Nonfouling Polycarboxybetaine-Grafted Surfaces by Nitroxide Mediated Free Radical Polymerization

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Statement of Purpose: Engineering surfaces to enhance the biocompatibility of materials has garnered considerable attention. However, the major obstacle inhibiting their application *in-vivo* revolves around the nonspecific adsorption of plasma proteins, which ultimately dictates the general host response to these foreign materials. Leading, for example, to concomitant reactions like the initiation of the immune system, inflammatory response, and cellular uptake. This is a major clinical issue with many blood and soft tissue contacting devices, where the material-tissue interface plays an extremely important role in determining the ultimate therapeutic efficacy of the blood contacting material. Modifying these interfacial properties, mainly by covalently coupled coatings, physisorption, physiochemical treatments etc. is the most common approach for improving bio-compatibility of biomaterials. Poly(ethylene glycol) (PEG) and phosphoryl choline (PC) being the most commonly studied anti-fouling surface modifiers; surface treatments that yeild an improved blood compatibility, however the former can rapidly autoxidize in the presence of oxygen[1] and the latter is hard to synthesize.[2] Therefore, the demand is high for a stable and effective non-fouling material to address this clinical issue in order to shepherd in major advancements in bio-medical applications.

Recently, charged materials like sulfobetains and carboxybetains have been identified as providing antifouling properties to modified surfaces and render surfaces functionalizable for immobilizing bio-active elements cell-based studies.[3] But currently adopted synthesis strategies utilize hazardous transition metal catalysts that minify its role in increasing the materials biocompatibility. Herein, a new surface modification chemistry, rendering ultra-low biofouling surface behavior with functional groups suited for ligand immobilization, is presented. Zwitterionic poly(carboxybetaine methacrylamide) (PCBMA) anchored surfaces were synthesized by nitroxide mediated free radical polymerization (NMFRP) using an 'as synthesized' biocompatible initiator. This initiator can be bonded to diverse surfaces by various conjugation reactions, from which the polymer chains can grow. This seems to be an ideal method to produce multifunctional biocompatible materials.

Methods: Carboxybetaine methacrylate monomer was synthesized by reacting 2-(N,N-dimethylamino)propyl methacrylate with methyl bromoacetate at 50 ^{O}C in acetonitrile. Thus, obtained monomer ester was hydrolyzed by passing over Amberlite IRA-400 (OH) ion-exchange resin. NMFRP initiator was designed with siloxane moiety for grafting to silicon wafers for *in-vitro* biocompatibility studies. The initiator was synthesized by a two step reaction. Initially the nitroxide was prepared by reacting α-aminophosphonate, obtained from isobutyraldehyde and tert-butylamine, with m-chloroper benzoic acid. It was then coupled with freshly prepared 2-bromo-*N*-3-(trimethoxysilyl)propyl propanamide, obtained by reacting 3-(aminopropyl) trimethoxysilane and 2-bromopropionyl bromide. The nitroxide initiator was anchored onto the silicon surface and further polymerization was done in vapor phase.

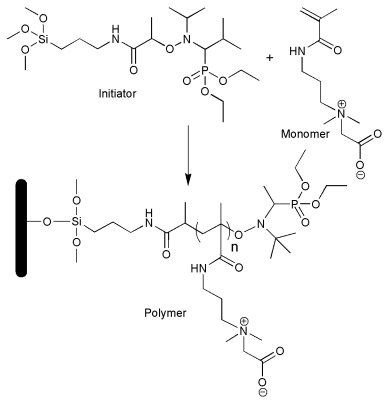

Figure 1. Surface initiated polymerization scheme.

Results: Extremely pure intermediates and compounds were obtained by synthesis and flash chromatographic purifications. All chemical compounds were characterized by NMR, IR and Mass spectroscopy. Surface modified wafers were cleaned by Soxhlet extraction overnight to remove loosely bonded physisorbed materials. The surface coverage of initiator on silicon wafer was monitored by ellipsometry. After immobilization, the ellipsometric thickness increased by 1.8 ± 0.2nm which is comparable with the initiator size. Preliminary studies have yeiled a PCBMA film thickness of ~ 30nm, after 2 hrs of polymerization. Moreover, data suggest that PBMA does not readily autoxidate.

Conclusion: A functionalizable and stable surface modification technique for biomaterials has been demonstrated. For the first time, nitroxide mediated polymerization technique was employed for grafting zwitterionic polymer chains to biomaterial surfaces.

Future Work: It is thought that the surface modified with PCBMA will be highly resistant to the non-specific adsorption of plasma proteins (human). Further work will focus upon elucidating the effect of film properties on plasma protein deposition, viz., the effect of film thickness and polymer packing density on plasma protein adsorption will be studied.

References:

1) Ostuni E. Langmuir 2001; 17(18): 5605-5620.
2) Feng W. J polym Sci Part A Polym Chem 2004; 42(12): 2931-2942
3) Zhang Z. Biomacromolecules 2006; 7(12):3311-3315