Bioinspired phospholipid polymers for controlling biological responses on the medical devices

Kazuhiko Ishihara
Department of Materials Engineering, Department of Bioengineering, ,
The University of Tokyo, Tokyo 113-8656, Japan

Introduction: Conventional polymer materials using in the biomedical field do not have enough biocompatibility and blood compatibility; therefore, infusion of an anticoagulant is required during clinical treatments when using these medical devices, to avoid biological responses. To improve their properties, some surface modification methods using newly designed polymeric materials have been studied. One of the most effective polymers for this purpose is phospholipid polymer (2-methacryloyloxyethyl phosphorylcholine (MPC) polymer), which is prepared with inspiration from cell membrane surface. In this communication, molecular design and fundamental performance of MPC polymers are described. Moreover, improvement of the bio/blood compatibility of the medical devices using the MPC polymers to suppress unfavorable biological responses at the interface between the medical devices and living organisms are explained.

Design of phospholipid polymer biomaterials: A cell membrane is a hybrid mainly consisting of two chemical classes, phospholipids and proteins. There is no covalent bonding to bind each molecule; thus, the surface of a cell membrane is heterogeneous and dynamic. The development of new biomaterials was proposed based on mimicking a simple component present on the extracelluar surfaces of the phospholipid bilayer, namely, the phosphorylcholine (PC) group. PC is an electrically neutral, zwitterionic head group of the phospholipid head groups and inert in coagulation assays. However, mechanical property of these phospholipid membranes is not enough to make medical devices, some method for stabilization should be needed. Ishihara proposed new concept for making blood compatible polymer materials, which have good stability, and applicability using a methacrylate monomer with a phosphorylcholine group, MPC. The MPC polymers (Fig. 1) with various properties are obtained. Since the MPC polymers are useful for surface modification of substrate, some application for obtaining biocompatibility on the medical devices is also explained.

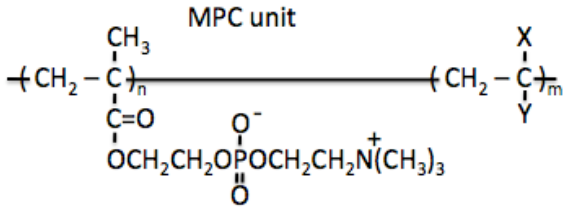

Fig. 1. Chemical structure of MPC polymer.

The synthesis of the MPC was difficult; however, in 1987, Ishihara improved the synthetic conditions for MPC dramatically and a sufficient amount of MPC with excellent purity could be obtained. In the present time, Japanese Chemical company, NOF, Co. Ltd. produces the MPC and MPC polymers in the industrial scale and provides them as not only biomaterials but also raw material for cosmetics, hear-care and eye-care items.

Application of MPC polymer for implantable medical devices:

1) Blood circulation devices. Poly(MPC-co-*n*-butyl methacrylate(BMA)(PMB)) is useful for obtaining blood compatibility. Yamazaki *et al*. prepared a blood circulation rotary-type pump made by titanium alloy (Left ventricular assist system (LVAS) : EVAHEART®). The PMB was coated on inner surface of the blood pump. A PMB-coated LVAS was implanted in goat and operated for more than 800 days without anticoagulation. The blood contacting surfaces were virtually free of thrombus. More than 80% of the pump surface area was still coated with PMB. Function of the major organs of the goat obtained from rheological study was within the normal range compared to control calves. From these results, the PMB on titanium alloy was stable and functioned well for preventing thrombosis formation even when it was contact with whole blood with very high rate. This blood circulation pump on LVAS is now implanting 18 human patients in Japan.

2) Artificial hip joint. Ishihara cooperated with Takatori and Moro have developed a novel artificial joint system with MPC polymer grafted onto the surface of cross-linked polyethylene(CLPE), which is used as a liner of artificial joint (CLPE-g-MPC). The MPC grafting on the surface of CLPE liner markedly decrease the friction and the wear. In addition, even if wear particles are produced, they are biologically inert in respect to phagocytosis by macrophages and subsequent bone resorptive actions. Furthermore, the MPC grafting can successfully inhibit the bone resorptive response to wear particles to levels similar to those of recently developed pharmacological therapies such as cytokine antagonists and osteoprotegerin. This new type artificial hip joint has been implanted to patients in Japan to obtain clinical results.

3) Other medical devices. The MPC polymers have been applied to cardiovascular stent (Endeavor®: Medtronic), oxygenator ($PrimO_2x$®: Sorin), contact lenses (Proclear®: Cooper Vision), and other medical devices, diagnosis devices and nanobiodevices.

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