Plasma Surface Graft of Acrylic Acid onto a Porous Poly(vinylidene fluoride) Membrane and Its Riboflavin Permeation

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SYNOPSIS

Acrylic acid was grafted onto the surface of commercial poly(vinylidene fluoride) (PVDF) membrane using plasma polymerization techniques. Graft reaction was confirmed by X-ray photoelectron spectroscopy (XPS) spectra and attenuated total reflectance Fourier transform infrared spectra. Grafting rate was dependent on plasma exposure time. For argon plasma at 30 W, grafting rate decreased after maximum rate was observed at 30 s exposure. PVDF membrane with 30 s plasma exposure and subsequently grafted with acrylic acid (AA-3) showed the greatest O_{1s}/F_{1s} area ratio in XPS spectra. Thus its graft density and degree of polymerization were the largest among the graft membranes. Permeation of riboflavin through all poly(acrylic acid)-*g*-PVDF membranes showed a decrease in permeability of riboflavin in pH 4–5. © 1996 John Wiley & Sons, Inc.

INTRODUCTION

Many researchers have reported on the controlled drug delivery system utilizing drugs loaded on the polymer matrix.[1-18] Drug delivery systems received much attention because they could maximize the healing effect to maintain the effective drug concentration in the blood through zero-order release for a prolonged period of time. Among the polymeric drug delivery systems, macromolecular drugs, polymeric membrane systems, polymer hydrogels, and lipids have been suggested as effective tools for drug delivery systems. Recently, much attention has been paid to the stimuli-responsive drug delivery systems. Stimuli include electricity,[5-6] pH,[7-10] glucose concentration, and temperature.[15-18]

Several studies have reported on the surface modification of porous membranes by grafting acrylic monomers utilizing corona discharge, glow discharge, and ultraviolet (UV) techniques.[19-23] Iwata and colleagues reported on the graft polymerization of acrylamide onto a polyethylene[19,20] using corona discharge and of *N*-isopropylacrylamide onto a poly(vinylidene fluoride) (PVDF)[21] using glow discharge technique. Osada and coworkers[22] grafted poly(methacrylic acid) onto a porous poly(vinyl alcohol) membrane using plasma treatment, and their ion transport, albumin, and poly(ethylene glycol) permeation behaviors were studied. X-ray photon spectroscopy (XPS) was utilized to confirm the graft reaction.[19-21] Recently, Ito and colleagues[23] reported on the water permeation through porous polycarbonate membrane having poly(carboxylic acid) on the membrane surface by pH and ionic strength. Masuoka and coworkers[24] grafted *N,N*-dimethylacrylamide onto porous polypropylene membrane using plasma techniques.

In our previous study, we reported on the grafting of acylic monomers onto porous polyurethane and polyamide membranes for pH- and temperature-sensitive membranes prepared by chemical,[25] UV, and plasma[26] initiation methods. However, it was not possible to determine the size of the graft chain that may affect the permeability of the solute upon changing pH or ionic strength of the solution, since the porous base membrane, particularly the polyamide membrane, was not soluble in polar aprotic solvent such as dimethylformamide (DMF), which

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is essential for determining the content of functional groups.

The aim of this study is to synthesize the intelligent stimuli-responsive material device by grafting acrylic acid monomer onto the porous PVDF membrane. The effects of graft density or degree of polymerization (DP) of the graft chain on the pH-dependent permeability of riboflavin as a model drug through poly(acrylic acid) (PAA)-*g*-PVDF membrane was examined.

EXPERIMENTAL

Acrylic acid (AA), from Junsei Chemical Co. (Tokyo), was used after vacuum distillation. Riboflavin purchased from Junsei Chemical Co. was used without any further treatment. Porous PVDF membrane from Millipore Co. (Bedford, MA) has 100 μm in thickness, 0.22-μm pores, and 70% porosity. It was used after cleaning in methanol.

For plasma polymerization, bell-jar-type plasma reaction apparatus was used to accommodate AA monomer. After washing in methanol and freeze-drying at −50°C for 24 h, porous membrane was placed on the bottom electrode of the reaction apparatus and was evacuated to 50 m torr. Then, 30-W argon plasma was treated in varying times up to 3 min. Treated polymer membrane was immediately exposed to air and dipped into prepared 20 wt % AA solution. After the reaction under nitrogen atmosphere at 60°C for 2 h, it was dipped into deionized water at 60°C for 24 h to remove any residual monomers and homopolymers, and then freeze-dried at −50°C for 24 h.

Graft reaction of AA onto porous PVDF membrane was confirmed by XPS (Surface Spectrometer, Inc., Model 2803-S) using MgK_{α}-X line and the spectra were obtained at the takeoff angle (θ) of 90 degrees. Fourier transform infrared spectroscopy (FTIR) (Nicolet Model Magna 550) was also used to confirm the graft reaction. For plasma-treated membranes, the amount of peroxide formed on the surface was quantified with 1,1-diphenyl-2-picrylhydrazyl (DPPH).[20] The reacted membrane was exposed to air and dipped into the DPPH/toluene solution (1×10^4 mol/L) at 60°C for 2 h to decompose the peroxides formed on and near the surfaces. The DPPH molecules consumed were measured from the difference in transmittance at 520 nm using spectrophotometer between the virgin and PAA-grafted membrane.

The grafted PVDF membranes were washed well with deionized water, dried, and dissolved in DMF. The DMF solution was subjected to the determination of carboxyl groups in the PAA-grafted membrane by the Rhodamin method.[27] Rhodamin 6G (10 mg) was dissolved in a phosphate-buffered saline (PBS; pH 11, 10 mL) and extracted with toluene. The Rhodamin 6G/toluene extract (2 mL) was mixed with a DMF solution (2 mL) of the grafted PVDF membrane. The mixture was incubated in the dark for 30 min, and the absorbance at 534 nm was measured. A calibration curve was obtained with DMF solution containing AA of known concentrations. All measurements were done for at least three specimens and the standard deviations from the average was within ± 5%.

For the measurement of permeability of riboflavin, a permeation cell has two compartments of equal volume (100 ml). Each chamber was mechanically stirred at 750 rpm to eliminate the boundary-layer resistance. All measurements were made at 37°C in this study. One compartment of the cell was filled with PBS at pH 7.4, and the other side with a solution of riboflavin. Aliquots of the buffer solution were taken out after a given period of time. The UV absorbance of the solution was measured with a spectrophotometer (Spectronic 21, Milton Roy Co.) at 444 nm in wavelength to determine the concentration of riboflavin in the feed and in the permeate. The solute permeability coefficient P was calculated from the equation which was obtained from the mass balance equation.[12] The average of at least three measurements is reported here and the standard deviation was within ± 5%.

RESULTS AND DISCUSSION

One of the advantages of plasma polymerization technique was that the polymerization reaction was limited to the surface of the membrane. After the plasma exposure, the membrane was taken out of the plasma reactor and exposed to the air. Upon dipping into the 20 wt % AA monomer solution, the graft reaction initiated very rapidly. Peroxides seemed to be the most plausible species for initiating the graft copolymerization onto the plasma-treated surface. One of the reasons was that the plasma-treated membranes were always stored not in vacuum but in air prior to graft copolymerization. During this storage in air, most of the free radicals eventually remaining in the surface region of the film must be converted to peroxides. The mechanism of

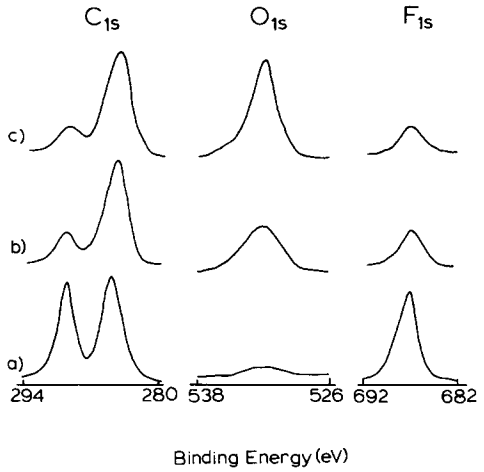

Figure 1 XPS spectra of the surface of (a) PVDF, (b) AA-1, and (c) AA-3 membranes.

this kind of reaction involves the generation of free radicals from the main chain of the polymer and the formation of peroxide upon air exposure, followed by the initiation and propagation of the AA monomers.[20,24]

XPS spectra of virgin and grafted PVDF membranes are seen in Figure 1. The XPS spectra of the untreated PVDF membrane (a) are composed of a highly intense F_{1s} peak and double C_{1s} peaks corresponding to the carbon of $-CH_2-$ at the lower binding energy and to the carbon of $-CF_2-$ at the higher binding energy. When AA was grafted onto the PVDF membrane, the intensity of the F_{1s} spectrum and of the component $-CF_2-$ of the C_{1s} spectrum at high binding energy decreased, and concomitantly an O_{1s} spectrum appeared. This is due to the removal of F atoms by Ar plasma and introduction of oxygen onto the membrane surface during the subsequent exposure to air and AA. C_{1s} components between 286 and 289 eV also appeared, and are assigned to ether, ketone, peroxide, and other oxygen-containing functional groups.[28] These tendencies are in good agreement with findings in the Ar plasma treatment of polyethylene[20] and of *N*-isopropylacrylamide onto PVDF membrane.[21] As summarized in Table I, the area ratio O_{1s}/F_{1s} increased as AA was grafted with a maximum at 30 s exposure, indicating the increase of grafting content with plasma exposure time.

The structure of argon plasma-graft membranes was also confirmed by attenuated total reflectance (ATR) FTIR spectra showing the absorption peak at 1730 cm^{-1} due to the presence of carboxyl groups in AA graft membranes (Fig. 2).

Table I Elemental Ratios of Surface of Plasma-Polymerized PVDF Membranes

Sample Code	Exposure Time (s)	O_{1s}/F_{1s} Area
PVDF	0	0.05
AA-1	10	0.44
AA-2	20	0.32
AA-3	30	0.82
AA-4	40	0.44

The DPPH method[20] was found to be effective for determining the concentration of peroxides formed. The principle of this method is to measure the consumption of DPPH when the plasma-treated membrane is put in a toluene solution containing a given amount of DPPH and kept at 60°C to decompose the peroxides.

Figure 3 illustrates the concentration of decomposed peroxide formed on the surface of PVDF membrane as a function of exposure time determined by the consumption of DPPH. It can be seen that the dependence of the peroxide formation on the plasma exposure time is not monotonous but shows a maximum. The amount of peroxide formed on the PVDF membrane surface decreased after a maximum rate was observed at 30 s exposure (AA-3). Clearly, longer Ar plasma exposure does not guarantee the formation of larger amounts of peroxide. It should be noted that low peroxide concentrations at long plasma exposures were not due to

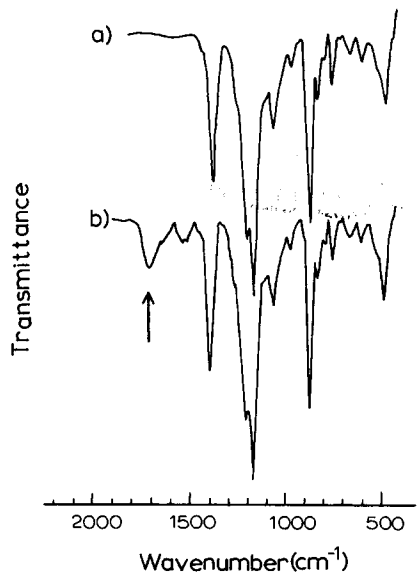

Figure 2 ATR FTIR spectra of (a) PVDF and (b) AA-3 membranes.

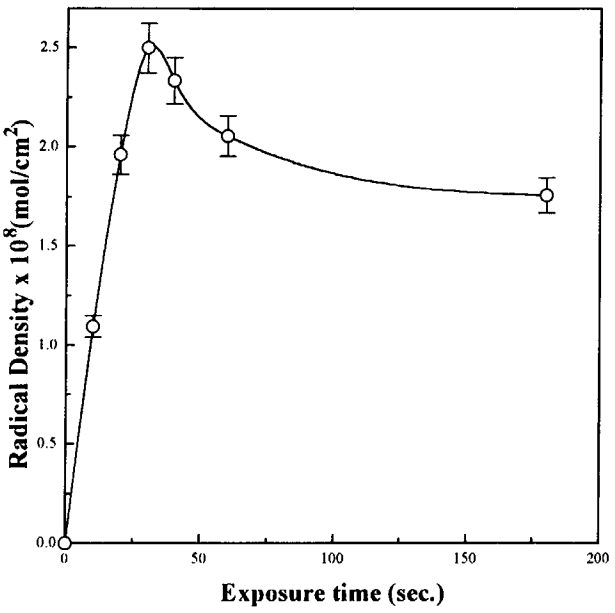

Figure 3 Effect of plasma exposure time on the radical density or peroxide concentration measured by DPPH method.

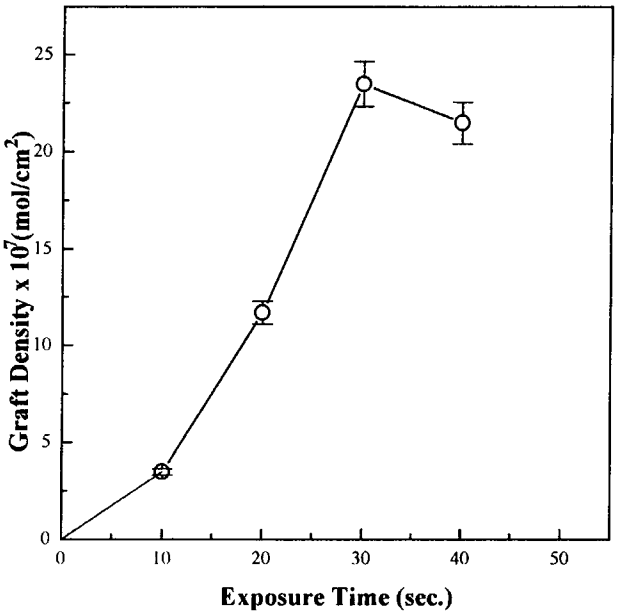

Figure 4 Amount of graft chain (graft density) as a function of plasma exposure time as determined by Rhodamin 6G.

direct decomposition of the formed peroxide by plasma because the plasma exposure was carried out in the atmosphere containing no oxygen but only the Ar gas, which should result in no peroxide formation. The peroxides must have been produced during the exposure of the membrane to air after the plasma treatment. The peroxides formation mechanism was well proposed by Suzuki and colleagues[20] and Masuoka and coworkers.[24]

The amount of PAA grafts was identified by using the Rhodamin 6G method[27] to determine the number of carboxyl groups present on the membrane surface. Rhodamin 6G is a dye reagent which will adsorb carboxylic acid present on the membrane surface. The results are tabulated in Table II and illustrated in Figure 4 as a function of plasma exposure time. The number-average DP of graft chains was calculated on the assumption that radicals produced on the membrane surface were all used for initiation of graft polymerization. As shown in Table II, DP of PAA grafted onto PVDF membrane ranges between 32 to 94, and shows the maximum at 30 s exposure (AA-3). This tendency is the same as that of the formation of the peroxides as listed in Table I. It is expected that DP of the surface-grafted PAA chain may affect the permeability of the solute.

For the virgin PVDF membrane, the permeability of riboflavin was constant as pH varies. However, as seen in Figure 5, PM-*g*-PVDF membrane showed the pH-dependent permeability of riboflavin. Particularly at pH 4–5, these membranes showed a rapid decrease in permeability of riboflavin. A drastic drop

Table II Graft Density and Degree of Polymerization of Poly(acrylic acid)-*g*-PVDF Membrane

Sample	Exposure Time (s)	Radical Density[a] × 10^8 (mol/cm^2)	Graft Density[b] × 10^7 (mol/cm^2)	DP of Graft Chain[c]
AA-1	10	1.10	3.5	32
AA-2	20	1.96	11.8	60
AA-3	30	2.50	23.4	94
AA-4	40	2.34	21.7	33

[a] Determined by DPPH method.
[b] Determined by Rhodamin 6G method.
[c] (Graft density)/(radical density).

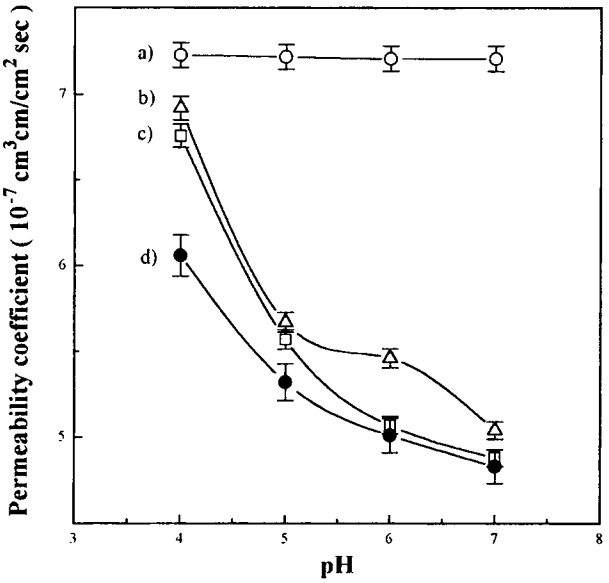

Figure 5 Effect of pH on the riboflavin permeation through (a) PVDF, (b) AA-1, (c) AA-2, (d) AA-3, and (e) AA-4 membranes.

in permeability at pH 4–5 can be explained from the fact that PAA is an ionic polymer showing pK_a = 4.8,[23,29] dissociates into carboxylate ions in methanol and basic solutions, and exhibits the extended conformations because of the ionic repulsion forces resulting in the decrease of the effective pore sizes as the solution range increases above pK_a = 4.8. At the lower pH range, the polymer chain forms a contracted conformation contributing to an increase in effective pore sizes and thus the increase in the solute permeability.

Figure 5 also shows that as the DP of the graft chain in PVDF membrane increases, the permeability of riboflavin decreases in all pH ranges, meaning that the effective pore size of the graft membrane becomes smaller. AA-3 membrane treated 30 s in plasma reactor (having DP of 94) showed the smallest permeability values and the smallest changes in permeability. We expected that a longer PAA chain might contract to a great extent so that the pH sensitivity, as measured by the ratio of permeability at pH 4 and pH 7, should be the largest among the samples prepared. However, the result was somewhat beyond our expectation. AA-1 membrane having DP of 32 showed the largest changes in permeability. This result led to a conclusion that the largest DP or chain length does not correlate with the effective pore size. This means that there exists an optimum point in radical formation and the chain-growth radical reaction of AA for the permeation of riboflavin.

CONCLUSIONS

We prepared pH-sensitive polymer membranes by grafting AA, utilizing the plasma polymerization technique. The structure of the graft chain was confirmed by XPS and ATR FTIR spectra. Comparing the XPS spectra of the virgin and grafted PVDF membranes, the area ratio of O_{1s}/F_{1s} increased with the Ar plasma exposure time with a maximum at 30 s exposure. The DP of the graft PAA chain ranges from 32 to 94 depending on the plasma exposure when the monomer solution concentration was 20 wt %. The graft rate and thus the degree of polymerization of the graft chain were maximum at 30 s Ar plasma exposure time. The change in permeability of the model drug, riboflavin, occurs at pH 4–5 for AA. Membranes having DP of about 30–60 AA units in the graft chain showed the largest changes in permeability of riboflavin at pH 4–7. Longer graft chain did not help increase the permeability nor the pH sensitivity. This means that there exists an optimum exposure time and graft chain length for the permeation of riboflavin.

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