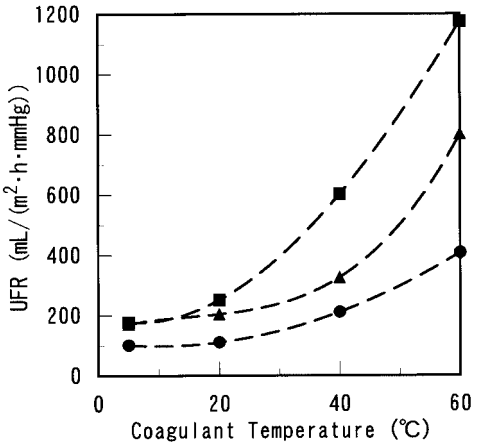

Figure 1 Relationship between UFR of water and coagulant temperature. Cellulose concentration in the dope: (■) 6 wt %; (▲) 7 wt %; (●) 8 wt %. Coagulant: water.

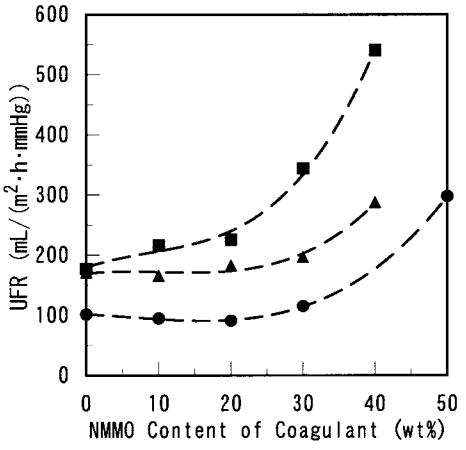

Figure 2 Relationship between UFR of water and coagulant composition. Cellulose concentration in the dope: (■) 6 wt %; (▲) 7 wt %; (●) 8 wt %. Coagulation temperature: 5°C.

sufficient UFR compared with that of the cuprammonium rayon membrane, given that it is well known that the UFR of the conventional regenerated cellulose membrane is in the range of 10 to 20 mL/(m^2 · h · mmHg).

Next, the effect of the coagulant composition on UFR is described. In this investigation, the coagulant temperature was kept at 5°C, and the NMMO concentration in the coagulant was varied from 0 to 50 wt %. In the case of the coagulant with 50 wt % of NMMO, the 6 and 7 wt % cellulose dopes did not give any membrane, which indicates that this coagulant is too soft for the dopes to form a membrane. The results of UFRs of the membranes are shown in Figure 2. In the case of the membranes prepared from 7 and 8 wt % cellulose dopes, the UFR keeps a nearly constant value in the range of 0 to 30 wt % of the NMMO concentration in the coagulant; however, the UFR increases in the range over 30 wt % of NMMO concentration. On the contrary, in the case of the membrane prepared from the 6 wt % cellulose dope, the UFR increases sharply with an increase in the NMMO content in the coagulant. The mutual tendency observed in all series of membranes is the increase of the UFR with an increase in the NMMO concentration in the coagulant.

Sieving Performance

Recently, the removal of the low-molecular proteins such as β_2-MG (11,800 Da) from the blood of the patient with chronic renal failure has been required in the hemodialysis treatment, together with the efficient removal of water, because the accumulation of these substances will cause the chronic side reactions such as amyloidosis. Such substances, which are not removed sufficiently by dialysis, can be removed by the molecular-sieving mechanism. On the other hand, it is necessary for some valuable proteins with middle or high molecular weight such as albumin (66,000 Da) not to be sieved at all. Therefore, the sieving feature in the range of the molecular weight from 10,000 to 100,000 Da is one of the most important performances that should be characteristic of a hemodialysis membrane. This performance was evaluated by measuring the SC of dextran.

First, the effect of the coagulation temperature on the sieving performance of the membrane is described, where the membranes used were the ones prepared from 6, 7, and 8 wt % cellulose dopes using water as a coagulant. The results are shown in Figure 3. In the figure, the SC = 1 means that the substance can permeate through the membrane without any resistance, and the SC = 0 means that the substance cannot permeate at all through it. Figure 3(a) shows that for the membrane prepared from 8 wt % cellulose dope, the SC curve changes drastically in shape according to the change of the coagulant temperature. The SC at 100,000 Da decreases drastically from 1 to 0.13, with a decrease in the coagulant temperature from 60 to 5°C. On the other hand, it is observed in the membranes prepared from the 6 and 7 wt % cellulose dopes that the coagulation temperature has little or no effect on the shape of the SC curves, and these membranes are characterized by low sieving performance, even in the high molecular weight region. The SCs for the membranes prepared in water at 5°C are over 0.79, even at 100,000 Da; moreover, the membranes prepared at 40 and 60°C show little sieving performance, that is, the SC is about 1 within the entire molecular weight range of 1000 to 100,000 Da [Fig. 3(b) and (c)]. From these results, it can be concluded that the low coagulation temperature and the dope with the high cellulose concentration give a membrane with good sieving performance.

Next, the effect of the coagulant composition on the sieving performance of the membrane is described, where the investigation was carried out by using the membrane prepared under the following conditions: cellulose concentration in the dope, 8 wt %; coagulant temperature, 5°C; NMMO concentrations of the coagulant, 0, 10, 20, 30, 40, and 50 wt %. The results are shown in

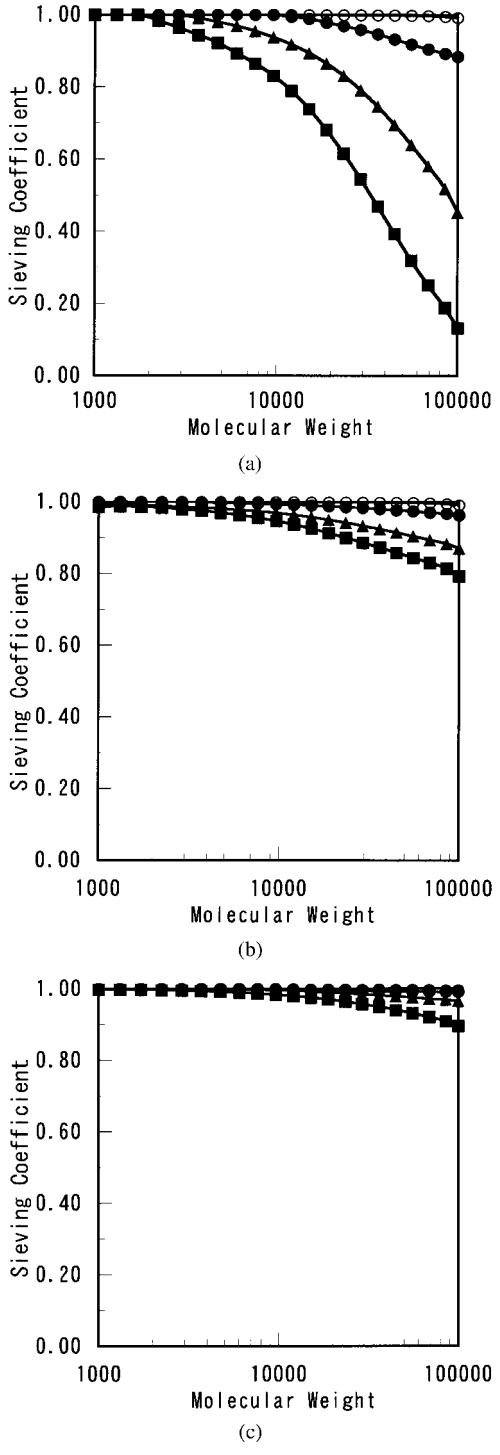

Figure 3 Effect of coagulation temperature on sieving coefficient. Cellulose concentration in the dope: (a) 8 wt %; (b) 7 wt %; (c) 6 wt %. Coagulant: water. Coagulation temperature: (■) 5°C; (▲) 20°C; (●) 40°C; (○) 60°C.

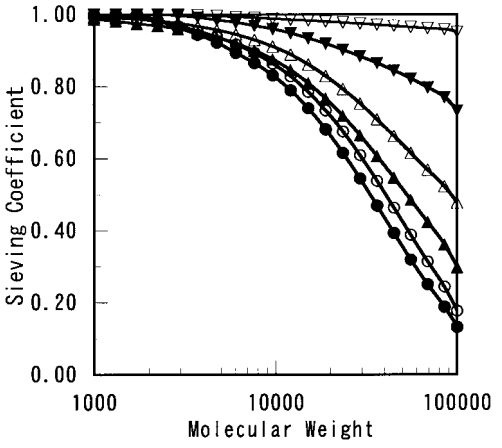

Figure 4 Effect of coagulant composition on sieving coefficient. Cellulose concentration in the dope: 8 wt %. NMMO content of coagulant: (●) 0 (water); (○) 10 wt %; (▲) 20 wt %; (△) 30 wt %; (▼) 40 wt %; (▽) 50 wt %. Coagulation temperature: 5°C.

Figure 4, where one can notice that the slope of the SC curve is strongly affected by the coagulant composition, and that the influence of the composition appears markedly in the high molecular weight region (10,000 to 100,000 Da). For example, the SCs of the membrane prepared in water are 0.8 at 10,000 Da and 0.13 at 100,000 Da. This sieving performance is excellent for a hemodialysis membrane. On the other hand, the SCs of the membrane prepared in the 50 wt % NMMO solution are 1.0 at 10,000 Da and 0.95 even at 100,000 Da, which indicates that this membrane scarcely has any sieving performance. From these results, shown in Figures 3 and 4, it is concluded that the conditions giving the best sieving performance to the membrane are as follows: the coagulant is water, its temperature is 5°C, and the cellulose concentration in the dope is 8 wt %. In addition, it is revealed that the coagulant composition and its temperature both influence the sieving performance, but their effects are virtually negligible when compared with the effect of the cellulose concentration in the dope.

In this study we reported only the relationship between membrane preparation conditions and membrane performance. Further investigations, such as the observation of membrane morphology by scanning electron microscopy (SEM) and atomic force microscopy (AFM), and analysis of the crystalline structure of the membrane by X-ray diffraction, are now in progress and will be reported elsewhere.

CONCLUSIONS

The dialysis membrane was prepared from a cellulose/NMMO solution (dope) by using the phase-inversion method. The cellulose concentration in the dope was varied from 6 to 8 wt %. The coagulants used were aqueous NMMO solutions, of which NMMO concentration and temperature were varied from 0 to 50 wt % and from 5 to 60°C, respectively. The UFR of pure water and the SC of dextran for the obtained membranes were evaluated against the factors comprising the above-mentioned membrane preparation conditions. The decrease in the cellulose concentration in the dope and the increases in the temperature and NMMO concentration of the coagulant gave a higher-flux membrane. The sieving performance of the membrane was strongly affected by the cellulose concentration in the dope. The membrane prepared from 6 wt % cellulose dope showed no sieving performance, even in the high molecular weight region (10,000 to 100,000 Da), regardless of the other coagulation conditions. On the other hand, the 8 wt % cellulose dope could produce membranes with various levels of performance by varying the coagulation conditions. Consequently, the membrane having the preferable performances as a hemodialysis membrane was obtained when the dope was coagulated in water at 5°C. The performance of SCs, at 10,000 and 100,000 Da, was 0.8 and 0.13, respectively; and the UFR was about 100 mL/($m^2 \cdot h \cdot mmHg$). These results indicate that the NMMO method has the potential of generating a high-performance membrane that is applicable to clinical usage.

REFERENCES

1. Gejyo, F.; Yamada, T.; Odani, S. Biochem Biophys Res Commun 1985, 129, 701.
2. Hongo, T.; Inamoto, M.; Iweata, M.; Matsui, T.; Okajima, K. J Appl Polym Sci 1999, 72, 1669.
3. Inamoto, M.; Miyamoto, I.; Hongo, T.; Iwata, M.; Okajima, K. Polym J 1996, 28, 507.
4. Manabe, S.; Kamatas, S.; Iijima, H.; Kamide, K. Polym J 1987, 19, 391.
5. Hiyoshi, T.; Miyazaki, M.; Fukuda, M. Maku (Membrane) 1997, 22, 74.
6. Fukuda, M.; Hiyoshi, T.; Sakai, K.; Kokubo, K. Jpn J Artif Organs 2000, 29, 411.
7. Lenz, J.; Schurz, J.; Wrentschur, E. Colloid Polym Sci 1993, 271, 460.
8. Seymour, R. B.; Johnson, E. L. J Appl Polym Sci 1976, 20, 3425.
9. Chanzy, H.; Nawrot, S.; Peguy, A.; Smith, P.; Chevalier J. J Polym Sci Polym Phys Ed 1982, 20, 1909.
10. Chanzy, H.; Noe, P.; Paillet, M.; Smith, P. J Appl Polym Sci 1983, 37, 239.
11. Woodings, C. R. Int J Biol Macromol 1995, 17, 305.
12. Seita, Y.; Mochizuki, A.; Nakagawa, M.; Takanashi, K.; Yamashita, Y. J Appl Polym Sci 1997, 65, 1703.
13. Kesting, R. E.; Barsh, M.; Vincent, A. J Appl Polym Sci 1965, 9, 1873.