

Photografted Zwitterionic Hydrogel Coating Durability for Reduced Foreign Body Response to Cochlear Implants

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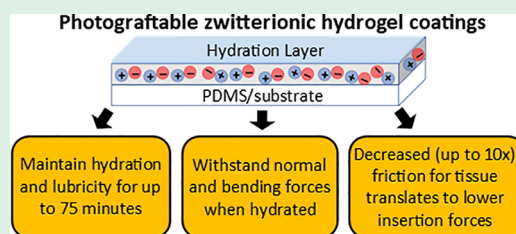
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ABSTRACT: The durability of photografted zwitterionic hydrogel coatings on cochlear implant biomaterials was examined to determine the viability of these antifouling surfaces during insertion and long-term implant usage. Tribometry was used to determine the effect of zwitterionic coatings on the lubricity of surfaces with varying hydration levels, applied normal force, and time frame. Additionally, flexural resistance was investigated using mandrel bending. Ex vivo durability was assessed by determining the coefficient of friction between tissues and treated surfaces. Furthermore, cochlear implantation force was measured using cadaveric human cochleae. Hydrated zwitterionic hydrogel coatings reduced frictional resistance approximately 20-fold compared to uncoated PDMS, which led to significantly lower mean force experienced by coated cochlear implants during insertion compared to uncoated systems. Under flexural force, zwitterionic films resisted failure for up to 60 min of desiccation. The large increase in lubricity was maintained for 20 h under continual force while hydrated. For loosely cross-linked systems, films remained stable and lubricious even after rehydration following complete drying. All coatings remained hydrated and functional under frictional force for at least 30 min in ambient conditions allowing drying, with lower cross-link densities showing the greatest longevity. Moreover, photografted zwitterionic hydrogel samples showed no evidence of degradation and nearly identical lubricity before and after implantation. This work demonstrates that photografted zwitterionic hydrogel coatings are sufficiently durable to maintain viability before, during, and after implantation. Mechanical properties, including greatly increased lubricity, are preserved after complete drying and rehydration for various applied forces. Additionally, this significantly enhanced lubricity translates to significantly decreased force during insertion of implants which should result in less trauma and scarring.

KEYWORDS: *antifouling, lubricity, fibrosis, sensorineural hearing loss, implant insertion force*



1. INTRODUCTION

Medical implants have advanced significantly in recent years, expanding capability and function.¹ In particular, cochlear implants (CIs) have increasingly been used to rehabilitate hearing loss for those who suffer from severe to profound sensorineural hearing loss. Recent advancements in “hybrid” CIs enable restoration of high-frequency hearing via electrical stimulation while preserving residual acoustic hearing in the lower frequencies in patients with only partial hearing loss^{2–4}; this electro-acoustic stimulation significantly improves hearing outcomes, particularly for complex listening tasks.^{5,6} While CIs and other neural implants provide beneficial and restorative functions, the foreign body response may impede the implant function over time and induce other deleterious effects.^{7–9} When a CI is inserted, nonspecific proteins adsorb to the surface which then recruit other proteins and cells, such as macrophages.^{10,11} One study showed that over 95% of cochleae from CI patients contained significant quantities of foreign body giant cells.¹² In some cases, phagocytosed titanium and silicone (the primary materials composing CIs) have been found throughout the body.¹³ If cells cannot digest the foreign material, a fibrous capsule is formed around the

implant. This dense tissue development around a CI can significantly impede electrical signals from reaching the target neural cells, which can dramatically reduce the hearing quality.^{14–17} Additionally, the tissue buildup and resultant scarring may even propagate fibrotic damage to more distal areas of the cochlea, resulting in partial or complete loss of residual low-frequency hearing for those with hybrid implants.^{18–22}

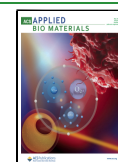
Various solutions have been proposed to inhibit or negate the foreign body response, thus enhancing the lifetime and efficacy of medical implants. One strategy is to modify the implant surface to become more like native tissue, leading to a reduction in the fibrotic response. For example, polyethylene glycol (PEG) coatings produce a more inert surface that limits binding sites for biomolecules.²³ While PEG derivatives are

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considered to be antifouling, these coatings often do not prevent deleterious long-term fibrosis effects.^{24,25} A different avenue explored for prevention of the foreign body response is the inclusion of agents such as dexamethasone, an anti-inflammatory drug, or metal nanoparticles into a coating.^{26,27} At sufficient concentrations, these additives can mitigate the foreign body response. Unfortunately, due to the relatively short delivery time frame, effectiveness for long-term, indwelling implants such as CIs is limited.

More recently, zwitterionic polymers have been explored as an alternative means to reduce the foreign body response.^{28,29} In particular, zwitterionic polymer networks swell significantly while strongly binding surface water, leading to a large decrease in protein adhesion and cellular response.³⁰ The positive and negative charges of the zwitterions readily interact with water, which causes the formation of a water layer that makes it difficult for biomolecules to interact and adhere to the surface. To take advantage of these antifouling characteristics, significant efforts have been devoted to modifying the surface of other materials using brush zwitterionic polymers. However, these brush polymers are quite thin and, as a linear polymer, lack the durability to remain viable as a coating for high-abrasion implant situations, including CI implantation. To enhance stability, cross-linker can be added to zwitterionic systems to form a hydrogel.^{31–33} These hydrogels also may lack significant mechanical stability and thus are often not suitable coatings for metal implants or those produced from stiffer polymers.^{34,35} To incorporate zwitterionic hydrogels for effective antifouling and reduced fibrosis of implants such as CIs, the stability of the coatings must be sufficient to withstand mechanical deformation during the coating process, throughout surgical insertion, and the implant lifetime.

Previous work has demonstrated that zwitterionic thin films can successfully be coated on biomaterials by simultaneous photografting and bulk photopolymerization, using Type II and Type I photoinitiators, respectively.³⁶ Photografting allows rapid and spatially controlled covalent attachment of zwitterionic hydrogels to the sample surface which significantly decreases biofouling.^{37–39} A compromise between mechanical integrity and antifouling capability was observed as a function of cross-link density for the photografted zwitterionic hydrogel thin film system.³¹ Additionally, CIs undergo bending and encounter hard tissue during implantation,⁴⁰ requiring that coatings be robust and remain attached. This work focuses on the application of zwitterionic thin films to CI biomaterials to enhance antifouling and lubricity. The durability of the photografted zwitterionic hydrogel coatings was examined during exposure to extreme but relevant conditions, including desiccation under ambient conditions, increasing normal forces, and bending. Polydimethylsiloxane (PDMS), typically the housing for electrode arrays of CIs, was coated with zwitterionic hydrogels, and lubricity was compared between coated and uncoated samples to determine if the surface properties are maintained. Durability of coated PDMS samples under bending forces and desiccation was also examined. Material properties and integrity were also determined before and after explantation to confirm long-term durability in vivo. This work demonstrates that CI biomaterials can be successfully coated with zwitterionic hydrogels that remain intact and adhered during implantation and throughout the functional lifetime of the implant.

2. METHODS

2.1. Monomer Solutions. Photoinitiator 2-hydroxy-1-[4-(2-hydroxyethoxy) phenyl]-2-methyl-1-propanone (HEPK, Sigma-Aldrich) was dissolved into deionized water to obtain an approximately 0.077 wt % solution. The two zwitterionic monomers used (chemical structures shown in Figure 1) were sulfobetaine methacrylate (SBMA,

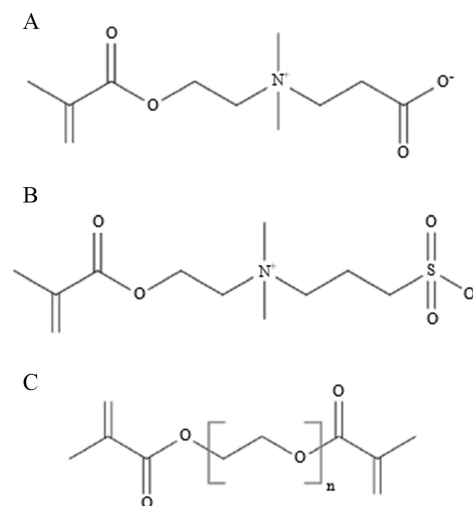


Figure 1. Chemical structures of (A) sulfobetaine methacrylate (SBMA) (B) carboxybetaine methacrylate (CMBA) and (C) poly(ethylene glycol) dimethacrylate (PEGDMA).

2-methacryloyloxy)ethyl]dimethyl-(3-sulfopropyl)ammonium hydroxide, Sigma-Aldrich) and carboxybetaine methacrylate (CBMA, 3-[[2-(methacryloyloxy)ethyl]-dimethylammonio]propionate, TCI Chemicals). Poly(ethylene glycol) methacrylate (PEGMA, 400 g/mol, Polysciences) and 2-hydroxyethyl methacrylate (HEMA, Sigma-Aldrich) were used as nonzwitterionic monomer controls. Poly(ethylene glycol) dimethacrylate (PEGDMA, 400 g/mol, Polysciences) was used as the cross-linker (chemical structure shown in Figure 1) for all monomer systems. Monomer and cross-linker were added at various ratios totaling 35 wt % of the prepolymer solution, with the remaining 65 wt % composed of the water/HEPK mixture. Monomer solutions and resultant hydrogel films are identified with the percent of the total monomer that is PEGDMA (cross-linker).

2.2. Coated Samples. Reinforced medical grade PDMS (Bentec Medical) was cut into disks (2.54 mm thick with 25 mm diameter or 0.016 mm thick with 12 mm diameter) or rectangles (35 × 75 × 1 mm). PDMS samples were soaked in a 50 g benzophenone (Sigma-Aldrich)/L acetone solution for 1 h. The PDMS samples were then removed from the solution and vacuum-dried for at least 20 min to evaporate any residual acetone. Prepolymer solution (20 μ L for 25 mm diameter disks, 5 μ L for 12 mm diameter disks, and 200 μ L for rectangles) was pipetted onto the benzophenone-treated PDMS and dispersed with glass coverslips (Fisher Scientific). The solution was then polymerized using an Omnicure S1500 lamp at 30 mW/cm² for 10 min under full spectrum light (300–520 nm) to simultaneously photograft and form the hydrogel coating.³⁶ Coated PDMS samples were placed in Dulbecco's phosphate-buffered saline solution (PBS, Gibco, Thermo Fisher Scientific) for at least 24 h to allow hydrogel coatings to swell to equilibrium.

2.3. In Vivo Implantation. To examine in vivo durability, coated and uncoated PDMS samples were implanted subcutaneously in mice for 16 days or six months and then explanted. For 16-day samples, representative images were collected using confocal microscopy, while for six-month implants, coatings were imaged using scanning electron microscopy.

Additionally, antifouling was verified by insertion of samples into the subcutaneous tissue of mice in accordance with methods approved by the University of Iowa Institute of Animal Care and Use

Committee (IACUC #1101569). Briefly, the subject was placed under 1–5% isoflurane anesthesia gauged by the pedal response, and a small incision and pocket were made in the dorsal skin, followed by insertion of the sample. The skin was closed with dissolvable sutures. After 6 weeks, the implanted sample, overlying skin, and underlying subdermal tissues were immediately removed as one specimen, following euthanasia.

The samples were then prepared for capsule analysis, as described previously.⁴¹ Briefly, the samples were fixed overnight in 4% paraformaldehyde (Sigma-Aldrich) in PBS, processed through increased concentrations of sucrose in PBS, and then embedded via Tissue-Tek OCT (Thermo Fisher Scientific) compound via flash liquid nitrogen freezing. Sections were prepared on a LEICA CryoJane system at a thickness of 20 μm to preserve tissue architecture despite the difference in compressive modulus between biological dermis and PDMS.

2.4. Tribometry. The lubricity of disk samples was evaluated using a pin-on-disk tribometer (TRB³, Anton Paar) as previously described.⁴² Typically, each sample was examined for 20 cycles (~ 8 min) at a rotational speed of 1.3 mm/s using the tribometer liquid setting while immersed in PBS. Samples were subjected to a one N normal force using a sapphire probe. A coefficient of friction curve was generated for each sample (see Figure S1A as an example), giving the mean coefficient of friction for the experimental run time. To determine the longevity of samples, coefficient of friction data were collected over 2500 cycles (~ 1000 min) for coated and uncoated samples. The values for all coated samples were normalized to those of bare PDMS (uncoated). To examine varying forces, the normal force applied for each run was varied between 1 and 15 N.

To investigate the effects of rehydration, samples were initially swollen to equilibrium followed by exposure to ambient conditions for 24 h and placed under vacuum for 10 min to achieve complete desiccation. The samples were then rehydrated in PBS for 24 h prior to testing. The coefficient of friction was determined using the tribometer and compared to control samples, which were swollen to equilibrium without desiccation. Further, to ascertain the effects during desiccation on the coefficient of friction, coated PDMS samples, initially swollen to equilibrium in PBS, were tested without additional liquid in the tribometer sample holder to allow water evaporation. The tribometer probe exerted normal forces while the coefficient of friction was measured for 90 min or until the coefficient of friction reached an asymptotic maximum value. Using the range of minimum to maximum coefficient of friction, T10 and T90 values were calculated where T10 is the time for the coefficient of friction to increase to 10% of the total range for the sample and T90 is the time to reach 90% of the range (see Figure S1B for tribometry results with T10 and T90 values indicated).

2.4.1. Tribometry Ex Vivo and after Implantation. Tissues were harvested from guinea pigs following approved methods (IACUC #9092245). Selected tissues were cut into 1 $\times$ 1 cm pieces. The explanted tissues were then used to cover a steel probe prior to tribometry, as illustrated previously.⁴² Coefficient of friction was measured between the tissues and coated-PDMS surfaces. For additional control, the coefficient of friction for dermis on dermis was measured after the dermis tissue was fixed to PDMS using tissue glue. The coefficient of friction for uncoated PDMS with each tissue was also measured. Smaller diameter (12 mm) PDMS disks, both coated and uncoated, were implanted subcutaneously in 10-week-old CBA/J mice for 3 weeks, following protocols approved by the University of Iowa IACUC. After removal from the mice, the lubricity was measured with samples immersed in PBS. For comparison, pristine samples, identical to those implanted but simply stored in PBS for the duration of implantation, were also examined.

2.5. Mandrel Bend. Flexural failure of coated rectangular samples was examined using a mandrel bending apparatus.^{43,44} All samples not containing 100 wt % cross-linker withstood failure for bending around all diameter (2–32 mm) cylinders when fully hydrated. To ascertain the effect of dehydration, samples were subjected to ambient conditions, allowing desiccation, and bent around a five mm diameter mandrel every 5 min. The time to failure indicates the time at which

cracks in the coating were observed from when samples were first removed from the PBS in the hydrated state.

2.6. Insertion Force of Cochlear Implant Electrode Arrays. SBMA thin films were coated on CI electrode arrays using a previously published method.⁴² In brief, electrode arrays were pretreated for one hour in an acetone solution with 50 g/L benzophenone, as above. After removal from the solvent and drying under vacuum, the implants were inserted into rigid cylindrical sleeves of transparent PDMS (inner diameter 0.76 mm) filled with a 10 wt % cross-linker monomer solution. To enable adequate dispersion of the hydrophilic monomer solution over the hydrophobic PDMS surface, 0.8 wt % surfactant (dimethylsiloxane-acetoxy terminated ethylene oxide block copolymer, 75% nonsiloxane, Gelest, Inc.) was included. This system was exposed to 30 mW/cm² light for 5 min in an oxygen-free environment. Following removal of the sleeve, the system was cured for an additional 10 min to ensure complete polymerization. Coated arrays were soaked in a fluorescein disodium salt solution to allow for visual comparison with uncoated arrays. Both coated and uncoated cochlear implant electrode arrays (Cochlear Slim Straight and Advanced Bionics Slim J with lengths of 23–25 mm) were inserted into human cadaveric cochleae. The cochleae were mounted on a force transducer to assess the increase in force associated with an insertion run.⁴² The raw output was reported over time for each implant.

3. RESULTS AND DISCUSSION

Hydrogels have been used extensively for a variety of biomedical applications,^{45–49} including as materials to mitigate the foreign body response.^{50–54} One major drawback of a typical hydrogel is its inherent lack of durability.^{55,56} For a hydrogel to be reliably used for in vivo applications, but especially for coatings on indwelling implant systems, sufficient mechanical long-term stability is necessary to ensure viability during implantation and for the lifetime of the coated implant.⁵⁷ Zwitterionic hydrogels photografted as biomaterial coatings have shown great promise in inhibiting the foreign body response by creation of a stable water layer, leading to greater longevity and efficacy of materials and implants. Prior work has demonstrated that zwitterionic hydrogels are quite stable, especially when chemically cross-linked, and resist degradation from environmental factors.^{58,59} Additionally, zwitterionic hydrogels, while antifouling, exhibit high degrees of biocompatibility.⁶⁰ To apply the unique characteristics of zwitterionic systems to various biomaterials and in vivo devices, the hydrogels must be sufficiently durable and maintain desirable properties throughout handling, implantation, and device lifetime. For example, CIs could greatly benefit from the antifouling capabilities of zwitterionic coatings to preserve the function of the implant and avoid the loss of residual hearing from scar tissue formation. At the same time, coatings must withstand handling prior to insertion and the normal and bending forces during insertion to be viable in this application.

To enable the use of zwitterionic hydrogel coatings, a further understanding and characterization of mechanical properties and overall stability are required. Previous work has shown that by using simultaneous photografting and photopolymerization, zwitterionic hydrogel network systems can be reliably attached to PDMS surfaces.³⁶ The housing of the electrode array for most CIs is composed of PDMS, a common biomaterial that provides an excellent case study for zwitterionic hydrogel coatings on biomaterials. Herein, properties including bending resistance, coefficient of friction, and in vitro forces were determined to understand the mechanical durability under various conditions including implantation, desiccation, in-

creased normal force, and bending of the photografted zwitterionic hydrogel coatings.

3.1. Durability of Thin Films In Vivo. To determine the attachment and film integrity of photografted zwitterionic thin film hydrogels in vivo, PDMS samples coated with zwitterionic hydrogels of varying cross-link density were subcutaneously implanted in mice. After incubation for 2 weeks or six months, samples were excised and imaged (Figure 2). Films,

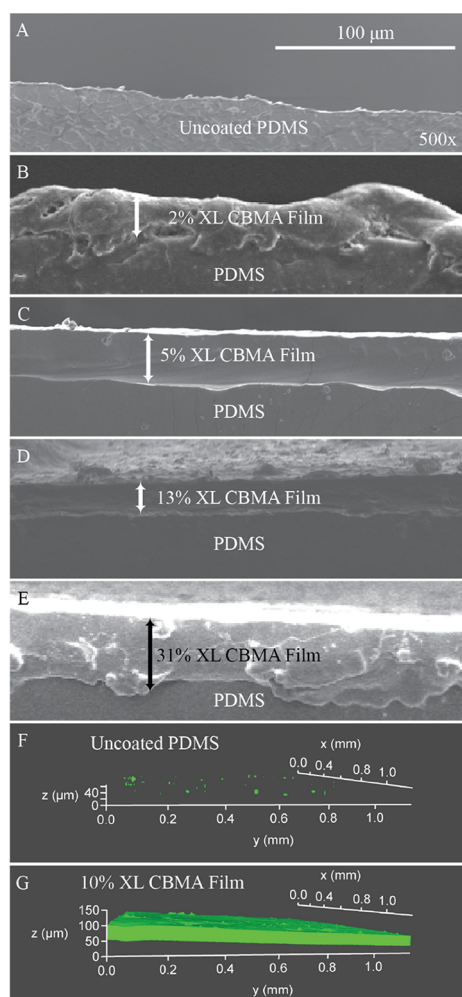


Figure 2. Scanning electron microscope cross-section images of six-month implants of (A) uncoated PDMS and (B–E) CBMA-coated PDMS with indicated cross-linker (XL) percentages. Scale bar and magnification for (A–E). Confocal microscopy z-stack images of 16-day implants immersed in fluorescein (green) are also shown of (F) uncoated and (G) 10 wt % XL CBMA-coated PDMS.

independent of cross-link density, remained intact with little to no evidence of delamination observed via scanning electron microscopy, as shown in Figure 2B–E. The films with 2 wt % cross-linker appeared to have a more irregular surface, whereas the surface of films with 5–31 wt % cross-linker was relatively smooth with uniform thickness. Confocal z-stack imaging of fluorescein-immersed samples implanted for 16 days (Figure 2F,G) also showed that thin film hydrogels incorporating 10 wt % cross-linker retained mechanical integrity without any visible defects or deformation, indicating high-level durability for handling, surgical insertion, incubation, and removal.

In addition, the antifibrotic properties of the zwitterionic coatings were evaluated. Fibrotic capsule formation around

coated and uncoated implants was measured by histology after a six-week subcutaneous incubation in mice. The fibrotic capsule thickness reported includes both the immune cell-rich interface and the collagen-rich layer immediately adjacent (Figure 3). The fibrotic response to CBMA-coated PDMS was

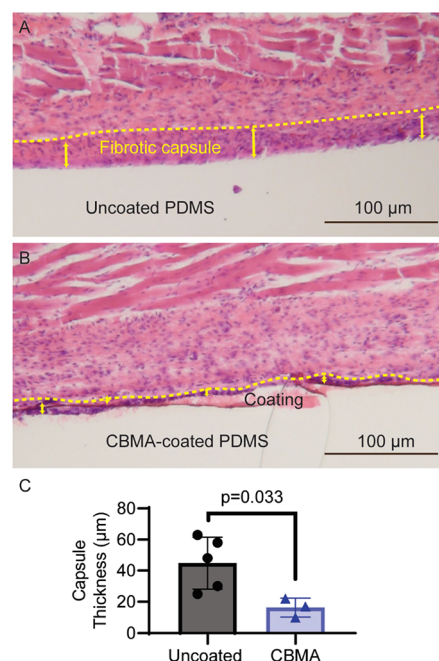


Figure 3. Hematoxylin and eosin staining of (A) uncoated and (B) CBMA-coated (5 wt % cross-linker) PDMS after 6 weeks of incubation in subcutaneous BL/6 *Mus musculus* tissue and (C) a plot of the significant ($p = 0.033$) reduction in measured fibrotic capsule thickness when comparing uncoated and CBMA-coated PDMS under the same conditions for (A, B).

over 60% less ($p < 0.05$) than the capsule for uncoated PDMS. Further, the cell-rich interface appeared to bear fewer cells, and the collagen-rich layer appeared to be almost entirely absent. Overall, short-term durability of photografted zwitterionic hydrogels in vivo and significant reduction of fibrosis were demonstrated. Additionally, recently published results for similar systems show minimal scarring and inflammation, with no evidence of degradation or loss of function, up to one year in vivo.⁴¹

3.2. Lubricity Following Implantation in Mice.

Zwitterionic hydrogels are primarily of interest as biomaterial coatings to prevent biofouling due to their ability to bind water with the charged ion groups while being net neutral.^{28,61} Another significant benefit imparted by hydrogel coatings, particularly zwitterionic hydrogels, is increased lubricity of the material surface as demonstrated by low coefficients of friction in aqueous environments.^{62–64} The significant increase in lubricity for coated surfaces should lead to less scarring and trauma during implantation but only if the coating remains stable and retains these lubricious properties. Previous work has shown that photografted zwitterionic coatings result in an approximately 90% reduction in the coefficient of friction relative to uncoated PDMS.^{31,42,65} While antifouling is largely due to chemical interactions and should remain as long as the coating is present, lubricity is more dependent on the mechanical integrity of the film. Additionally, the lubricity is reflective of the hydration state and indicative of the long-term

stability of the coating. Thus, the coefficient of friction was examined under various settings to determine both the inherent effects of different conditions on lubricity and the implications for hydration and further stability.

To determine if zwitterionic hydrogel coatings remain stable without changes in frictional resistance, coated and uncoated PDMS samples were implanted subcutaneously into mice for 3 weeks. The coefficient of friction was then determined for explanted samples and those simply stored in PBS for 3 weeks. No significant difference was observed between the pristine and explanted samples (Figure 4), demonstrating that the

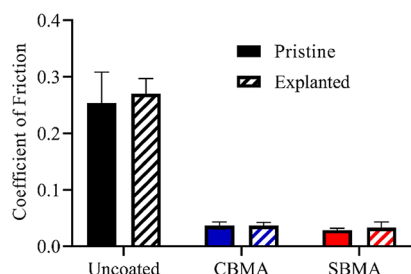


Figure 4. Coefficient of friction of uncoated, CBMA-coated, and SBMA-coated PDMS for pristine samples and samples explanted from mice after 3 weeks of incubation measured with tribometry using PBS as immersive solution and sapphire probe setup. Error bar indicates standard error of mean for $n \geq 4$.

zwitterionic hydrogels were stable and maintained integrity through implantation and explantation. Additionally, no difference was evident between implanted and pristine samples for either CBMA- or SBMA-coatings, all exhibiting approximately 90% reduction in coefficient of friction relative to uncoated PDMS. Therefore, the large reduction in frictional resistance observed for biomaterials coated with zwitterions should remain following implantation and long-term use. As lubricity is directly related to the hydration state, these results also suggest that the zwitterionic hydrogels retain similar levels of hydration following implantation. Hydration has been directly related to the antifouling capacity indicating that these materials should also have minimal interaction with biological moieties as shown elsewhere.⁶⁶

3.3. Lubricity of Coatings Relative to Guinea Pig Tissue. While enhanced lubricity could lead to less scarring in the body and serve as a useful marker for other hydration properties, the innate decrease in friction should also lead to less trauma during insertion. For many implants, the trauma from insertion may cause deleterious effects as much as, if not more than, the innate immune response from the presence of a foreign body. For example, CI implantation led to loss of residual hearing and neo-ossification in conjunction with evidence of insertion trauma for about 50% of patients over two case studies.^{67,68} One study found that hearing outcomes were improved when insertional trauma was minimized,⁶⁷ suggesting that decreasing insertion trauma with increased lubricity alone will provide great benefit. For the coefficient of friction measurements, a steel or ceramic probe is typically moved across a surface of interest, and the frictional force resisting movement is measured. Using such probes thereby results in measuring lubricity relative to steel or ceramic, not biologically relevant tissues.

To understand if the innate lubricity of zwitterionic hydrogels translates well to biological systems, the coefficient

of friction between various tissues and zwitterionic coatings was examined by covering the tribometer probe tip with various freshly excised guinea pig tissues. This modification provided a direct perspective on the effect of hydrogel coatings on the lubricity between implants and surrounding tissue, especially as might be relevant during implantation, such as the associated trauma for CIs. The coefficient of friction was examined between a variety of freshly excised guinea pig tissues and photografted 5 wt % cross-linker SBMA coatings, as well as uncoated PDMS controls, as shown in Figure 5A. The

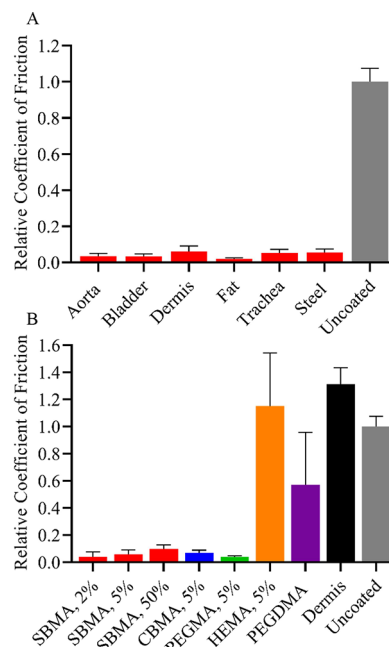


Figure 5. Coefficient of friction relative to uncoated PDMS for (A) 5 wt % SBMA hydrogel coated PDMS against various guinea pig tissues or nontissue covered steel probe and (B) different hydrogel coatings (percents are cross-linker wt %) or dermis itself against the dermis-covered probe. Uncoated PDMS value for dermis-covered probe 0.301. Error bar indicates standard error of mean for $n \geq 3$.

zwitterionic coating induced at least a 90% reduction in friction relative to uncoated PDMS for all tissues. Slightly higher coefficient of friction values were observed between the zwitterionic hydrogel and dermis and trachea tissues, similar to that observed simply with the steel probe. To determine if changes in hydrogel composition affected the lubricity with tissue, the coefficient of friction between dermis tissue and various hydrogel coatings, including SBMA with different cross-link densities and CBMA and other monomer systems with 5 wt % cross-linker, was investigated (Figure 5B). Dermis was chosen as the representative tissue, both for ease of use and because it showed the highest coefficient of friction of the tissues tested. A slight increase in the coefficient of friction was evident as the cross-link density increased for SBMA coatings, similar to trends observed in previous work for the zwitterionic hydrogel system using an uncovered sapphire probe,³¹ though the friction reduction relative to uncoated PDMS was still significant. At 5 wt % cross-linker, both CBMA and PEGMA coatings showed a similar reduction in coefficient of friction (~95%) as SBMA relative to uncoated PDMS with dermis tissue. Conversely, HEMA with 5 wt % cross-linker and PEGDMA coatings induced much higher friction, with the

highly cross-linked PEGDMA coating only reducing the coefficient of friction by about 50% and HEMA demonstrating a similar value to uncoated PDMS. Interestingly, when the dermis was tested as both probe covering and substrate, the coefficient of friction was about 30% higher than that of the dermis with uncoated PDMS, showing that the zwitterionic hydrogels dramatically reduce frictional resistance beyond what might even occur between native tissues in the body. These results also indicate that zwitterionic hydrogel coatings should reduce the friction experienced during implantation for CIs, thus significantly decreasing the trauma experienced by the surrounding tissues.

3.4. Coating Stability with Desiccation. All implants and implant materials are exposed to various forces, whether during insertion or within the body. Materials used for indwelling implants are sufficiently durable to withstand minute changes within the body, so basic properties and performance are not affected. Because hydrogels are characterized by high water content, properties will largely be determined by the degree of hydration and the surrounding environment. Therefore, loss of water will lead to significant changes in properties, such as lubricity, which could interfere with effective implantation and function. Hydrogels swell less with increasing cross-link density, which leads to an increase in some mechanical properties but is accompanied by decreased flexibility.^{31,69,70}

To examine the impact of desiccation, the lubricity of zwitterionic hydrogel coatings was investigated as a function of drying time and cross-linker concentration. Hydrogels were swollen to equilibrium in PBS. Frictional resistance was then measured immediately after removal from the solution while allowing water to evaporate in ambient conditions. To quantitatively compare when hydrogel coatings start to lose lubricity with decreased hydration, T10 and T90 values (i.e., times at which the coefficient of friction has reached 10 and 90%, respectively, of the total range of observed values; see Figure S1B) were determined. The T10 value was indicative of when the coating first began to dry/fail, whereas T90 occurred when the coating no longer imparted significant added lubricity to the coated PDMS. Both values indicate the stability of the film and give benchmarks of how long a coating remains viable while exposed to air. T10 provides information regarding the time a film could be exposed to ambient conditions without significant loss of lubricity, e.g., how long a coated CI could be removed from solution prior to implantation without significant loss of coating surface properties. T90, on the other hand, indicates when the coating becomes largely dehydrated and represents the maximum time a coating can be exposed to air to maintain any additional lubricity.

Lower cross-link density hydrogel coatings resisted failure longer than those with higher cross-link density. The films proved to be quite durable, with lubricity remaining relatively constant for extended periods of time. CBMA coatings with lower cross-link densities, which also have greater resistance to fibroblast and macrophage adhesion,³¹ showed T90 values over 60 min, whereas T90 values decreased to around 30 min with higher cross-link density films (Figure 6A). Even at higher cross-link densities, the T90 values are significantly longer than would typically be required for handling and implantation. T10 values, indicating when lubricity starts to measurably decrease, followed the same trend with shorter times at higher cross-link densities. CBMA hydrogels at low cross-link density especially

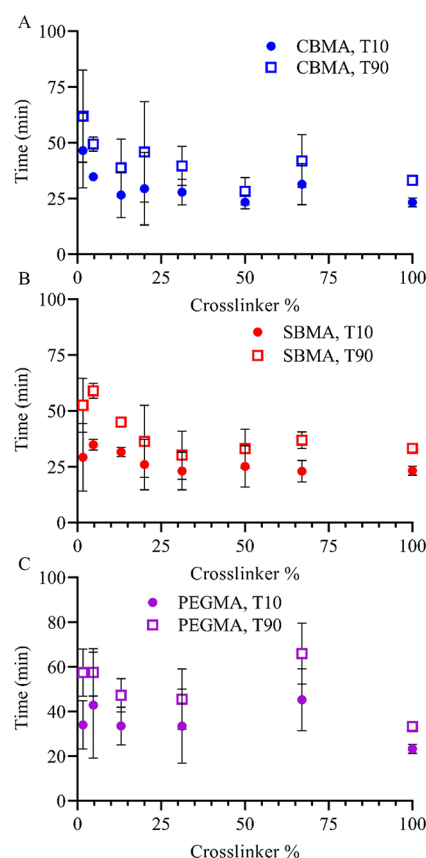


Figure 6. Time for (A) CBMA, (B) SBMA, and (C) PEGMA coatings to reach 10% (T10) and 90% (T90) of the maximum coefficient of friction value over a range of cross-link densities. Hydrogels were swollen to equilibrium in PBS prior to testing but measured without additional PBS. Error bar indicates standard deviation for $n \geq 3$.

showed marked resistance to initial desiccation (T10), likely due to the greater propensity of CBMA to bind water molecules.³⁰ The lower cross-link density films showed T10 values around 40 min, while more cross-linked films lost measurable lubricity as early as 20 min. Similarly, SBMA coatings (Figure 6B) required up to 60 min to reach the T10 threshold, again with decreasing values as the cross-linker percent increases. T10 values were comparable between the two zwitterionic thin films with CBMA remaining intact for slightly longer times at low cross-link densities. PEGMA, a nonzwitterionic hydrogel, (Figure 6C) exhibited T90 times up to approximately 60 min at lower cross-link densities. While the trend was not as consistent, PEGMA T10 values decreased with increasing cross-linker percent in the same order as the zwitterionic systems. While T10 and T90 values for PEGMA were higher than CBMA and SBMA for some cross-linker percents, the actual coefficient of friction of PEGMA-coated samples was also higher initially. For example, the initial coefficient of friction for PEGMA with 2 wt % cross-linker was 0.058 compared to 0.041 and 0.047 for CBMA and SBMA, respectively, with the same amount of cross-linker. Thus, zwitterions demonstrate the capability to retain water and decrease lubricity in ambient conditions for similar lengths of time to PEG systems while imparting a greater reduction in the overall coefficient of friction.

Many biomaterials bend during implantation or while in the body. Coatings must remain attached and withstand both

bending and normal forces to maintain the zwitterionic functionality. CI electrode arrays, in particular, undergo significant bending when inserted to conform to the coiled cochlear structure; therefore, withstanding such forces is critical for successful materials. Thus, hydrogel coatings were also examined for robustness when subjected to bending forces by using a modified mandrel bend test. Mandrel bend results overall confirmed the stability of the coatings in a hydrated state while also determining the time these zwitterionic hydrogel coatings remain hydrated and durable during bending even when exposed to air (Figure 7). For all hydrogel coatings

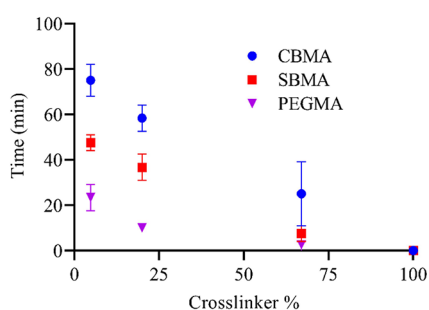


Figure 7. Time until failure was noted for hydrogel coatings when subjected to 5 mm diameter mandrel bend test for a range of cross-link densities. Hydrogel coatings were swollen to equilibrium and then exposed to air (allowed to dry) starting at time 0. Error bar indicates standard error of mean for $n \geq 3$.

except 100 wt % cross-linker (PEGDMA), completely hydrated coatings remained unaffected after bending over the range of diameters, demonstrating that insertion should not cause delamination or cracking, even at extreme angles, for swollen coatings. To quantify the effects of bending and desiccation, coatings were exposed to ambient conditions to allow for water loss. Each system was then bent around a 5 mm cylinder every five min until cracking was observed. Both CBMA and SBMA coatings displayed viability for reasonably long periods of time, especially at lower cross-link densities. With 5 wt % cross-linker, CBMA and SBMA did not exhibit signs of failure until 75 and 50 min, respectively. The time to failure for CBMA decreased with cross-linker percent, but coatings remained viable for up to 30 min even with more than 60 wt % cross-linker. In contrast to the results discussed previously, PEGMA systems behave much differently than zwitterionic systems when exposed to bending forces under desiccation. The PEGMA samples failed at least 25 min earlier than SBMA and 50 min earlier than CBMA at low to intermediate cross-linker percents, showing greater water binding and hydration by zwitterionic coatings. Sufficient hydration is key in allowing hydrogels to remain viable under bending forces, providing another example of the advantages of zwitterion coatings over PEG systems, which retain less water over time. The neat cross-linker (PEGDMA) hydrogel failed upon bending when still in the equilibrium hydration state.

3.5. Lubricity before and after Desiccation. The effects of complete desiccation on the coefficient of friction were also investigated. Through handling before implantation, hydrogel coatings may become desiccated. To determine the level of recovery from such situations, the integrity of the film and lubricity were analyzed after drying and rehydration with different cross-linker concentrations using the coefficient of friction for SBMA hydrogel coatings with different amounts of

cross-linker. Samples were completely desiccated before being rehydrated to the equilibrium state, whereas typically coatings are hydrated to equilibrium directly following polymerization. For coatings containing less than 25 wt % cross-linker, the coefficient of friction was basically identical between the desiccated/rehydrated and pristine samples, demonstrating that lower cross-link density zwitterionic coatings are sufficiently stable to undergo desiccation without loss of lubricity and integrity, as shown in Figure 8. As the cross-linker

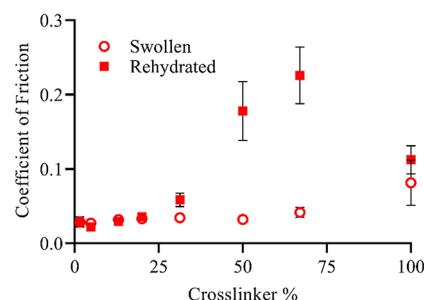


Figure 8. Coefficient of friction for SBMA hydrogels as a function of the cross-linker percent in swollen state immediately after polymerization and following complete desiccation and rehydration. The value for uncoated PDMS error bar indicates standard error of mean for $n \geq 4$. Uncoated PDMS had an average value of 0.179.

percent increased, flaking of the coating was observed during the desiccation period, which was reflected in greatly increased frictional resistance following rehydration, demonstrating a disparity between rehydrated and pristine samples. At higher concentrations of cross-linker, the rehydrated samples exhibit coefficient of friction values similar to that of uncoated PDMS. Qualitatively, these higher cross-linked coatings were quite fragile when dried with almost complete failure and little coating remaining when the sample was rehydrated in PBS, suggesting that the rehydrated sample was primarily uncoated PDMS. Even though the zwitterionic coatings swelled much more at lower cross-linker percents,³¹ desiccation and rehydration did not damage the hydrogel network. On the other hand, for intermediate to high cross-link densities, the coatings were brittle and did not exhibit sufficient integrity during rehydration.

Although the PEGDMA (100 wt % cross-linker) film displayed an increase in the coefficient of friction following dehydration, the difference was not as great as for the highly cross-linked zwitterionic films. This difference can be attributed to lower initial swelling (due to the absence of zwitterionic moieties), which does not induce as much of a physical change upon complete desiccation, leading to the peak for the coefficient of friction of rehydrated films occurring at 67 wt % cross-linker. Thus, at lower cross-link densities, the zwitterionic network is much more flexible, even with water removal and rehydration. Samples without cross-linker displayed a much higher coefficient of friction after initial swelling relative to other SBMA coatings with no significant change noted after drying and rehydration. These results provide a range of cross-linker percents for zwitterionic coatings that are sufficiently stable to maintain film integrity and high lubricity even if desiccation does occur at some point following the coating process. While more loosely cross-linked films do show the ability to rehydrate and maintain lubricity if

not stressed in other ways, desiccated coatings did fail if exposed to bending or normal forces.

3.6. Long-Term Lubricity. While desiccation will affect utility before implantation, the stability of the coating must also be maintained for the lifetime of the implant. Some implants may be intended for short-term use, but many implants, including CIs, are intended to be permanent. For zwitterionic coatings to be viable material components, they must match the longevity of the coated implant. To ascertain the effect of implant duration on zwitterionic hydrogel coatings, the coefficient of friction as a function of cross-link density was measured for SBMA-coated PDMS using tribometry over 2500 cycles equating to nearly 17 h under force. The average coefficient of friction for the first and last hundred cycles, corresponding to approximately 40 min of measurement, was compared to show the difference in surface properties under constant load. Figure 9 demonstrates that the

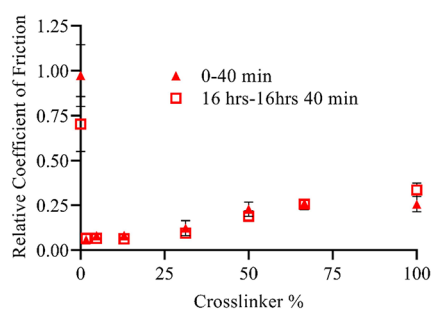


Figure 9. Average coefficient of friction (relative to uncoated PDMS) for the first and last 100 cycles of a 2500 cycles test of SBMA-coated PDMS as a function of cross-linker percent. The cycle time equates to a total testing period of 1000 min, with sampling occurring over the first and last 40 min. Error bar indicates standard error of mean for $n \geq 4$. Average coefficient of friction of for uncoated PDMS was 0.197.

coefficient of friction relative to PDMS remained stable over extended time frames for SBMA coatings across the range of cross-link densities, with no statistical difference between the first and last 100 cycles. Some degree of cross-linking is necessary to withstand the force applied during tribometry, as without cross-linking the grafted polymer did not significantly increase lubricity compared with an uncoated PDMS surface. Although this brush-like coating did appear to become somewhat more lubricious over time, this anomaly is likely due to the uncross-linked coating failing and covering the probe tip, leading to a slight decrease in the coefficient of friction. Conversely, even with higher amounts of cross-linker, the initial and final coefficient of friction values of zwitterionic coatings were not significantly different showing high degrees of durability for a prolonged time. A slight, though statistically insignificant, increase in the coefficient of friction was observed for 100 wt % PEGDMA samples from repeated loading.

3.7. Coefficient of Friction with Different Applied Normal Force and Speed. Additionally, the effect of probe speed was investigated to determine if the insertion rate would impact stability (Figure S2). No significant difference was noted in the measured coefficient of friction with an increasing speed from 1 to 6 mm/s of the applied force from the probe tip. For most implants, the greatest movement will be experienced during insertion. Kontorinis et al. reported that as the insertion rate was increased from 0.17 to 3.3 mm/s for standard CIs, both mean and maximum force also increased

following a roughly linear trend.⁷¹ Because the coefficient of friction appears to remain approximately the same even at higher probe speeds, the zwitterionic hydrogel may negate the force differences due to the insertion rate, further reducing the trauma experienced.

A third factor, along with duration and speed, which may impact the durability of the hydrogel coating is force magnitude. Variable forces will be encountered during implantation and in the body. While some biomaterials are intended for short-term use, such as catheters, many are intended to be permanent. Thus, the implant life can vary widely as well as how the implant interacts with the body once implanted. Implants may go through repeated interaction with harder surfaces, such as bone, and must be sufficiently durable to withstand such challenges for the life of the implant. An increase in force will typically increase the coefficient of friction for hydrogel coatings. At critical forces, the coating will fail and delaminate from the surface, as indicated by the coefficient of friction approaching that of the uncoated substrate.

The effect of increasing force was quantified by the determination of the coefficient of friction for SBMA coatings with 5 wt % cross-linker, a composition that has demonstrated an appropriate balance between biological efficacy and mechanical properties.³¹ As shown in Figure 10, a nearly

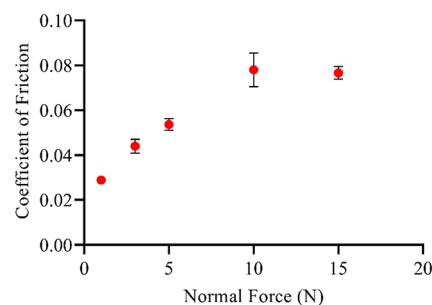


Figure 10. Coefficient of friction for SBMA hydrogels (5 wt % cross-linker) with increasing normal force applied. Uncoated PDMS value for normal force 1 N 0.19. Error bar indicates standard error of mean for $n \geq 4$.

linear increase in the coefficient of friction was observed up to 10 N, raising the coefficient of friction by 250%. Even with greater normal force, the coatings still maintained a coefficient of friction much lower than that of uncoated PDMS. Qualitatively, the hydrogels showed few, if any, noticeable defects at low normal force. At higher forces, however, the wear track became visible after tribometry was completed.

Previous research has shown the linear relationship between normal force and frictional force, particularly for skin tissue.⁷² Thus, as expected, the increase in normal force applied to the zwitterionic hydrogel coatings led to greater coefficient of friction values. Even with a 15 N normal force, the coefficient of friction values remained well below those of uncoated PDMS. While PDMS did not experience as significant of an increase in the coefficient of friction over the range of forces, the coefficient of friction for the zwitterionic hydrogels was consistently less than half that of PDMS for the entire force range. Notably, at higher forces, wear tracks developed in the hydrogel coatings, indicating some loss of integrity. However, these results should not affect CI usage since maximum forces during CI implantation range between 0.18 and 0.42 N.⁷¹ The majority of implants, similarly, should not experience forces

anywhere near this magnitude. On the other hand, the effect of increasing force should be considered, especially if used in load-bearing implants.

3.8. CI Insertion Force with Zwitterionic Coatings. As demonstrated, zwitterionic hydrogels impart increased lubricity and exhibit significant durability under a variety of conditions. During CI implantation, insertional and frictional forces from interactions with the PDMS housing of the CI are transferred to the surrounding tissue,^{40,73} leading to trauma and scarring. With the decreased frictional resistance from the coatings, it is reasonable to believe that insertional forces should also decrease with zwitterionic coatings. Zwitterionic hydrogels were coated on CI electrode arrays by using simultaneous photografting and photopolymerization, as described earlier. As evident by visualization using a fluorescein dye, the hydrogel coated the CI uniformly (Figure 11).



Figure 11. Representative image of uncoated (top) and hydrogel-coated (bottom) cochlear implant arrays. The coated array was soaked in a fluorescein solution for better visualization.

To determine if these zwitterionic hydrogel coatings impact insertional forces in biological tissues, the force required to implant both coated and uncoated CI lateral wall electrode arrays into cadaveric human cochleae was investigated, which should be indicative of the forces experienced by the surrounding tissue during implantation. Figure 12 shows representative insertion force profiles as a function of insertion time for both SBMA-coated and uncoated electrode arrays from two different manufacturers. Videos showing the insertion of both coated and uncoated arrays can be found in the Supporting Information. For array type I, the measured force for the uncoated array began to rapidly increase about halfway through the insertion with a maximum value of around 90 mN. On the other hand, the coated array type I experienced a gradual increase to a maximum force of only around 25 mN (Figure 12A). The type II uncoated array required increased force from the onset with a maximum of around 45 mN, while the coated array reduced the required force to approximately 35 mN (Figure 12B).

The maximum force for each implantation was also determined, as shown in Figure 13. For both array types, a significant reduction ($\sim 30\%$) in the maximum insertion force was observed between the uncoated and coated samples (Figure 13A). Array type 2 coated systems experienced about 20 mN less force consistently over the entire insertion time than the uncoated implant (Figure 13B). On the other hand, array type 1 coated systems showed no significant change in force for about the first half of insertion but maintained a low

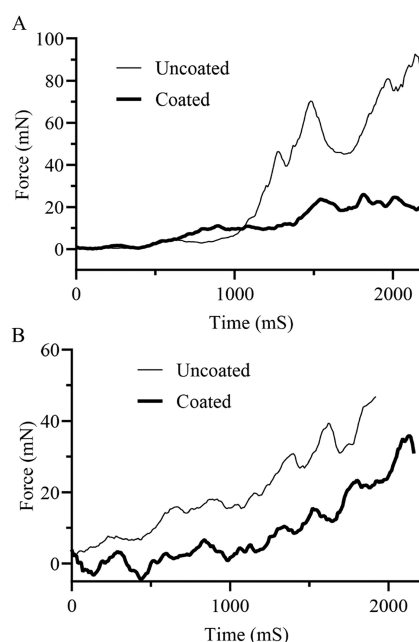


Figure 12. Representative force insertion profiles for uncoated and SBMA-coated electrodes depicted over the course of electrode insertion, wherein the lower maximum force and lower overall force over time can be seen for two manufacturers: (A) Array Type 1 and (B) Array Type 2.

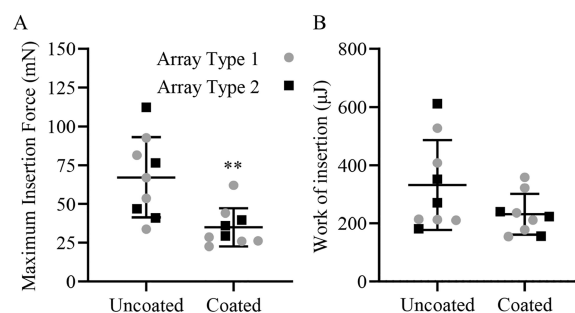


Figure 13. (A) Maximum force of insertion during insertions of uncoated ($n = 9$) and coated ($n = 9$) human electrode arrays. (B) Area under the curve analysis of the force over the average distance of insertion was found for insertion and averaged as a correlative measure of total work of insertion depicted in microjoules (μJ). The maximum force was significantly reduced ($**p < 0.003$) and overall work of insertion tended to be reduced, though this was not significant ($p = 0.19$).

force relative to an approximately 40 mN sharp increase for the uncoated array during the second half of the implantation (Figure 13A). The work of insertion was calculated using the area under the force curve for both array types, comparing uncoated and SBMA-coated implants. A decrease in the work was also observed, although the values did not statistically reflect a significant difference for coated and uncoated arrays due to high variability, especially from the uncoated systems (Figure 13B). Interestingly, the overall deviation in both work and maximum force is substantially lower for coated versus uncoated arrays. The cochleae experienced at least a 50% reduction in the maximum insertion force and a 30% reduction in the work of insertion for SBMA-coated implants relative to those of uncoated systems (Figure 13). The difference in insertion force was also observed qualitatively, as seen in the videos in the Supporting Information. Less force and

manipulation were required with the coated arrays which should result in less trauma to the surrounding tissue. This decrease in insertional force would likely lead to substantially reduced scarring and trauma during implantation and thereby improved outcomes. Less dense or minimal scar tissue surrounding the implant may allow significantly improved signal transduction for CI systems leading to higher-quality long-term hearing.

4. CONCLUSIONS

To successfully reduce the foreign body response to CIs or other biomedical implants, photografted zwitterionic hydrogel coatings must remain intact and viable during implantation and the implant lifetime. This work demonstrates that zwitterionic hydrogel coatings on PDMS are sufficiently stable to withstand desiccation and both bending and normal forces. The coatings stayed attached and intact following implantation. Zwitterionic hydrogels remained hydrated, flexible, and durable for up to 80 min under both normal and bending forces when allowed to desiccate in ambient conditions. The frictional resistance between zwitterionic coatings and biological tissue was up to 20 times lower than that with uncoated PDMS, even after implantation in mice. Insertion of cochlear implant electrode arrays into cochleae showed that friction forces can be dramatically reduced when coated by zwitterionic hydrogels. These results clearly show that photografted zwitterionic hydrogel coatings on PDMS are sufficiently durable to be practically used for an array of biomedical implants and devices, including CIs, leading to a potential reduction in both trauma during implantation and the long-term foreign body response.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsabm.4c00156>.

Representative tribometer curves for samples that are (A) hydrated and (B) undergoing desiccation with a visual representation of T10 and T90 values; coefficient of friction for varying test speeds (PDF)

Insertion of uncoated cochlear implant electrode array into explanted cochleae (MP4)

Insertion of coated cochlear implant electrode array into explanted cochleae (MP4)

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Notes

The authors declare no competing financial interest.

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