Amphiphilic Silicone Coatings for Enhanced Blood-Compatibility

Melissa A. Grunlan, Ranjini Murthy, and Brennan M. Bailey

Department of Biomedical Engineering, Material Science and Engineering Program
Texas A&M University, College Station, TX 77843-3120

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The extreme hydrophobicity of silicones causes particularly high plasma protein adsorption and subsequent thrombosis leading to reduced device efficacy and even safety.[1] In contrast, polyethylene glycol (PEG or polyethylene oxide; PEO) is a neutral, hydrophilic polymer with exceptional resistance to protein adhesion.[2] Thus, to improve protein resistance and blood compatibility of silicones, PEG-silanes have been introduced via bulk crosslinking and surface grafting. These processes involve silanization reactions of PEG-silanes containing appropriate end-functionalized silane reactive groups such as alkoxysilanes. The structure of the PEG-silane will influence its ability to prevent protein adsorption onto the surface. The exceptional protein resistance of PEG is attributed not only to its high water content but also to its high chain mobility which leads to an "exclusion effect" by which proteins are repelled from the surface and also an entropic penalty of chain compression if protein adsorption were to occur..

Novel PEG-Silanes with Siloxane Tethers. In this work, we sought to enhance chain mobility of PEG introduced into silicone in order to reduce protein adsorption. The nature of the PEG-silane spacer or tether by which the PEG segment is connected to the reactive end group will affect PEG configurational mobility and hence resistance to protein adsorption. Conventional PEG-silanes used to introduce PEG into silicones consist of a PEG segment separated from the reactive group by a short alkane spacer [e.g. propyl as for $(RO)_3Si\text{-}(CH_2)_3\text{-}(CH_2CH_2O)_n\text{-}OCH_3$)] which may limit PEG mobility. We have prepared novel linear[3] and branched[4] PEG-silanes with a siloxane tethers of varying lengths (Figure 1).

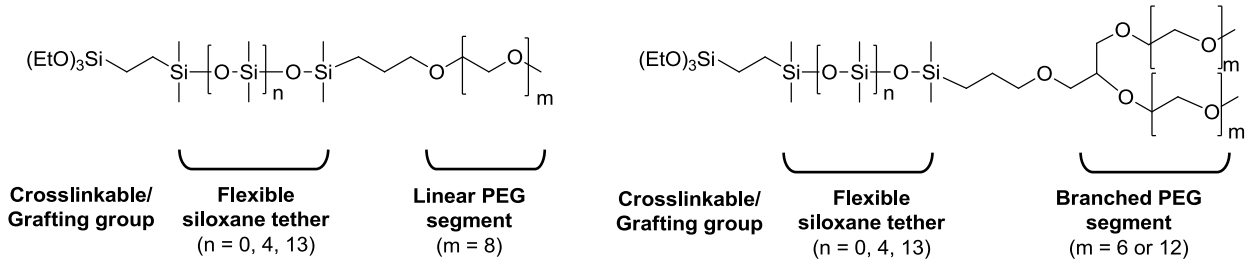

Figure 1. New linear PEG-silanes (left) and branched PEG-silanes (right) with siloxane tethers.

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Thus, the PEG segments are separated from the crosslinkable ethoxysilane group by a flexible siloxane tether. The flexibility of the siloxane tether is due to the wide bond angle (~145°) and low barrier to linearization (~0.3 kcal/mol) of Si-O-Si of dimethylsiloxanes. The dynamic flexibility of the Si-O-Si backbone produces polymers with low glass transition temperatures (T_gs) (e.g. PDMS, T_g = -125 °C).

Preparation and Characterization of Amphiphilic Silicones Prepared from PEG-Silanes. Two types of amphiphilic silicones were prepared with PEG-silanes: **(i)** bulk crosslinked coatings prepared by the *in-situ cure* of a mixture of PEG-silanes and silanol (Si-OH) terminated PDMS[3,5] **(ii)** surface grafted coatings prepared by the c*ovalent grafting* of PEG-silanes onto surfaces of silicon.[4] Bulk crosslinked coatings were prepared via the sol-gel crosslinking of mixtures of each PEG-silane and Si-OH-terminated PDMS (M_n = 3k g/mol) in a 2:3 molar ratio with 3 mol% H_3PO_4 (based on total mixture) as the catalyst. Mixtures (1 mL) were prepared atop glass microscope slides and cured at 150 °C. Surface grafted coatings were prepared by exposing clean, oxidized silicon wafers to grafting solutions comprised of a PEG-silane at a specified concentration in toluene. Chain density was calculated via measurements obtained by ellipsometry.

Surface hydrophilicity was measured via static and dynamic contact angle measurements of water droplets at the film surface at different time points. The adhesion of Alexa Fluor 555 dye conjugate of bovine serum albumin (AF-555 BSA; MW = 66 kDa) and Alexa Fluor 546 dye conjugate of human fibrinogen (AF-546 BSA; MW = 340 kDa) onto coating surfaces was studied by fluorescence microscopy. AFM analysis was performed using a MultiMode Nanoscope IIIa with Nanoscope 5.12r3 software version. The surface morphology in air was studied in the tapping mode and in water in the contact mode. Surfaces were exposed to protein solutions (0.1 mg/mL in PBS) for 3 hr both before and after conditioning the surface in PBS.

Bulk Crosslinked Amphiphilic Silicones. For silicone coatings prepared with both linear and branched PEG-silanes, surface hydrophilicity increased with increased siloxane tether length. This indicates that PEG segments were more effectively driven to the film-water interface with longer siloxane tethers (Figure 2).

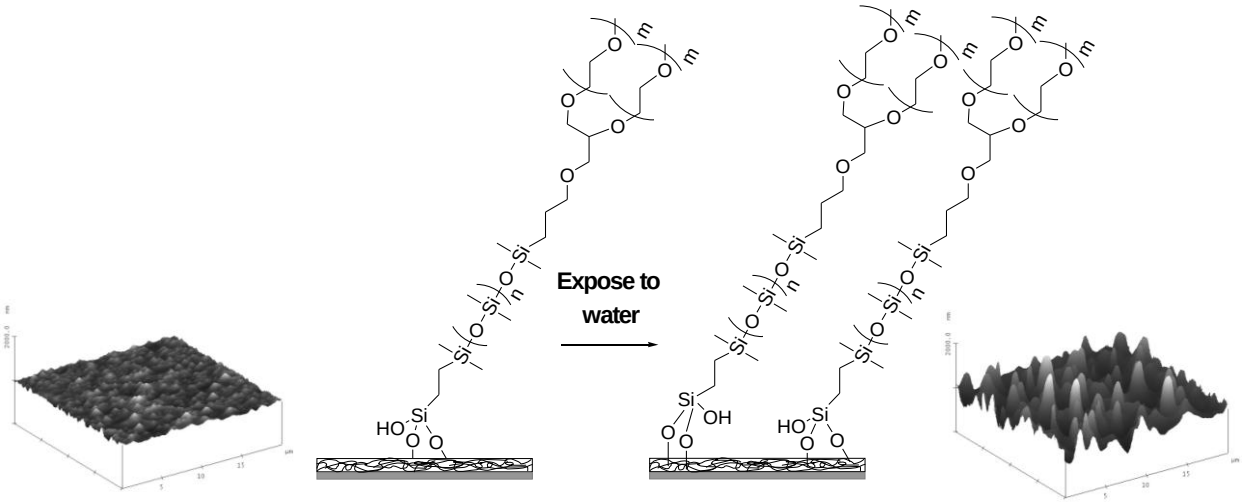

Figure 2. For bulk crosslinked amphiphilic silicones, surface hydrophilicity increased with increasing siloxane tether length, particularly after exposure to an aqueous environment, indicating that the PEG segments buried in the bulk were more readily driven to the surface. [The AFM images are shaded according to the height (z-axis) such that the higher features (PEG) are lighter and the lower features are darker].

The reconstruction of the coating surfaces upon exposure to water is evident in the AFM images (Figure 2). Protein adsorption for all amphiphilic silicones was reduced versus the pure silicone control. Furthermore, protein adsorption decreased as the length of the PEG-silane siloxane tether increased.

Surface Grafted Coatings. In the bulk-crosslinked coatings, reorganization of PEG segments in response to the environment (i.e. air or water) caused changes to the PEG surface concentration. To understand the effect of siloxane tether length on the ability of PEG segments to reduce protein adsorption, linear PEG-silanes were grafted to oxidized silicon wafer. Because the surface of the silicon wafer is stable, the surface concentration of covalently grafted PEG-silanes is conveniently maintained thereby permitting evaluation of the effect of PEG-silane structure. Surfaces were also grafted with $(RO)_3Si\text{-}(CH_2)_3\text{-}(CH_2CH_2O)_n\text{-}OCH_3$) (i.e. no siloxane tether) which served as a PEG-control. For a given PEG-silane, increased grafting solution concentration generally produced increased chain density and was increasingly more pronounced with decreased siloxane tether length. A series of grafted surfaces with similar thicknesses (h = ~4 nm) were selected to compare surface properties. Chain density [σ = chains/nm^2] increased in the order: n = 13 [σ = 1.63] < n = 4 [σ = 2.57] < n = 0 [σ = 3.23] < PEG-control [σ = 4.25]. As a result of increased PEG surface concentration and decreased hydrophobic siloxane tether length, surface hydrophilicity increased in the order: n = 13 < n = 4 < n = 0 < PEG-control. If protein adsorption was controlled by only surface hydrophilicity, one would expect that the "PEG-control" would adsorb the least amount of protein. However, we observed that protein adsorption decrease with increased siloxane tether length. Thus, enhanced configurational mobility of the PEG segments and the amphiphilic nature of PEG-silanes with siloxane tethers may contribute to the reduction in protein adsorption. The grafting of these linear PEG-silanes and also branched PEG-silanes to common biomaterials including silicones may provide enhanced blood compatibility.

References:

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