Successful Development of Biocompatible Polymers Designed by Nature’s Original Inspiration

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Abstract

Novel polymer biomaterials, which can be used in contact with blood, are prepared with strong inspiration from the surface structure of cell membranes. That is, the polymers with a phospholipid polar group in the side chain, 2-methacryloyloxyethyl phosphorylcholine (MPC) polymers were synthesized. The MPC polymers can inhibit surface-induced clot formation effectively, when they are in contact with blood even in the absence of an anticoagulant. This phenomenon was due to the reduction of plasma protein and suppression of denaturation of adsorbed proteins, that is the MPC polymers interact with blood components very mildly. As the molecular structure of the MPC polymer was easily designed by changing the monomer units and their composition, it could be applied to surface modification of artificial organs and biomedical devices for improving blood and tissue compatibility. Thus, the MPC polymers are useful polymer biomaterials for manufacturing high performance artificial organs and biomedical devices to provide safe medical treatments.

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1. Bioinspired Concept for Preparing Phospholipid Polymers

The cell membrane is a sophisticated, nanostructured separator in living organisms. The membrane is mainly composed of phospholipid molecules, which play an important role in dividing intracellular cytoplasm from the outer environment, and glycoproteins as receptor and membrane penetrate proteins are also faced on the surface (Figure 1). The phospholipids have hydrophobic alkyl chains and a hydrophilic and a hydrophilic polar group, and they are spontaneously associated as a continuous membrane in an aqueous medium. The association shows unique characteristics not only in biological
aspects but also in physicochemical functions. The favourable characteristics of the cell membrane are as follows: (i) it has the mechanical strength to keep cell morphology; (ii) it has the ability to maintain concentration of specific chemicals in the cytoplasm and (iii) it can act as a scaffold for functional membranes with proteins and glycoproteins. In living organisms, the cell membrane is also utilized as an important communication interface between cell-cell junctions. Higher-ordered associates at the nanoscale would be excellent for expressing several kinds of functions. The cell membrane structure is the most attractive candidate for the fabrication of nanostructured biomaterials, which involves bio-, nano-, and information-technologies. The phospholipid molecule is the fundamental unit in the construction of the cell membrane. In particular, one of the major phospholipid polar groups on the cell membrane is phosphorylcholine, which is an electrically neutral, zwitterionic head group. In biomimetic chemistry, phospholipid molecules have been used in the preparation of the cell membrane-like structures such as liposomes, as drug delivery carriers. However, the major disadvantage of the liposome is chemical and/or physical stability. In this review, bioinspired phospholipid polymers for biomedical applications are systematically summarized. These phospholipid polymers are not biomimetic polymers but bioinspired polymers. The bioinspired approach to nanostructured biomaterials is widely applicable in the preparation of biointerfaces, bioconjugations, and biomatrices. The phospholipid monomers and polymers were prepared with attention to the chemical structure of phospholipid molecules and researched from an organic synthesis and polymerization perspective.

2. Synthesis of 2-Methacryloyloxyethyl Phosphorylcholine Polymers

Synthesis of the phospholipid monomers was attempted; however, the purity and yield of the monomers were not enough to justify investigating them further as polymer materials. In 1990, Ishihara et al. reported the significant functions of phospholipid polymer materials in the biomedical field and successfully synthesized phospholipid monomers with higher yield and excellent purity [1]. The representative monomer, 2-methacryloyloxyethyl phosphorylcholine (MPC), is methacrylate with phosphorylcholine unit as a phospholipid polar group, whose synthetic route and chemical structure are shown in Figure 2. The MPC can polymerize and copolymerize with other vinyl compounds by a conventional radical polymerization [2]. Also, progress of polymerization science provides well-defined MPC polymer via living radical polymerization [3,4]. Most of the bioinspired phospholipid polymer
chemistry has been based on the novel phospholipid monomer; natural unsaturated phospholipid, styrene derivatives with phospholipid polar group, and methacrylate derivatives with phospholipid polar group, and has been widely examined to create many functions in living systems such as a stimuli-responsive function; recognition, processing, and transformation of outer environment. However, the amount of phospholipid monomer synthesis would regulate the research activity for application. In the case of MPC, 1 kg of the monomer could be synthesized on laboratory scale per year in 1990. In those days, the major research on MPC polymer chemistry was on the interfacial properties of MPC polymer coating. In 1999, MPC was prepared on an industrial scale [by Nippon Oil and Fats (NOF) Co., Ltd, Tokyo, Japan], and the amount of MPC produced was roughly 10 tons. Thus, recent phospholipid polymers based on MPC polymer chemistry has been recognized worldwide [5,6]. The bioinspired approach using phospholipid polymers has the potential to develop many kinds of biomaterials and medical devices.

![Chemical structure of MPC](image)

Fig. 2. Technical transfer of synthetic procedure of MPC from laboratory to industry

3. Preparation of Biocompatible Surface by Coating of the MPC Polymer

Polymer coating is a valuable surface modification technique for preparation of biomedical devices. Generally, biomedical devices are assembled from a large number of complicated parts; organs such as artificial hearts and artificial lungs are typical models. There are two processes in the coating; one is a dip coating and the other is a spin coating. In the case of dip coating, the devices are simply immersed into the polymer solution directly, and then all of the devices are available for coating (thickness of coating: 30-100 nm). On the other hand, a very nice thin coating layer is obtained by spin coating (thickness of coating: below 30 nm). The devices are spun on the spin coater apparatus, which coating process would be one of regulation for the coating treatment. In this chapter, coatings with phospholipid polymers are described in terms of interfacial characterization and biological application. Protein adsorption on a biomaterial in contact with a body fluid and blood is a regular phenomenon. The amount of protein adsorption dominates biocompatibility and blood compatibility. Therefore, surface modification is an important technique for the improvement of compatibility. Many attempts have been made, using various approaches, for example, physicochemical, interfacial chemical, biochemical, and biological. Among them, a coating with phospholipid polymers is the most effective approach not only in reducing protein adsorption but also in maintaining biological function as shown in Figure 3. The nanometer-scale
phospholipid polymer layers provided a novel bioinspired interface; the evaluation of reducing protein adsorption by the phospholipid polymer has been energetically investigated since early 1990 [7-9]. The mechanism of reducing proteins was discussed. Ishihara et al. hypothesized that the mechanism of reduction of protein adsorption was discussed in terms of water structure on the phospholipid polymer coating surface [10]. Lu et al. clearly explained the protein adsorption on the polymer surface by structure of water molecule; bound water and free water [11]. Generally, proteins and polymer surfaces have a fraction of bound water, which is shared between them. The tightly adsorbed proteins, owing to sharing bound water molecules, would be denatured by the conformational change. The water fraction of the polymer surface was evaluated using DSC to determine the level of water structure. The free water showed an exothermic peak around 0 °C, and the free water fraction was calculated to the water content in equilibrium state. In the case of 0.36 hydration [(weight of water in the polymer)/(weight of polymer saturated with water)], the MPC polymer showed 0.69 of free water fraction whereas poly(2-hydroxyethyl methacrylate) [poly(HEMA)] showed only 0.28. This result indicated that the hydrated MPC polymer had a large amount of free water fraction.

Furthermore, the highly free water surface would provide stabilization of biomolecules such as enzyme and protein, even when the biomolecules adsorbed on the surface. Ishihara et al. proved the stabilization of bovine serum albumin (BSA) by using circular dichroism (CD) spectra. In the CD spectra, the native BSA in phosphate-buffered solution (PBS) showed negative value of the mean molar residual ellipticity ($\theta$) from 205 to 250 nm [10]. The obtained molar ellipticity at 208 and 222 nm indicated the secondary structure of BSA; $\alpha$-helix structure and $\beta$-sheet structure, respectively. In the case of BSA adsorbed on the MPC polymer-coating surface, the molar ellipticity showed almost the same spectrum, which indicated native BSA. Poly(HEMA) coating surface, which showed the lower free water fraction, showed significant difference spectrum. The content of the $\alpha$-helix and $\beta$-sheet structures decreased with adsorption of protein solution. BSA adsorption on the poly(HEMA) surface (1.7 µg/cm²) was eight times that on the MPC polymer surface (0.22 µg/cm²). The adsorbed protein would be denatured by hydrophobic hydration following the adsorption of higher protein by the sharing of bound water. Due to
this, the bioinspired MPC polymer surface provided a higher fraction of free water, and the suppression of biomolecules adsorption and the stabilization of their properties were achieved.

When poly(MPC) brush surface was prepared, amount of protein adsorbed on the surface was less than 5 ng/cm² [12]. This value is less than the minimum amount of proteins, which platelets adhere and activate to induce thrombus formation.

4. Development of Artificial Organs Using The MPC Polymers

We have developed a novel artificial joint with poly(MPC) grafted onto the surface of cross-linked polyethylene (CLPE), which is used as a liner of artificial joint [13]. The poly(MPC) graft layer with 100-150 nm in thickness was formed on the CLPE surface. This layer markedly decreased the friction and the wear of CLPE, which was revealed on 7×10⁷ cycles hip simulator test. This new type artificial hip joint system (Aquala®, Japan Medical Materials) has been implanted to patients in Japan.

The other MPC polymers have been applied to develop some medical devices such as cardiovascular stent (Endeavor®, Medtronic), left ventricular assist device (EVAHEART®, Sun Medical) oxygenator (PrimO₂X®, Sorin), and soft contact lenses (Proclear®, Cooper Vision).

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References