Optimization of Super-Lubricious Copolymer to Improve Microgel Lubricity for the Treatment of Knee Osteoarthritis

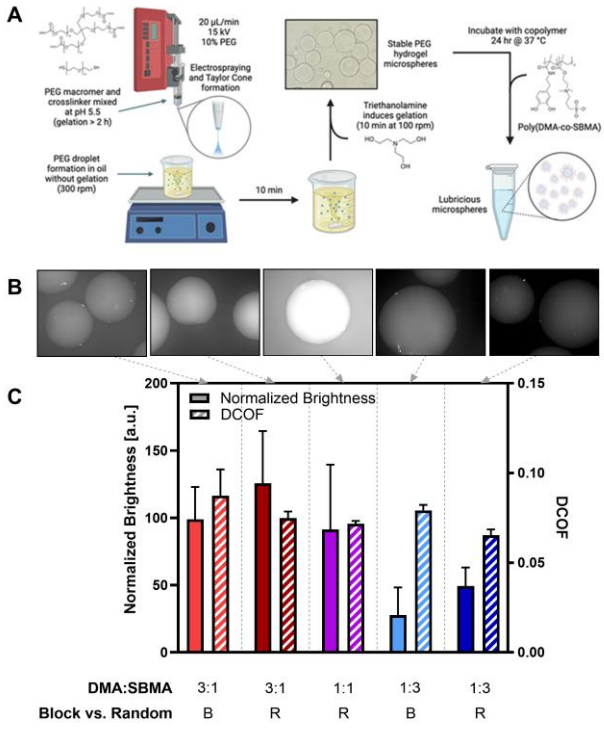
Hannah P. Johnson[1], Samuel Stealey [1], Maitreyi Bhagat[2], Tarini Karnati[1], Nathan Ly[1], Paul Jelliss[2], Silviya P. Zustiak[*1]
[1]Saint Louis University, Department of Biomedical Engineering, St. Louis, MO, [2]Saint Louis University, Department of Chemistry, St. Louis, MO
hannah.p.johnson@slu.edu

Disclosures: Hannah Johnson (N), Samuel Stealey (N), Maitreyi Bhagat (N), Tarini Karnati (N), Nathan Ly (N), Paul Jelliss (N), Silviya P. Zustiak (N)

INTRODUCTION: Knee osteoarthritis (OA) affects over 32 million individuals in the United States alone, causing pain, stiffness, and reduced joint mobility due to cartilage degradation and inadequate joint lubrication. The progression of OA involves dysregulation of biomechanical and biochemical homeostasis, leading to degradation and reduced production of natural lubricants such as hyaluronic acid (HA) and lubricin. This increase in friction further exacerbates articular cartilage wear and perpetuates the progression of OA. Current treatments to rescue this joint lubrication focus on bolus HA injections, though the relief is often temporary and requires multiple injections. Here, we aim to develop hydrogel microspheres with a super-lubricious coating to reduce friction for up to 30 days. These microspheres are fabricated from polyethylene glycol (PEG), which has been demonstrated to be biocompatible and biodegradable with tunable mechanical and physical properties. These PEG microspheres are coated with a custom-synthesized copolymer consisting of mussel glue-like dopamine methacrylate (DMA) for adhesion to PEG and zwitterionic sulfobetaine methacrylate (SBMA) to impart enhanced lubrication. Different copolymer configurations were compared, where it was expected that DMA-rich formulations would adhere more efficiently to the hydrogel microspheres, while SBMA-rich formulations would provide better lubricity. This study aims to optimize the PEG microsphere and copolymer formulation with regard to copolymer adsorption to PEG microspheres and the lubrication performance of the coated microspheres. The successful fabrication of these super-lubricious hydrogel microspheres is expected to reduce friction and enhance the natural lubrication within the knee.

METHODS: Poly(DMA-co-SBMA) was synthesized using a RAFT-mediated alkene polymerization. Five different copolymer configurations were developed: random and block DMA-rich, random and block SBMA-rich, and a random copolymer with DMA:SBMA ratio of 1:1. The copolymers were synthesized with the fluorophore Rhodamine B (RhoB) to visualize copolymer adsorption to the PEG microspheres, and the product was isolated by dialysis against water. FTIR and ^{1}H NMR were used to confirm the presence of and quantify DMA and SBMA. To identify polymer molecular weight and polydispersity, size exclusion chromatography (SEC) was used. UV-vis spectroscopy was used to confirm the incorporation of RhoB into the copolymer. To prepare the hydrogel microspheres, 4-arm PEG-acrylate (10 kDa) and PEG-dithiol (3.4 kDa) were reacted via Michael-type addition to form a chemically crosslinked mesh network. The PEG solution was put through a modified electrospraying setup to form microspheres (**Figure 1A**). After gelation, microspheres were dip-coated in copolymer dissolved in deionized water. To confirm copolymer absorption onto the hydrogel microspheres, fluorescent microscopy and confocal imaging were used. The mechanical properties of copolymer-coated hydrogel microspheres were analyzed with rheology, evaluating the stiffness of copolymer-coated versus uncoated spheres. Additionally, a custom tribo-rheology setup was used to determine the coefficient of friction (COF) of coated spheres in comparison to simulated healthy and OA synovial fluid. The injection force of copolymer-coated microspheres was also determined and compared to uncoated spheres, simulated healthy synovial fluid, and simulated OA synovial fluid. To optimize the copolymer configuration, various properties of coated spheres were compared between the different copolymer configurations, including copolymer absorption, release, and mechanical properties.

RESULTS SECTION: Five different poly(DMA-co-SBMA) copolymers with incorporated RhoB were successfully synthesized with molecular weights of ~40 kDa for all formulations. PEG hydrogel microspheres were fabricated via electrospraying with a mean diameter of ~100 µm prior to washing, which swelled to ~150 µm following washing. Adsorption of poly(DMA-co-SBMA) to the microspheres was confirmed via fluorescent microscopy, as microspheres exhibited bright fluorescence that was localized near the surface of the microspheres (**Figure 1B**). Longer coating times of the microspheres in copolymer solution resulted in spheres with higher fluorescence, suggesting greater copolymer adsorption to the microspheres. The fluorescence of copolymer-coated microspheres was maintained for over 21 days, highlighting the coating stability over time. Comparing different copolymer formulations, DMA-rich and random copolymer-coated microspheres had the best copolymer adsorption to the hydrogel microspheres (**Figure 1C**). Tribological analysis revealed that coated microspheres achieved a lower COF than did uncoated PEG microspheres and simulated healthy or OA synovial fluid, indicating enhanced lubrication. Furthermore, the SBMA-rich copolymer variants exhibited a lower COF than the DMA-rich variants (**Figure 1C**). Injection testing showed that coated microspheres could be extruded through a 31 G syringe needle.



DISCUSSION: These findings demonstrate the development of an optimized super-lubricious poly(DMA-co-SBMA) copolymer and the successful fabrication of injectable, stable poly(DMA-co-SBMA)-coated PEG microspheres to be used as a lubricant in the treatment of knee OA. The hydrogel microspheres demonstrated enhanced lubrication compared to simulated healthy and OA synovial fluid, which was further enhanced by the addition of the copolymer coating. By adjusting the relative ratios of DMA and SBMA in the copolymer coating, improved adherence to the hydrogel microspheres or increased lubricity of coated hydrogel microspheres can be achieved. As expected, DMA-rich coatings demonstrated improved adherence to the hydrogel microspheres, while the hydrogel microspheres coated in SBMA-rich copolymer exhibited better lubricity.

SIGNIFICANCE/CLINICAL RELEVANCE: This device aims to restore lubrication and reduce friction within the knee. Once fully developed, this device could alleviate pain for patients and slow the progression of OA.

IMAGES AND TABLES: **Figure 1: A.** Schematic of the electrospraying process of PEG microspheres and subsequent dip-coating with poly(DMA-co-SBMA) copolymer. **B.** Representative widefield fluorescent microscopy imaging of PEG microspheres dip-coated with each configuration of poly(DMA-co-SBMA-co-RhoB), demonstrating copolymer adsorption to microspheres. **C.** Comparison of normalized brightness value [a.u.] and measured dynamic coefficient of friction (DCOF) of microspheres coated with each copolymer configuration.