



Boundary mode lubrication of articular cartilage with a biomimetic diblock copolymer

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We report the design of a diblock copolymer with architecture and function inspired by the lubricating glycoprotein lubricin. This diblock copolymer, synthesized by sequential reversible addition–fragmentation chain-transfer polymerization, consists of a cationic cartilage-binding domain and a brush-lubricating domain. It reduces the coefficient of friction of articular cartilage under boundary mode conditions (0.088 ± 0.039) to a level equivalent to that provided by lubricin (0.093 ± 0.011). Additionally, both the EC₅₀ (0.404 mg/mL) and cartilage-binding time constant (7.19 min) of the polymer are comparable to purified human and recombinant lubricin. Like lubricin, the tribological properties of this polymer are dependent on molecular architecture. When the same monomer composition was evaluated either as an AB diblock copolymer or as a random copolymer, the diblock effectively lubricated cartilage under boundary mode conditions whereas the random copolymer did not. Additionally, the individual polymer blocks did not lubricate independently, and lubrication could be competitively inhibited with an excess of binding domain. This diblock copolymer is an example of a synthetic polymer with lubrication properties equal to lubricin under boundary mode conditions, suggesting its potential utility as a therapy for joint pathologies like osteoarthritis.

lubricin | biomimetic | boundary mode lubrication | osteoarthritis

As the primary bearing surface, articular interfaces exhibit remarkable tribological function over decades of use (1). The impressive lubricity and durability of articular cartilage has inspired the design of synthetic macromolecules that mimic the architecture of lubricating biomolecules (2–9). However, very few synthetic polymers achieve lubrication comparable to endogenous articular surfaces, strongly supporting the need for new synthetic materials that rival the efficacy of natural materials. Here, we report the design and synthesis of a diblock copolymer with substantial lubrication capacity whose architecture is inspired by the structure of lubricin, a natural glycoprotein that lubricates joints under boundary mode conditions (i.e., high normal load and slow speed).

Lubricin is a glycosylated protein found in synovial fluid (10) which plays a pivotal role in joint boundary mode lubrication (11, 12) and the prevention of osteoarthritis (11, 13, 14). Lubricin reduces the coefficient of friction (COF) of articular cartilage under boundary mode conditions by as much as 70% (12). The potent lubrication arises from its structure: a central mucin-like domain to attract and retain water and a cartilage-binding domain at the C terminus to affix the molecule to the cartilage surface (15). This architecture of lubricin is crucial to boundary mode lubrication of articular cartilage, as denaturation in either domain of lubricin causes partial or complete loss of lubrication capability (15, 16). We defined the design criteria for a synthetic boundary mode lubricant inspired by lubricin's architecture: a diblock copolymer consisting of a large lubrication block ($M_n \sim 200$ kDa) to mimic the mucin-like domain of lubricin and a small cartilage-binding block ($M_n \sim 3$ kDa) to mimic the C-terminus domain (Fig. 1). The lubrication domain of the diblock copolymer

is made of a polyacrylic acid (pAA) backbone with polyethylene glycol (PEG) brushes, which enables the polymer to retain water and to resist compression. The binding domain is made of a pAA backbone decorated with quaternary ammonia groups to non-specifically interact with negatively charged cartilage surface components such as aggrecan. Applying this polymer to lubricin-deficient bovine articular cartilage in PBS resulted in a significant reduction in COF under boundary mode conditions.

Results and Discussion

The diblock copolymer was synthesized in three steps, as shown in Fig. 2. Starting with RAFT (reversible addition–fragmentation chain-transfer) polymerization of 2-(dimethylamino)ethyl acrylate, a precursor “prebinding” domain was produced (17). Subsequent RAFT polymerization of poly(ethylene glycol) methyl ether acrylate (M_n 480), using the “prebinding” domain as the macroinitiator, added the lubrication domain to the copolymer. Finally, the tertiary amines in the “prebinding” cartilage-binding domain precursor were converted to quaternary by treatment with an excess of ethyl bromide to give the final product [$M_n \sim 200$ kDa, polydispersity index (PDI) = 1.6].

To evaluate the polymer as a synthetic boundary mode lubricant we assessed its tribological characteristics using a custom-built tribometer (18). Cartilage samples were obtained from the patellofemoral groove of neonatal bovine stifles and incubated in

Significance

Lubricin is a glycoprotein that protects cartilage in weight-bearing joints under boundary mode conditions, which defines the conditions under which physical cartilage damage takes place. The natural expression of lubricin decreases with age, and when the joint is damaged. Replacement of lubricin by intraarticular injection reestablishes boundary mode lubrication and can protect against osteoarthritis. However, the manufacture of lubricin is difficult. We set out to create a synthetic mimetic of lubricin by mimicking its structure and functional composition. The result is a diblock copolymer that reduces the coefficient of friction on cartilage, under boundary mode conditions, to a level equivalent to native lubricin. This paper reports coefficients of friction in a boundary mode system that are equivalent to lubricin.

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Conflict of interest statement: Z.S., L.J.B., and D.P. are listed as inventors on a patent filing. The patent is not yet issued and the patent is not licensed to any entity.

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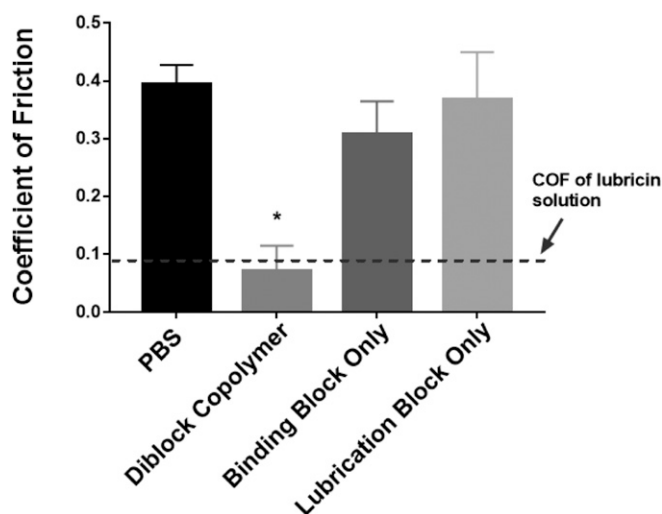


Fig. 3. The lubricin-mimetic diblock copolymer significantly decreases COF of articular cartilage compared with samples treated with PBS, binding block only, or lubrication block only (* $P < 0.0001$). Dashed line represents COF of samples tested in recombinant human lubricin solution at 50 $\mu\text{g/mL}$ (12). One-way ANOVA was used to determine the statistical difference among the tribological results associated with the polymers in solution and the controls on articular cartilage.

synthetic lubricants using pristine mica surfaces. However, while these materials lubricated the mica surface, the physiological relevance of the results is unknown. Grinstaff and coworkers (7) reported a more physiologically relevant polyanionic biolubricant that performs similar to synovial fluid in an ex vivo human cartilage mode. By mimicking the structure of hyaluronic acid, this polymer reduced the friction at the interface of cartilage and demonstrated its potential in joint lubrication as a new type of viscosupplement. In our previous work, an analog of bottle-brush polymers with a mucin-like structure successfully lubricated articular cartilage under boundary mode condition with COF ranging from 0.140 ± 0.024 to 0.248 ± 0.030 , and binding time constants ranging from 20 to 39 min (24). However, the cartilage binding mechanism(s) that led to these results were unclear and the low binding limited their further application. Elisseff and coworkers (25) cleverly bound cartilage-binding peptides to hyaluronic acid to facilitate its close interaction with tissue surfaces to induce lubrication. Most recently, Benetti and coworkers (26) reported the protection of cartilage from enzymatic degradation through the covalent linkage of cyclic polymer grafts to the cartilage surface.

In this work, where both key lubrication characteristics are engineered into the lubricant by adopting a diblock architecture that facilitates binding and localization of the polymer to the cartilage surface, we show the importance of polymer architecture to lubrication. The diblock copolymer with its lubricin-mimetic structure successfully lubricates articular cartilage surfaces in the boundary mode as effectively and efficiently as natural lubricin. This work demonstrates the importance of the polymer architecture to its tribological properties and the necessity for the coexistence of binding and lubrication blocks for effective lubrication under these conditions. This approach toward the molecular design of boundary mode lubricants could serve as a guide for future synthetic lubricants with even greater efficacy.

Materials and Methods

All chemicals were purchased from Aldrich or Fisher at the highest purity grade. All monomers were purified by a column filled with aluminum oxide (base or neutral) before use. The ^1H NMR spectra were performed on an

Inova 400-MHz spectrometer with deuterated chloroform or deuterium oxide as the solvent. Broad or overlapping peaks, noted in spectra of polymers, are denoted "br." Degree of polymerization was determined by initial monomer to CTA ratio and monomer conversion. Gel permeation chromatography (GPC) was performed with phosphate buffer saline (pH 7.4) at a flow rate of 0.8 mL/min. The eluent flowed through a Waters gel permeation chromatography system equipped with three Waters Ultrahydrogel columns in series (2,000 Å, 500 Å, and 250 Å) at 30 °C. The molecular weights were measured relative to poly(methacrylic acid), sodium salt standards (1,670–110,000 g/mol). DMAEA = 2-(dimethylamino)ethyl acrylate, ACPA = 4,4'-azobis(4-cyanopentanoic acid), CPADB = 4-cyano-4-(phenyl-carbonothioylthio)pentanoic acid, and PEGMEA = poly(ethylene glycol) methyl ether acrylate, $M_n = 480$. $R = -C(\text{CH}_3)(\text{CN})\text{CH}_2\text{CH}_2\text{COOH}$ and $R' = -S(\text{C} = \text{S})\text{Ph}$.

Synthesis of PDMAEA₂₄. DMAEA (4.30 g, 30 mmol) was added to a solution containing ACPA (14.0 mg, 0.05 mmol) and CPADB (139.5 mg, 0.5 mmol) in 5 mL of anisole. The mixture was deoxygenated by five freeze–vacuum–thaw cycles before it was heated to 70 °C with stirring for 48 h. The reaction was then quenched by liquid nitrogen freezing, and the polymer gel was precipitated by the addition of 20 mL of hexane and vigorously stirring for 30 min. After decanting the solvent, the residue was redissolved in 5 mL of dichloromethane and precipitated after addition of 20 mL of hexane and vigorously stirring for 30 min (process was repeated four times) to yield a gel (1.68 g, 39% yield); ^1H NMR (400 MHz, CDCl_3): δ 4.13 [br, 2H, $-(\text{C} = \text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 2.55 [br, 2H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}(\text{CH}_3)_2$], 2.31 [br, 7H, $-\text{N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{C} = \text{O})-$], 2.02–1.36 [m, 2H, $-\text{CH}_2\text{CH}(\text{C} = \text{O})-$], 5.30 (s, residue dichloromethane).

Synthesis of PDMAEA₂₄-PEGMEA₄₀₀ (Diblock Copolymer). PEGMEA (3.46 g, 7.2 mmol) was added to a solution containing PDMAEA₂₄ (30.9 mg, 0.009 mmol) and ACPA (0.5 mg, 0.0018 mmol) in 6 mL of anisole. The mixture was deoxygenated by five freeze–vacuum–thaw cycles before it was heated to 65 °C with stirring for 8 h. The reaction was then quenched by liquid nitrogen freezing, and the residue polymer gel was precipitated by addition of 20 mL of hexane and vigorously stirring for 30 min. After decanting the solvent, the residue was redissolved in 5 mL of dichloromethane and precipitated by addition of 20 mL of hexane and vigorously stirring for 30 min (process repeated four times) to yield a gel (1.68 g, 48% yield); ^1H NMR (400 MHz, CDCl_3): δ 4.13 [br, 2H, $-(\text{C} = \text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.75–3.44 (m, 34H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$), 3.35 (s, 3H, $-\text{O}-\text{CH}_3$), 2.24 [br, ~1H, $-\text{CH}_2\text{CH}(\text{C} = \text{O})-$], $-\text{N}(\text{CH}_3)_2$], 1.93–1.26 [m, 2H, $-\text{CH}_2\text{CH}(\text{C} = \text{O})-$], 5.30 (s, residue dichloromethane). The resulting polymer was characterized by GPC using the method described above: $M_n = 44,900$; PDI = 1.58.

Synthesis of qPDMAEA₂₄-PEGMEA₄₀₀ (Diblock Copolymer). Ethyl bromide (0.3 mL, 4.0 mmol) was added dropwise into a solution containing PDMAEA₂₄-PEGMEA₄₀₀ (865.9 mg) in 3 mL of acetone at 0 °C. The mixture was stirred for

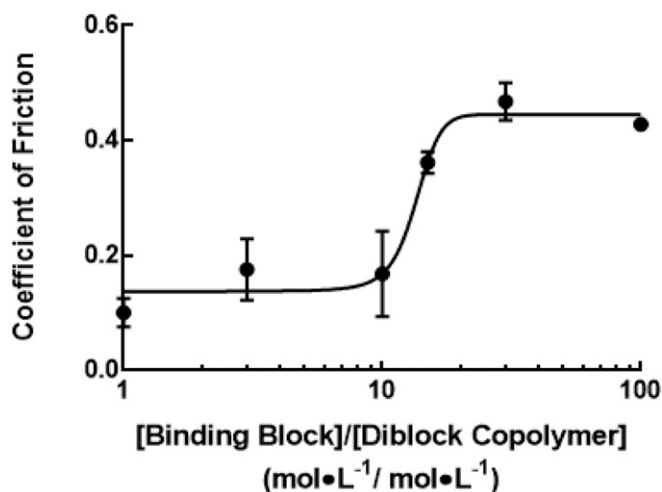


Fig. 4. Competitive inhibition analysis showing the binding block acts as an inhibitor of lubrication when mixed with the diblock copolymer at varying molar ratios. Line is a model fit of a sigmoidal dose–response relationship ($R^2 = 0.87$, $\text{IC}_{50} = 13.45$, $n = 3$ –9, error bars represent ± 1 SD).

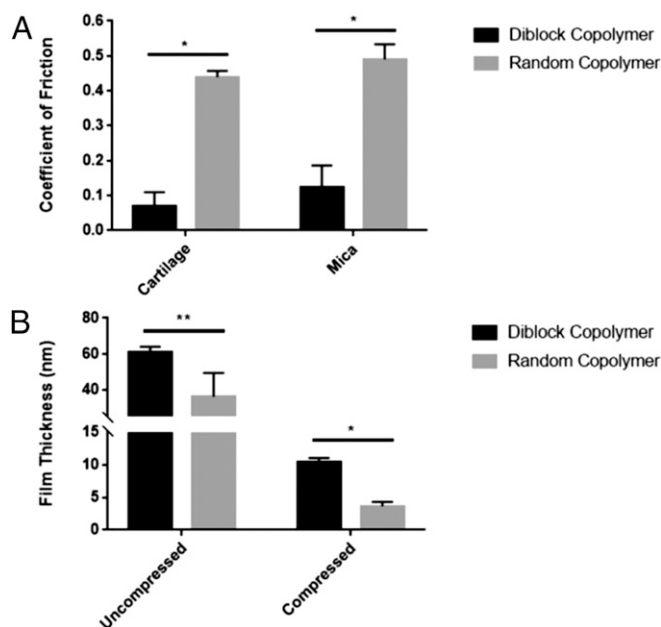


Fig. 5. (A) Random copolymer with the same composition but different architecture failed to lubricate cartilage and mica in comparison with the diblock copolymer architecture ($n = 4-6$, $*P < 0.0001$). (B) Mica samples treated with random copolymer had smaller film thickness under both uncompressed and compressed conditions in comparison with diblock copolymer using SFA measurement ($n = 3-5$, $*P < 0.0001$, $**P < 0.01$), indicating a less efficient binding of random copolymer to the mica surface. Two-way ANOVA was used to determine the statistical difference among the tribological results of the diblock copolymer and the controls on articular cartilage. Student's t test was used to determine the statistical difference of the film thickness of diblock copolymer and random copolymer under uncompressed and compressed conditions individually. Data are presented as mean $\pm$ SD.

48 h at room temperature and was then concentrated by evaporating the solvent with a dry nitrogen flow. The residue was dissolved in 3 mL of dichloromethane and precipitated with addition of 15 mL of hexane and vigorously stirring for 30 min (process repeated five times). The product was then dissolved in deionized (DI) water and further purified by dialysis using Spectra/Por regenerated cellulose dialysis tubing (2 kDa MWCO) against DI water for an additional 48 h before lyophilization. The product (851 mg) was collected as viscous gel in 98% yield; ^1H NMR (400 MHz, D_2O): δ 4.08 [br, 2H, $-(\text{C}=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.75–3.46 (m, 34H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$), 3.21 (s, 3H, $-\text{O}-\text{CH}_3$), 3.02 [s, $\sim 0.2\text{H}$, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$], 2.21 [br, 1H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 2.01–1.36 [m, 2H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 1.25 [br, ~ 0.1 H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$]. The resulting polymer was characterized with GPC using the method described above: $M_n = 46,100$; PDI = 1.58.

Synthesis of qPDMAEA₂₄ (Binding Block). Ethyl bromide (5 mL, 67 mmol) was added dropwise into a solution containing PDMAEA₂₄ (1.2 g, 0.35 mmol) in 50 mL of acetone at 0 °C. The mixture was stirred for 48 h at room temperature and was then concentrated by evaporating most of the solvent with a dry nitrogen flow. The residue was first purified by dissolution in 20 mL of methanol followed by precipitation through the addition of 100 mL of hexane and vigorously stirring for 30 min (process repeated five times). The purified product was then dissolved in DI water and further purified by dialysis using Spectra/Por regenerated cellulose dialysis tubing (2 kDa MWCO) against DI water for an additional 48 h before lyophilization. The product (1.95 g) was collected as orange crystal in 92% yield; ^1H NMR (400 MHz, D_2O): δ 4.40 [br, 2H, $-(\text{C}=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.61 [br, 2H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$], 3.38 [br, 2H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$], 3.02 [s, 6H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$], 2.41 [br, 1H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 2.02 to 1.45 [m, 2H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 1.26 [s, 3H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$].

Synthesis of PEGMEA₄₀₀ (Lubrication Block). PEGMEA (3.46 g, 7.2 mmol) was added to a solution containing CPADB (2.51 mg, 0.009 mmol) and ACPA (0.5 mg, 0.0018 mmol) in 6 mL of anisole. The mixture was deoxygenated by five

freeze–vacuum–thaw cycles before it was heated to 65 °C with stirring for 8 h. The reaction was then quenched by liquid nitrogen freezing, and the polymer gel was precipitated by addition of 20 mL of hexane and vigorously stirring for 30 min. After decanting the solvent, the residue was redissolved in 5 mL of dichloromethane and precipitated by the addition of 20 mL of hexane and vigorously stirring for 30 min (process repeated four times) to yield a gel (1.70 g, 40% yield). The structure of the purified product was characterized by ^1H NMR (400 MHz, CDCl_3): δ 4.12 [br, 2H, $-(\text{C}=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.81–3.39 [m, 34H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$], 3.34 (s, 3H, $-\text{O}-\text{CH}_3$), 2.10 [br, 1H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 2.02–1.36 [m, 2H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$]. The resulting polymer was characterized by GPC using the method as described above: $M_n = 33,800$; PDI = 1.52.

Synthesis of PDMAEA₂₄–PEGMEA₄₀₀ (Random Copolymer). PEGMEA (3.46 g, 7.2 mmol) was added to a solution containing DMAEA (61.8 mg, 0.43 mmol), ACPA (0.5 mg, 0.0018 mmol), and CPADB (1.3 mg, 0.0045 mmol) in 2 mL of anisole. The mixture was deoxygenated by five freeze–vacuum–thaw cycles before it was heated up to 70 °C with stirring for 48 h. The reaction was then quenched by liquid nitrogen freezing, and the polymer gel was precipitated by addition of 20 mL of hexane and vigorously stirred for 30 min. After decanting the solvent, the residue was redissolved in 5 mL of dichloromethane and precipitated by the addition of 20 mL of hexane and vigorously stirred for 30 min (process repeated four times) to yield a gel (865 mg, 25% yield); ^1H NMR (400 MHz, CDCl_3): δ 4.12 [br, 2H, $-(\text{C}=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.75–3.44 (m, 34H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$), 3.35 (s, 3H, $-\text{O}-\text{CH}_3$), 2.26 [br, $\sim 1\text{H}$, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], $-\text{N}(\text{CH}_3)_2$, 1.93–1.36 [m, 2H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 5.30 (s, residue dichloromethane). The resulting polymer was characterized with GPC using the method described above: $M_n = 32,700$; PDI = 1.94.

Synthesis of qPDMAEA₂₄–PEGMEA₄₀₀ (Random Copolymer). Ethyl bromide (0.5 mL, 6.7 mmol) was added dropwise into a solution containing PDMAEA₂₄–PEGMEA₄₀₀ (random copolymer) (1.47 g) in 5 mL of acetone at 0 °C. The

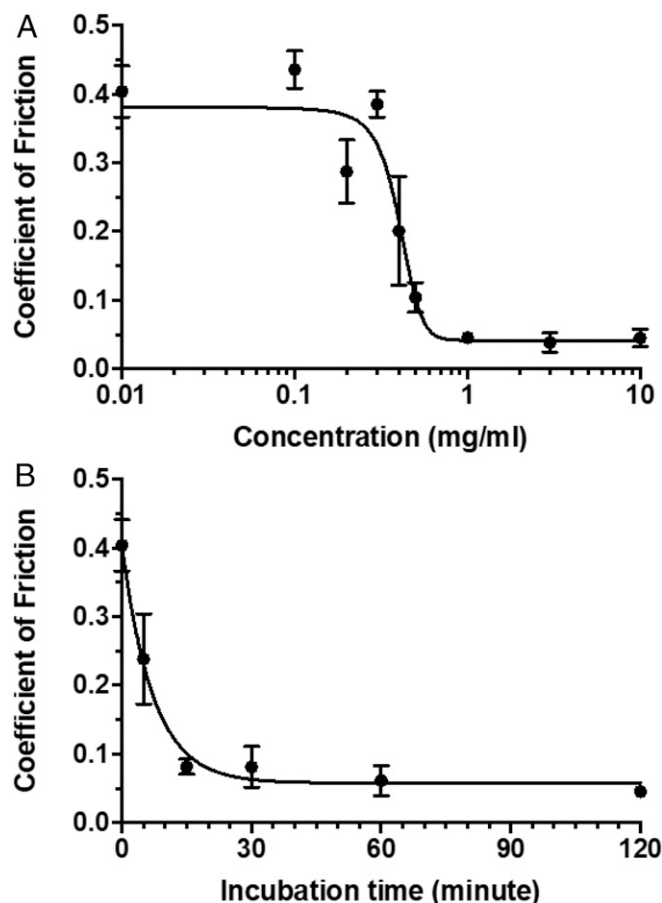


Fig. 6. Dose–response (A) and binding kinetics (B) curves of diblock copolymer ($n = 4-6$).

mixture was stirred for 48 h at room temperature and was then concentrated by evaporating most of the solvent with a dry nitrogen flow. The residue was dissolved in 3 mL of dichloromethane and precipitated with addition of 15 mL of hexane and vigorously stirred for 30 min (process repeated five times). The purified product was then dissolved in DI water and further purified by dialysis using Spectra/Por regenerated cellulose dialysis tubing (2 kDa MWCO) against DI water for an additional 48 h before lyophilization to yield a gel (1.36 g, 93%); ^1H NMR (400 MHz, D_2O) δ 4.08 [br, ~2H, $-(\text{C}=\text{O})\text{O}-\text{CH}_2-\text{CH}_2-$], 3.75–3.44 (m, 34H, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$), 3.21 (s, 3H, $-\text{O}-\text{CH}_3$), 3.02 (s, ~0.2H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$), 2.21 [br, 1H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 2.02–1.44 [m, 2H, $-\text{CH}_2\text{CH}(\text{C}=\text{O})-$], 1.25 [br, ~0.1H, $-\text{N}^+(\text{CH}_3)_2\text{CH}_2\text{CH}_3$]. The resulting polymer was characterized with GPC using the method described above: $M_n = 33,400$; PDI = 1.71.

General Procedure for Tribological Testing. Friction coefficients were measured on our custom-built tribometer (18). Cartilage samples were obtained from the patellofemoral groove of neonatal (1 to 3 d old) bovine stifles. Shaped into a cartilage disk (6 mm in diameter by 2 mm high) by biopsy punch, samples were incubated in 1.5 M NaCl solution for 30 min, in PBS for an additional 60 min, and then in polymer solution (in PBS) for 0 to 120 min. The cartilage samples were loaded onto the tribometer against a polished glass flat counterface in a PBS bath with a tilt pad configuration (18). Before a friction test, samples were compressed to 30% strain and depressurized to an average normal load of 3.4 N within 60 min. After the fluid pressure reached equilibrium, the glass counterface was reciprocated at a linear oscillation speed of 0.3 mm/s. Both the normal load and friction force were measured by a biaxial load cell. Coefficients were calculated as an average ratio of friction force to normal load during the sliding and averaged for both the forward and reverse sliding directions. One-way ANOVA and Student's t test were used to determine the statistical difference.

SFA Experiment, Materials. Mica was purchased from S&J Trading Inc. as optical grade. PBS was purchased from Sigma-Aldrich.

SFA Experiment, Sample Preparation. Thin, homogeneous pieces of freshly cleaved, silvered mica were glued silver-side-down onto semicylindrical fused

silica discs ($R = 1$ cm and $R = 2$ cm) with UV curing glue (Norland 61). The surfaces were mounted opposing each other in a cross-cylindrical configuration in the SFA. After mounting, 50 μL of 3 mg/mL polymer solution in PBS was injected between the surfaces and incubated for 1 h. The surfaces were then rinsed in PBS, and a droplet of PBS was injected, leaving only a surface-bound layer of polymer for friction and film thickness measurements.

SFA Experiment, Friction Force Measurement. Once samples were prepared in the SFA, both normal and friction force measurements were performed. For normal force measurements, the lower surface was mounted on a double-cantilever spring ($k = 1,650$ N/m and $k = 185$ N/m) for normal force detection. For friction force measurements, the lower spring was mounted on a double-cantilever spring ($k = 1,650$ N/m) attached to a piezoelectric bimorph slider. The bimorph slider was sheared across the upper surface, which was mounted on a semiconductor strain gauge at 30 $\mu\text{m/s}$ to detect friction. Friction measurements were measured under incrementally increasing loads and friction coefficients were calculated using the slope of the friction vs. load data, $\Delta F_{\text{friction}}/\Delta F_{\text{Load}}$.

SFA Experiment, Film Thickness Measurement. Once samples were prepared in the SFA, the surfaces were brought together using a stepper motor at speeds <10 nm/s. The interference pattern, known as fringes of equal chromatic order, was recorded and analyzed to determine both the uncompressed film thickness (the film thickness where surface interaction is initially detected) and the compressed film thickness.

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