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The biocompatibility of self-assembled brush polymers bearing glycine derivatives

Gahee Kim [a,1], Yecheol Rho [a,1], Samdae Park [a], Hyunchul Kim [a], Sejin Son [a], Heesoo Kim [b,**], Ik Jung Kim [b], Jung Ran Kim [c], Won Jong Kim [a,*], Moonhor Ree [a,***]

[a] Department of Chemistry, National Research Laboratory for Polymer Synthesis and Physics, Pohang Accelerator Laboratory, Center for Electro-Photo Behaviors in Advanced Molecular Systems, BK School of Molecular Science, Division of Advanced Materials Science, and Polymer Research Institute, Pohang University of Science & Technology (POSTECH), Pohang 790-784, Republic of Korea

[b] Department of Microbiology and Dongguk Medical Institute, Dongguk University College of Medicine, Gyeongju 780-714, Republic of Korea

[c] Department of Pathology and Dongguk Medical Institute, Dongguk University College of Medicine, Gyeongju 780-714, Republic of Korea

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ABSTRACT

We have synthesized brush polymers with various glycine derivatives as the end groups of their long alkyl bristles. The polymers are thermally stable up to 170–210 °C and form good quality films through conventional spin- or dip-coating and subsequent drying. Interestingly, the thin films of these brush polymers exhibit different molecular multi-layer structures that arise through the efficient self-assembly of the bristles with glycine derivative end groups. These brush polymer films have hydrophilic surfaces and exhibit some water sorption. The extent of the water sorption by these films depends upon the nature of the glycine derivatives in the bristle end. These films not only repel fibrinogen molecules and platelets from their surfaces, but also have high resistance to bacterial adherence. Moreover, the films were found to provide conducive surface environments for the successful anchoring and growth of HEp-2 cells, and to exhibit excellent biocompatibility in mice. These brush polymers have potential uses in biomedical applications including medical devices, especially blood contacting devices such as catheters, stents, blood vessels, and biosensors, due to their enhanced biocompatibility and the reduced possibility of post-operative infection.

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1. Introduction

Most conventional biomedical materials have drawbacks that vary according to their purpose and mode of action. One of the key requirements of biomaterials irrespective of their application is biocompatibility. The successful development of biomaterials having good biocompatibility could be achieved through the proper and in depth understanding of the interactions associated with biocompatibility phenomena [1].

With the aim of improving the biocompatibility of biomaterials, surface modification with established materials has recently been extensively studied [2–14]. Self-assembled monolayer (SAM) interfaces have gained wide acceptance, so this surface modification method has experienced rapid progress. Surface-initiated chemical reactions, graft polymerization on SAM interfaces, and functionalization are all employed to promote SAM formation on the surfaces of biomaterials. SAMs have been found to be very useful for achieving controlled cell responses [3,8,15–17], anti-fouling surfaces [9,18,19], and improved surface biocompatibility [12,20–23]. A large number of studies [2,10,20] have been directed toward this goal. SAMs formed from alkane thiols and other organosulphur adsorbates on gold surfaces have become a powerful and general tool for investigating the complex behaviors of organic surfaces and interfaces. However, SAMs have some drawbacks in spite of their wide applicability: they possess some structural defects due to the non-uniformity of their structure and their chemical stability [2], and these defects have to be rectified for practical applications. The major drawback of SAMs is that they cannot be used in *in vivo* systems, and thus they have been restricted to *in vitro* applications.

In this study, we synthesized brush polymers with various glycine derivatives conjugated to the parent ethylene oxide backbones via alkyl chain spacers, and evaluated their physicochemical and biological characteristics with respect to their use as

* Corresponding author. Tel.: +82 54 279 2104; fax: +82 54 279 3399.
** Corresponding author. Tel.: +82 54 770 2417; fax: +82 54 749 5538.
*** Corresponding author. Tel.: +82 54 279 2120; fax: +82 54 279 3399.
E-mail addresses: hskim@dongguk.ac.kr (H. Kim), wjkim@postech.edu (W.J. Kim), ree@postech.edu (M. Ree).
[1] These authors contributed equally to this study.

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biomaterials. The glycine was chosen as an amino acid because of its structural simplicity and, more importantly, isoelectric point of pH 6.06, hence remaining almost neutral at physiological pH. Furthermore, the incorporation of glycine derivatives into a polymer can facilitate SAM formation, as they can impart least steric hindrance during the SAM formation process by their hydrogen bonding ability. The glycine derivatives used in this study were methylglycine, dimethylglycine, and acetylglycine. We prepared biomaterials coated with these polymer solutions through spin coating onto silicon (Si) wafers and gold (Au) deposited prisms or simple dip coating onto slide glass substrates and polyethylene terephthalate (PET) sheets, and then assessed their surface wettability by using water contact angle analysis. Their water sorption ability was also investigated with ellipsometry. In addition, we investigated the thin films of the brush polymers to study their interactions with pathogenic bacteria as well as the adhesion, growth, and proliferation of HEp-2 cells. The blood compatibility of these polymers was also evaluated. For this purpose, these polymers were subjected to fibrinogen adsorption and platelet adhesion. In addition, the polymer solutions were coated onto PET discs and implanted into ICR mice to monitor the biocompatibility of these materials. Thin films of the brush polymers were found to form multi-bilayer structures, which mean that these brush polymers can accommodate functional glycine derivatives on the film surface through simple spin- and dip-coating methods and, as a result, their surface characteristics can be manipulated in a precise and controllable manner. Such surface manipulation can impart extreme diversity that makes it possible to overcome the defects of SAMs and their highly restricted applicability in *in vivo* systems. The brush polymer films have hydrophilic surfaces and some water sorption ability, and also exhibit excellent blood compatibility and biocompatibility with high resistance to the adherence of bacteria.

2. Materials and methods

2.1. Materials

All materials were purchased from Aldrich and used as received unless otherwise noted. Fibrinogen was purchased from Sigma (St. Louis, MO, USA). *Staphylococcus epidermidis* (ATCC No. 12228), *Staphylococcus aureus* (ATCC No. 6538), *Enterococcus faecalis* (ATCC No. 29212), and *Pseudomonas aeruginosa* (ATCC No. 15442) were obtained from the Korean Culture Center of Microorganisms (Seoul, Korea), and the HEp-2 cell line was received from the Korea Cell Line Bank (Seoul, Korea). ICR mice were purchased from Korea Research Institute of Bioscience & Biotechnology (Daejeon, Korea). Bacterial culture media were obtained from Difco Laboratories (Detroit, MI, USA). Cell culture media and reagents including fetal bovine serum (FBS), advanced minimum essential medium, L-glutamax and trypsin with ethylenediaminetetraacetic acid were purchased from Invitrogen (Grand Island, NY, USA). Other cell culture grade chemicals were obtained from Sigma–Aldrich (Milwaukee, WI, USA). Phosphate buffered saline (PBS; pH = 7.4) and Dulbecco's phosphate buffered saline (DPBS; pH = 7.4) were prepared as previously described elsewhere. Disposable laboratory supplies were obtained from Falcon (Franklin Lakes, NJ, USA).

2.2. Synthesis of brush polymers and film preparation

Polyepichlorohydrin (PECH) was synthesized as follows (Fig. 1). Epichlorohydrin (40 mL, 512 mmol) was cooled to −5 °C under nitrogen atmosphere. Triphenylcarbenium hexafluorophosphate (TCHP) (0.1 g, 0.256 mmol) was dissolved in dichloromethane (CH_2Cl_2) and slowly added into the epichlorohydrin at −5 °C by stirring. Thereafter, the reaction solution was further stirred at room temperature for 2 days. The obtained crude polymer was purified by precipitating several times from CH_2Cl_2 into methanol, and finally dried in vacuum at 40 °C for 12 h. Yield: 65%. Proton nuclear magnetic resonance (^{1}H NMR) spectrum (300 MHz, $CDCl_3$): δ (ppm) = 3.89–3.49 (br, 3H, OCH, OCH_2, CH_2Cl).

The obtained PECH polymer was converted to poly(oxy(11-hydroxyundecylthiomethyl)ethylene) (PECHOH) via the following reaction route (Fig. 1). The PECH polymer (3.38 g, 36.5 mmol) was dissolved together with sodium 11-hydroxyundecylthiolate (9.074 g, 39.70 mmol) in 40 mL of dimethylacetamide (DMAc) and stirred at room temperature for 1 day. Then, the reaction solution was poured into 100 mL of chloroform ($CHCl_3$), and the used DMAc solvent was eliminated by washing with water several times. The reaction solution was dried over anhydrous magnesium sulfate and filtered off. The filtrate was concentrated under reduced pressure, and poured into cold n-hexane. The precipitated white powders were filtered and then the obtained product PECHOH was dried in vacuum. The target polymer product PECHOH was obtained with 100% reaction yield. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ (ppm) = 3.70–3.59 (br, 3H, OCH, OCH_2), 2.75–2.52 (m, 4H, SCH_2), 1.57–1.13 (m, 18H, CH_2).

The hydroxyl (OH) bristle end groups of the obtained PECHOH polymer were further modified as follows (Fig. 1). The PECHOH polymer (0.80 g, 3.10 mmol OH bristle end group) was dissolved in methylene chloride (40 mL) at room temperature, and then *N*'-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (1.78 g, 9.30 mmol), *N*,*N*-dimethylaminopyridine (0.58 g, 4.56 mmol) and methylglycine (0.34 g, 3.72 mmol) was added to the polymer solution. After 72 h, the reaction solution was concentrated under reduced pressure. The concentrated reaction solution was purified by chromatography with silica using CH_2Cl_2 as an eluent and dried in vacuum, giving the target brush polymer, poly(oxy(methylaminoundecylesterthiomethyl)-ethylene) (PMUTE in Fig. 1). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ (ppm) = 4.35 (t, 2H,

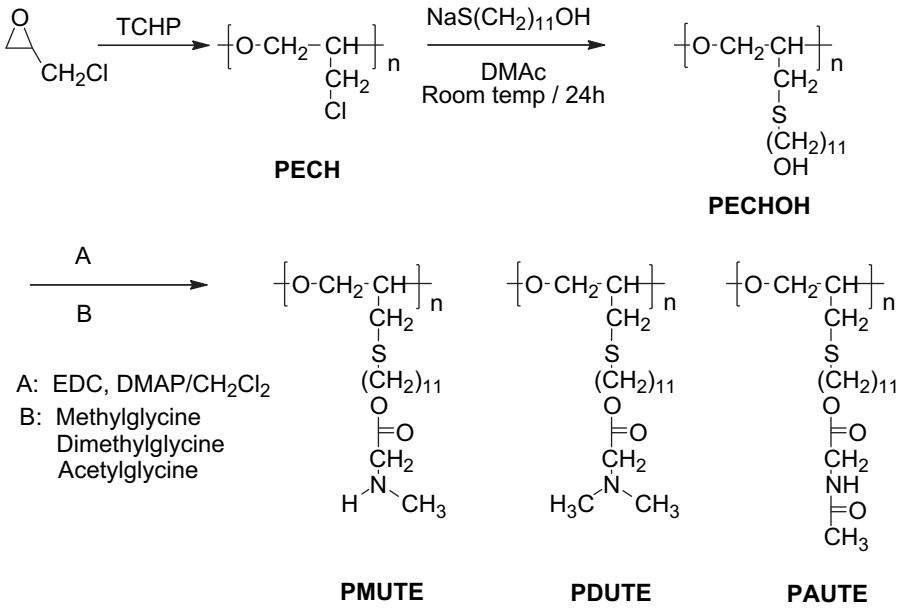

Fig. 1. Synthetic scheme of brush polymers with glycine derivatives: (a) poly[oxy(methylamino-n-undecylesterthiomethyl)ethylene] (PMUTE), (b) poly[oxy(dimethylamino-n-undecylesterthiomethyl)ethylene] (PDUTE), and (c) poly[oxy(acetylamino-n-undecylesterthiomethyl)ethylene] (PAUTE).

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