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Biocompatible Polymer Alloy Membranes Composed of Segmented Polyurethane and Phospholipid Polymer for Artificial Pancreas

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A novel polymer alloy membrane with both biocompatibility and permeability for fabrication of an implantable artificial pancreas was prepared. The polymer alloy was composed of a segmented polyurethane (SPU) and 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer. The SPU/MPC polymer alloy membranes were prepared by a solvent evaporation method. The MPC polymer constructed domains in the SPU matrix, but the X-ray photoelectron spectra indicated that the MPC polymer was located at the subsurface of the membrane. The mechanical properties of the SPU/MPC polymer alloy membrane were higher than those of silicone rubber. The glucose and insulin could permeate through the SPU/MPC polymer alloy membrane. The permeability was promoted by the MPC polymer domains which dispersed both on the surface and inside the membrane. It was concluded that the SPU/MPC polymer alloy membrane has useful functions for the fabrication of the implantable artificial pancreas.

Key words: Polymer alloy membrane, segmented polyurethane, 2-methacryloyloxyethyl phosphorylcholine polymer, permeability, artificial pancreas

1. Introduction

Controlled release systems of insulin are useful for the treatment of diabetes because the conventional insulin administration by injection causes wide fluctuations in the glucose levels. In order to maintain the blood glucose levels within the normal range, it is necessary for self-regulated release systems to have the capability of adapting the amount of insulin in response to changes in the glucose levels. Since early 1980's, many research regarding a glucose-responsible polymer system to control insulin release [1-4] have been done. Most of the polymer systems used enzyme glucose oxidase (GOD) as the glucose sensor, but non-enzymatic systems are also reported. These glucose-responsible polymer systems need an implantable and biocompatible vehicle when the systems will be applied to living organisms to control the blood glucose level. Thus, we prepared a biocompatible polymer alloy membrane to make the implantable vehicle, which can permeate the solutes including insulin in physiological conditions.

We have been prepared and researched that biomembrane mimicking surfaces indicate excellent bio/blood compatibility. In this research, the polymer having phosphorylcholine group, 2-methacryloyloxyethyl phosphorylcholine (MPC) polymers were investigated [5-7]. The MPC polymers effectively suppressed cell adhesion and activation. The MPC polymer has been investigated as the membranes of the hemodialyzer[8] and glucose sensors for improving biocompatibility.

Our next concern is the preparation of a polymer membrane that can encapsulate the glucose-responsive insulin release system. In this article, we focused on the polymer alloy composed of MPC polymer and segmented polyurethane (SPU). The SPU possesses excellent mechanical properties and processability. The MPC polymer easily absorbed water. The polymer alloy has a well-defined microdomain structure consisting of two polymer components. It is expected that water-soluble organic compounds and proteins (molecular weight<10^4) will diffuse in the microdomain consist of MPC polymer. Therefore, blending of the MPC polymer as an additive in the SPU was a useful technique to obtain a new polymer membrane. It was clarified that the SPU/MPC polymer alloy was

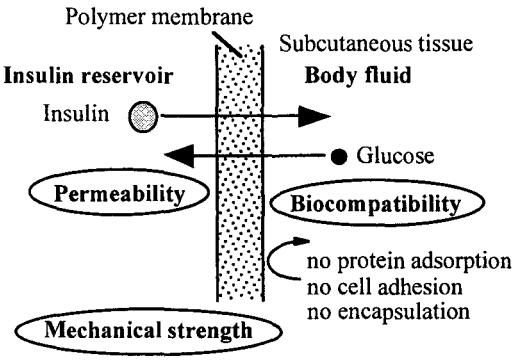


Figure 1. Properties of polymer membrane for implantable artificial pancreas.

a very promising bio/blood compatibility [9-10]. The SPU/MPC polymer alloy with solute permeability as a membrane was proposed for the chemically controlled release systems, that is, an artificial pancreas (Fig. 1).

2. Experimental

2.1. Materials

The MPC and 2-ethylhexyl methacrylate (EHMA) was copolymerized by a method reported in our previous study (Fig.2) [9]. SPU (Tecoflex® 60) was obtained from Thermedics, Inc. ,MA, USA, and purified by reprecipitation to remove all of the stabilizers and low-molecular weight impurities.

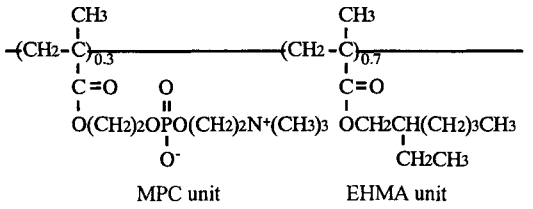


Figure 2. Chemical structure of poly(MPC-co-EHMA) (PMEH).

2.2. Preparation of SPU/MPC polymer alloy membrane

Three weight-percent solutions of both SPU and PMEH in a methylene chloride / ethanol mixture (7/3 by volume) were separately prepared. The solutions were mixed together in a 5/5 composition. The mixed solution was stirred and sonicated for 30 min. The polymer solution was spread on a Petri dish, and then the solvents were evaporated at 40°C under air for 24 h. The obtained membrane was dried in a vacuum condition to eliminate the residual solvent. The thickness of the membrane was controlled by amount of the polymer solution, and determined by a micrometer. The SPU membrane as a reference sample was also prepared by the same procedure described above.

2.3. Characterization of SPU/MPC polymer alloy membrane

Staining of the PMEH in the membrane with osmium tetraoxide (OsO_4) was carried out under the following conditions: The membrane was exposed to OsO_4 vapor for 20 min at room temperature; the stained membrane was then observed with an optical microscope.

The SPU membrane and the SPU/PMEH alloy membrane was analyzed using a X-ray photoelectron spectroscope (XPS, ESCA3300, Shimadzu, Kyoto, Japan).

Stress-strain curves of the membranes were measured using a tensile testing machine (STA-1150, ORIENTEC, Tokyo, Japan). The membranes were swollen in distilled water, and then measured.

The water content of the SPU/PMEH alloy membrane was measured. The membranes were immersed and swollen in a phosphate buffer solution (PBS, pH7.4) at room temperature. The water content of the membrane was calculated using the following equation:

$$\text{Water content}(\%) = \frac{Ws - Wd}{Ws} \times 100$$

where Ws and Wd represent the weight of the swollen and dry membranes, respectively.

2.4. Measurement of insulin and glucose permeation through the SPU/MPC polymer alloy membrane

Insulin permeation of the SPU/PMEH alloy membrane was carried out as follows. After the membrane was swollen in PBS, two chamber glass cells held the membrane. The effective permeation area of the cell was 0.79cm^2. Three mL of a pH3.0 aqueous solution containing 0.30mg of FITC labeled insulin (I2383, SIGMA, USA) was placed on one side of the cell and 3.0mL of a PBS (pH7.4) on the other side. Both solutions were slowly stirred. Aliquots of the buffer solution were taken out after given periods and the permeated insulin was determined with a fluorophotometer (FP-750; Jasco, Tokyo, Japan) (λex=318nm, λem=580nm). The permeation coefficient (P) was calculated from the slope of the permeation profile using Fick's first equation as follows:

$$Q = P \cdot (\Delta C \cdot A / \Delta x) \cdot t$$

where Q(g) is the amount of permeated insulin, ΔC(g/cm^3) is the difference in the insulin concentrations on both sides, A(cm^2) is the area of the membrane, Δx(cm) is the thickness of the membrane, and t(sec) is time.

The glucose permeation of the SPU/PMEH alloy membrane was carried out the same procedure for the insulin permeation experiment. Three mL of distilled water containing 9.0mg of glucose was placed on one side of the cell and 3.0mL of a PBS (pH7.4) on the other side. The permeated glucose was determined by the phenol-sulfuric acid method. The permeation coefficient (P) was then calculated.

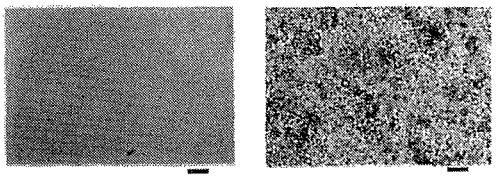
3. Results and discussion

3.1. Properties of SPU/MPC polymer alloy membrane

The polymer alloy composed of two components can effectively perform the functions of two polymers by successfully controlling the domain structure. In this study, the SPU/PMEH alloy is required to have biocompatibility and permeability.

Controlling the PMEH domains against the SPU matrix forms a high performance membrane structure having properties of the PMEH.

Fig. 3 shows optical microscopic pictures of the SPU/PMEH alloy membrane after staining with OsO_4. The polar sections in the



(a) 100μm (b) 100μm

Figure 3. Optical microscopic pictures of (a) SPU and (b) SPU/PMEH alloy membranes after staining with OsO_4.

membrane were stained. In fact, as shown in Fig. 3(b), many spots could be seen on the surface of the SPU/PMEH alloy membrane. On the other hand, there is no spot on the SPU membrane. For the SPU/PMEH alloy membrane, the hydrophilic PMEH parts were more strongly stained than the SPU part. The diameter of the spots on the surface was between 20 and 30μm. These spots corresponded to the domains of the PMEH in the SPU/PMEH alloy membrane.

To analyze the chemical composition on the SPU/PMEH alloy membrane surface, XPS measurements were carried out. Representative XPS charts of the SPU and SPU/PMEH alloy membranes are shown in Fig. 4. For the SPU membrane, the XPS signals attributed to nitrogen in -OCONH- at 402eV was observed. On the SPU/PMEH alloy membrane, a new nitrogen peak was found at 403.2eV, which was attributed to the choline group in the MPC unit. The phosphorus peak attributed to the phosphate group at 134.1eV was observed. These results indicated that the PMEH is located in the subsurface of the SPU/PMEH alloy membrane. In our previous article, antithrombogenicity was found on the SPU/MPC polymer alloy when the MPC polymer was located on the surface of the membrane [9,10]. These results from the XPS analysis and optical microscopic observations strongly suggested that the SPU/PMEH alloy membrane also effectively functions as antithrombogenic materials.

The mechanical properties of their membranes were calculated from the stress-strain curves and were summarized in Table I. The mechanical properties of silicone, which is used as a substitute of soft tissue in living organism, are summarized [11]. By comparing the mechanical properties between the SPU/PMEH alloy membrane and silicone, the SPU/PMEH alloy membrane is tough enough to use as an implant in the subcutaneous

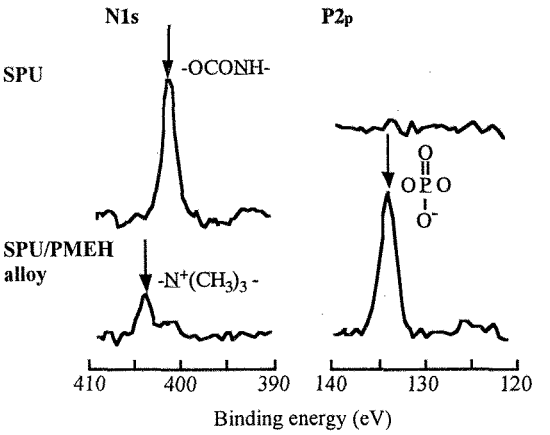


Figure 4. XPS charts of polymer membranes.

tissues.

SPU is widely used as biomedical materials because of its excellent mechanical properties. Even when the PMEH was blended with a 50% composition of SPU, the SPU/PMEH alloy had adequate mechanical properties. The chemical structure of the PMEH was designed for the molecular affinity between the EHMA unit and soft segment of the SPU.

From the measurement of the water content of membranes, the water content of the SPU/PMEH alloy membrane was 23 wt%. On the other hand, the water content of the SPU membrane was only 3wt%. Thus, the water content in the SPU/PMEH alloy membrane increased by blending the PMEH.

3.2. Solute permeation through the SPU/MPC polymer alloy membrane

In Table II, the permeation coefficients of insulin and glucose through the membranes including the SPU/PMEH alloy membrane are summarized. Permeation of both solutes through the SPU/PMEH alloy membrane was observed. On the other hand, the original SPU could not permeate both solutes. The insulin permeation coefficient of the SPU/PMEH alloy membrane was lower than that of the PMEH membrane. This means that the PMEH domains penetrate through the SPU/PMEH alloy membrane and solutes could pass through the domains. This consideration is supported by the optical microscopic observations of the membrane. The PMEH domains dispersed in the membrane were continuous through the membrane. The PMEH has a hydrophilic nature and swells in aqueous

Table I. Mechanical properties of polymer membranes

Membrane	Young's modulus (MPa)	Tensile strengh (MPa)	Ultimate elongation (%)
SPU	75	41.4	930
SPU/PMEH alloy	29	11.5	840
PMEH	15	3.6	390
Silicone rubber[11]	–	5.8 - 8.2	350 - 600

Table II. Permeation coefficient of glucose and insulin through polymer membranes

Membrane	Water content (%)	Permeation coefficient $x10^{-8}$ (cm^2/sec)	
		Glucose	Insulin
SPU	2.0	N.D.	N.D.
SPU/PMEH alloy	29	3.65	2.93
PMEH	33	22.8	7.41
SPU having hydrophilic soft-segment [12]	90	11.2	2.66
Poly (vinyl alcohol) having porous structure [13]	—	216	4.15

N.D. : Permeation was not detected.

medium. The hydrated PMEH domain prepared the permeation on pathway the solute. It is considered that water-soluble solutes can permeate through the water region of the hydrophilic polymer domain. The higher permeability of insulin and glucose was realized in the high PMEH composition.

The permeability of insulin through the polymer membrane has been discussed for application as an artificial pancreas system. Ward *et al.* [12] and Young *et al.* [13] reported the insulin permeability of a membrane that was used for encapsulating islets as a biohybrid artificial pancreas. The permeation coefficients of insulin through the hydrophilic SPU membrane and porous poly(vinyl alcohol) membrane are $2.66x10^{-8}$ cm^2/sec and $4.15x10^{-8}$ cm^2/sec, respectively (Table II). In our system, the permeation coefficient of insulin through the SPU/PMEH alloy membrane is $2.93x10^{-8}$ cm^2/sec. Taking these permeation coefficients into account, it was considered that the SPU/PMEH alloy membrane had adequate insulin and glucose permeability. On the other hand, the glucose permeability of the membrane is quite unique and strongly depended on the chemical and physical structure of polymer membrane. The reason is unclear, but it is considered that some kind of molecular interactions, such as hydrogen bonding influence the permeation.

4. Conclusion

We focused on a polymer alloy composed of SPU and MPC polymer for making a polymer membrane with good mechanical properties, permeability and biocompatibility. The SPU/MPC polymer alloy membrane was prepared by the solvent evaporation method. The SPU/MPC polymer alloy membrane could be adequately prepared with high mechanical properties. The MPC polymers formed domains inside the SPU/MPC polymer alloy membrane. The domains were connected to each other and acted as permeation pathway for the solutes. It is possible to think that the MPC polymers in the SPU/MPC polymer alloy effectively cover the membrane and reduce fibroblast adhesion. In the SPU/MPC polymer alloy, by controlling the MPC polymer domains against the SPU matrix, the SPU/MPC polymer alloy had both insulin permeability and biocompatibility. It is considered that the SPU/MPC polymer alloy membrane will be very useful in an insulin release system as an implantable reservoir. By incorporating a glucose-responsive system in the SPU/MPC polymer alloy membrane package, it appears that the SPU/MPC polymer alloy membrane could be applied to a chemically controlled insulin release device.

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