Preferable Structure of Poly(ethylene glycol) for Grafting onto a Cellulosic Membrane to Increase Hemocompatibility Without Reduction in Solute Permeability of the Membrane

TOSHIYUKI KANAMORI,[1,*] KIYOTAKA SAKAI,[1] MAKOTO FUKUDA,[2] and YASUHIKO YAMASHITA[2]

[1]Department of Chemical Engineering, Waseda University, 3-4-1, Okubo, Shinjuku-ku, Tokyo 169, Japan; [2]Hollow Fibers Development Department, Asahi Chemical Industry Co., Ltd., Asahimachi, Nobeoka-shi, Miyazaki 882, Japan

SYNOPSIS

Swelling layers formed by poly(ethylene glycol) (PEG) chains grafted onto surfaces of a cellulosic membrane are known to improve hemocompatibility of the membrane. Three types of hemodialysis membranes were derived from the same regenerated-cellulose hollow-fiber membrane by grafting PEG with different formulas onto the surfaces to clarify the influence of the grafted PEG chains on solute permeability of the membranes. Determination of volume fractions of nonfreezing water contained in the membranes by differential scanning calorimetry revealed that most of the PEG chains were grafted onto the external surfaces and less into the pores in the membranes. Permeability of vitamin B_{12} for the PEG-grafted membranes except for the one with the shortest PEG chains was reduced as compared with the original membrane, while that of tritium-labeled water for all the PEG-grafted membranes was the same as that of the original membrane. Structural parameters only of the PEG-grafted membrane with the largest alkyl groups at the terminal of the PEG chains were different from those of the other PEG-grafted and original membranes. The shorter PEG chains with the larger terminal alkyl groups are suitable for grafting onto a cellulosic membrane to increase hemocompatibility of the membrane without significant reduction in the solute permeability of the membrane. © 1995 John Wiley & Sons, Inc.

INTRODUCTION

New cellulosic membranes of which the surfaces have been grafted onto by poly(ethylene glycol) (PEG) have been developed.[1,2] Swelling layers consisting of PEG chains and water formed on the surfaces of the membranes improve the hemocompatibility of the membranes compared with regenerated-cellulose membranes.[3]

However, the swelling layers may simultaneously reduce the solute permeability of the membranes. In the present article, permeabilities of tritium-labeled water (HTO) and vitamin B_{12} (VB_{12}) for three PEG-grafted membranes derived from the same regenerated-cellulose membrane are compared. The authors determined the structures of the membranes using the tortuous capillary pore model[4] and discuss the preferable formula of the grafted PEG chains relating solute permeability of the membranes with the membrane structures including the swelling layers.

EXPERIMENTAL

Hemodialysis Membranes

A conventional hemodialysis hollow-fiber membrane (AM-SD) was produced from a cuprammonium cellulose solution with an ordinary technique. PEG was grafted onto both external surfaces of the conventional membrane by the polymerization procedure presented by Kishida and Ikada.[3] The formula of the PEG chains grafted onto the surfaces is supposed to be as follows on the basis of the starting materials:

* To whom correspondence should be addressed.

Journal of Applied Polymer Science, Vol. 55, 1601–1605 (1995)
 CCC 0021-8995/95/111601-05

Table I Technical Data on the Original Cellulosic and PEG-grafted Membranes

Type	n [−]	m [−]	Inner Diameter[a] (μm)	Wall Thickness[a] (μm)	Pure Water Permeability [m/(s·TPa)]	Water Content [−]
AM-SD	—	—	205 ± 11 (100)	23.1 ± 2.1 (200)	12.1	0.64
AM-PC(s)	7	1	202 ± 8 (100)	22.8 ± 1.4 (200)	12.1	0.64
AM-PC(m)	5	12	197 ± 21 (100)	23.9 ± 1.9 (200)	12.1	0.62
AM-PC(l)	10	12	204 ± 11 (100)	23.0 ± 1.7 (200)	9.8	0.63

[a] Data expressed as mean ± standard deviation (number of data).

(Cellulosic chain) $-OCOCH_2$

$$-(OCH_2\,CH_2)_n-OR_m \quad (1)$$

where R denotes an alkyl group, and m, the number of carbons in the group.

The technical data on the hemodialysis membranes tested are tabulated in Table I. The dimensions of the membranes were measured by optical microscopy under wet conditions at room temperature. The pure water permeability and water content were obtained from the standard methods presented in the previous article.[5] The ratios of the PEG weight contained in the membranes to that of the original membranes were approximately constant at 100 ppm regardless of types of the PEG chains.

Permeabilities of Vitamin B_{12} (VB_{12}) and Tritium-labeled Water (HTO)

Permeabilities of VB_{12} and HTO for a membrane were measured by the methods using optical fibers and a radioisotope, respectively, presented in previous articles.[6,7] The methods are capable of providing precise values of permeability for a single hollow fiber without the influence of flow conditions.

Volume Fractions of Nonfreezing Water Contained in Well-wetted Membranes

The heating process of well-wetted membranes was observed by differential scanning calorimetry (DSC). The equilibrium partition coefficient of HTO was determined by sorption of HTO into the membranes. Volume fractions of nonfreezing water contained in the membranes were calculated through the results.[5]

Structural Parameters of Membranes

Structural parameters of a membrane are obtainable from the tortuous capillary pore model presented by Sakai et al.[4] The permeability of HTO for the membrane required to analyze the structure with the model was measured by the method described in a previous article.[7]

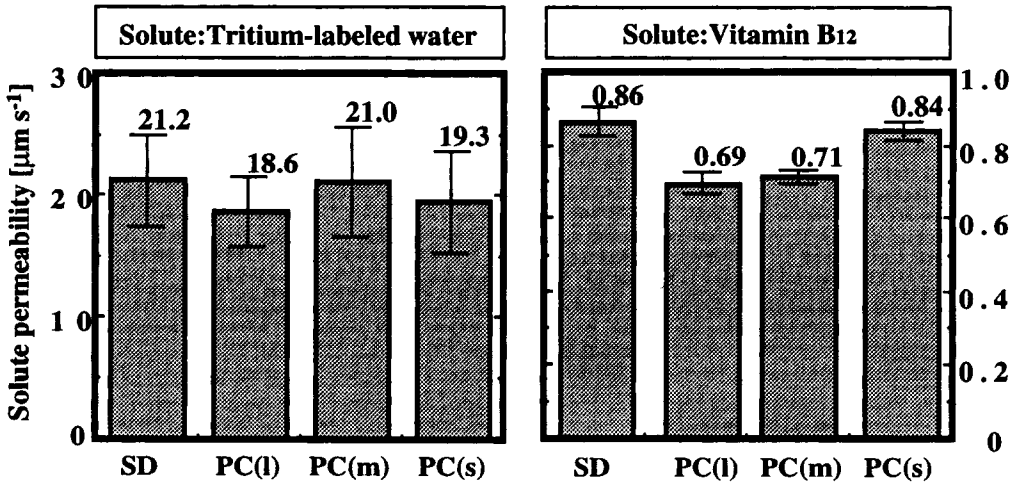

Figure 1 Permeabilities of HTO and VB_{12} for the original cellulosic membrane (AM-SD) and the PEG-grafted membranes (AM-PC).

Table II Volume Fraction of Nonfreezing Water Contained in the Membranes

Type	Partition Coefficient of Tritium-labeled Water K_{HTO} [−]	Volume Fraction of Nonfreezing Water H_{nf} [−]	H_{nf}/K_{HTO} [−]
AM-SD	0.549	0.203	0.370
AM-PC(m)	0.581	0.241	0.415

RESULTS AND DISCUSSION

Comparison of Solute Permeability for the PEG-grafted Membranes with That for the Original Cellulosic Membrane

Permeabilities of HTO and VB_{12} for the original cellulosic membrane and the PEG-grafted membranes are compared in Figure 1. Permeability of HTO for all the membranes was taken as nearly constant in spite of the grafting PEG chains, while pure water permeability for AM-PC(1) measured by filtration was somewhat smaller than that for the others, as shown in Table I. Permeability of VB_{12} for AM-PC(1) and AM-PC(m) is smaller than that for AM-SD and AM-PC(s).

Distribution of Grafted PEG Chains in the Membranes

The equilibrium partition coefficient of HTO for a membrane K_{HTO} [−] corresponds to the net volume fraction of the domains in which water molecules are distributed. Nonfreezing water in a membrane consists of the molecules of which the mobility is reduced by polymer chains in the membrane. A volume fraction of nonfreezing water H_{nf} [−] is calculated from K_{HTO} minus a volume fraction of freezing water which is determined by DSC.[5]

Table II shows the K_{HTO}, H_{nf}, and H_{nf}/K_{HTO} of AM-SD and AM-PC(m). The values of H_{nf}/K_{HTO} for cellulosic membranes are approximately constant at 0.37.[5] Hydrophilicity of PEG chains slightly increased the H_{nf}/K_{HTO} of the AM-PC(m), while the water content listed in Table I was substantially the same. Because the amount of the wall area of pores in a membrane is much larger than is the membrane external surface area, if many PEG chains were grafted onto the pore walls, H_{nf}/K_{HTO} and the water content would increase much more.

In the present article, most of the PEG chains are considered to exist on the external surfaces of the membranes.

Structural Analysis of the Membranes Using the Tortuous Capillary Pore Model

The tortuous capillary pore model[4] and the above consideration led to structural models of the original cellulosic membrane (AM-SD) and the PEG-grafted cellulosic membranes (AM-PC), as illustrated in Figure 2. The swelling layers consisting of PEG chains and water may enlarge the length of the pores and reduce the radius of those at the entrances.

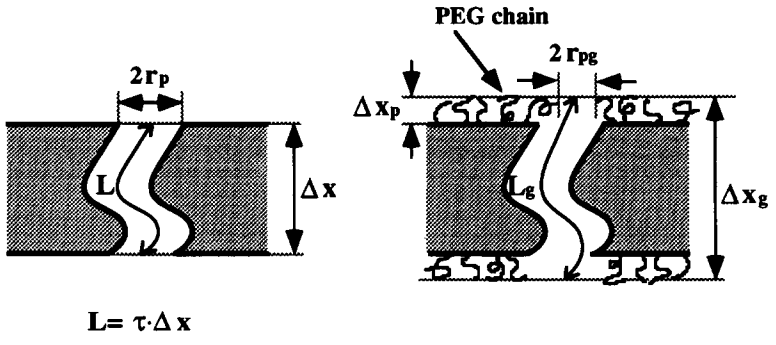

Figure 2 Structural models of the original cellulosic membrane (AM-SD) and the PEG-grafted membranes (AM-PC) based upon the tortuous capillary pore model.

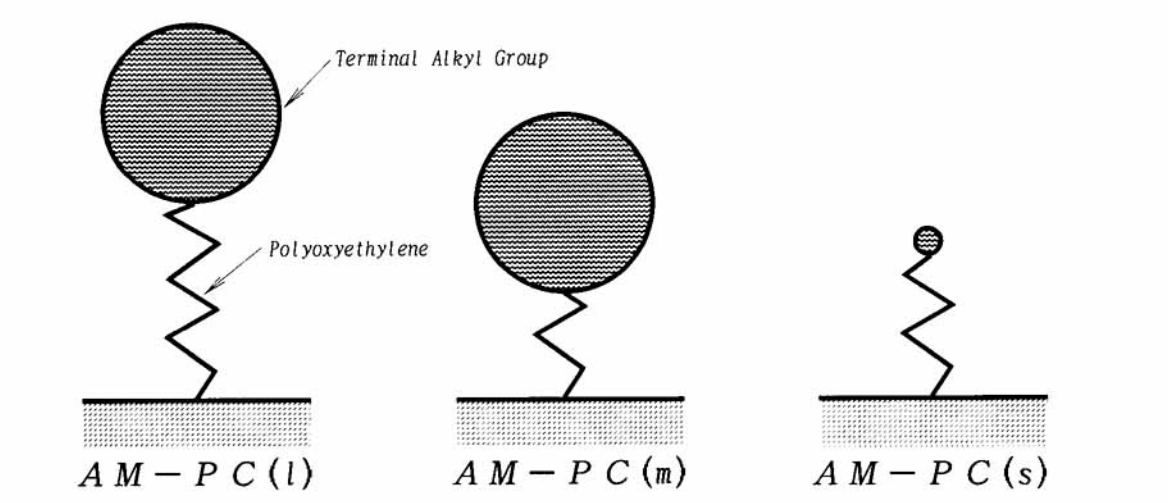

Figure 3 Structural scheme of the PEG chains grafted onto membrane surfaces in water.

Table III summarizes the structural parameters of the membranes determined by the tortuous capillary pore model. Thickness of the swelling layer was too thin to identify with optical microscopy compared with that of the membrane and gave no influence on water and solute permeabilities. The structural parameters only of AM-PC(1) were somewhat different from those of the others.

Preferable Structure of PEG Chains for Grafting onto Membrane Surfaces

Alkyl groups at the terminal of the PEG chains form aggregations in water because of their hydrophobicity and polyoxyethylene segments in the chains extend like "string," leading to an assumption for the structure of the PEG chains in water as shown in Figure 3. The size of the aggregation at the terminal and the length of the string in the PEG-chain structure depend on the numbers of m and n in eq. (1), respectively.

Because the tortuous capillary pore model assumes pores as uniform along the thickness of the membrane, strictly speaking, the model does not hold for such membranes as described in this study. However, even in the case of applying the model to an asymmetrically structural membrane, the model is capable of providing useful information on the membrane structure.

Table III Structural Parameters of the Original Cellulosic and PEG-grafted Membranes

Type	Pore Radius (μm)	Surface Porosity [−]	Tortuosity [−]
AM-SD	2.8	0.352	1.8
AM-PC(s)	2.8	0.349	1.8
AM-PC(m)	2.8	0.351	1.8
AM-PC(l)	2.7	0.327	1.9

Permeability of VB_{12} for AM-PC(m) was lowered in a similar manner as was that for AM-PC(1) in spite of no change in the structural parameters. The aggregation at the terminal of the PEG chains may reduce solute permeability by steric hindrance at the entrances of the pores. The PEG chains around a pore may cover part of the pore entrance, leading to a slight change in the structural parameters of AM-PC(1), having the largest string in the PEG-chain structure.

It has been reported that the effect of preventing platelet in a patient's blood from adhering to the membrane external surfaces increases with the size of the terminal alkyl groups in PEG chains, but an increase in the whole length of the PEG chains has no effect.[3,8]

Consequently, the shorter PEG chains with the larger terminal alkyl groups are suitable for grafting onto a cellulosic membrane to increase hemocompatibility without significant reduction in the permeability of the membrane for solutes with smaller molecular weight than that of VB_{12}.

CONCLUSIONS

Three types of hemodialysis membranes were derived from the same regenerated-cellulose hollow-fiber membrane by grafting PEG with different formulas onto the surfaces to clarify the influence of the grafted PEG chains on the solute permeability of the membranes. Determination of volume frac-

tions of nonfreezing water contained in the membranes by differential scanning calorimetry revealed that most of the PEG chains were grafted onto the external surfaces and less into the pores in the membranes.

The shorter PEG chains with the larger terminal alkyl groups are suitable for grafting onto a cellulosic membrane to increase hemocompatibility without significant reduction in the permeability of the membrane for solutes with smaller molecular weight than that of vitamin B_{12}.

REFERENCES

1. T. Akizawa, K. Kino, S. Koshikawa, Y. Ikada, A. Kishida, M. Yamashita, and K. Imamura, *ASAIO Trans.*, **35,** 333–335 (1989).
2. T. Akizawa, K. Kino, E. Kinugasa, S. Koshikawa, Y. Ikada, A. Kishida, Y. Hatanaka, and K. Imamura, *ASAIO Trans.*, **36,** M640–M642 (1990).
3. A. Kishida and Y. Ikada, *Jpn. J. Artif. Organs,* **17,** 47–50 (1988) (in Japanese).
4. K. Sakai, S. Takesawa, R. Mimura, and H. Ohashi, *J. Chem. Eng. Jpn.*, **21,** 207–210 (1988).
5. T. Kanamori, M. Fukuda, and K. Sakai, *J. Colloid Interface Sci.*, to appear.
6. T. Kanamori, K. Sakai, T. Awaka, and M. Fukuda, *J. Membr. Sci.*, **88,** 159–165 (1994).
7. K. Sakai, S. Takesawa, R. Mimura, and H. Ohashi, *J. Chem. Eng. Jpn.*, **20,** 351–356 (1987).
8. N. Kanamori, T. Akizawa, S. Koshikawa, Y. Hatanaka, M. Yamashita, K. Imamura, and Y. Ikada, in *Proc. 37th Congr. Jpn. Soc. Dial. Ther.*, 1992, p. 297 (in Japanese).

Received August 24, 1994
Accepted October 7, 1994