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A Synthetic Hydrogel Composite with the Mechanical Behavior and Durability of Cartilage

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This article reports the first hydrogel with the strength and modulus of cartilage in both tension and compression, and the first to exhibit cartilage-equivalent tensile fatigue strength at 100 000 cycles. These properties are achieved by infiltrating a bacterial cellulose (BC) nanofiber network with a poly(vinyl alcohol) (PVA)–poly(2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt) (PAMPS) double network hydrogel. The BC provides tensile strength in a manner analogous to collagen in cartilage, while the PAMPS provides a fixed negative charge and osmotic restoring force similar to the role of aggrecan in cartilage. The hydrogel has the same aggregate modulus and permeability as cartilage, resulting in the same time-dependent deformation under confined compression. The hydrogel is not cytotoxic, has a coefficient of friction 45% lower than cartilage, and is 4.4 times more wear-resistant than a PVA hydrogel. The properties of this hydrogel make it an excellent candidate material for replacement of damaged cartilage.

1. Introduction

Every year, ≈900 000 people in the United States suffer from damage to the articular cartilage that lines the ends of bones, with the knee being most commonly affected.[1] Articular cartilage lesions have a limited intrinsic ability to heal and often lead to osteoarthritis.[2] Treatment of cartilage lesions can alleviate debilitating pain and delay the need for a total knee replacement.[3–6] Current strategies for cartilage restoration include bone marrow stimulation (microfracture), autologous cartilage cell implantation, and osteochondral transplantation.[7–10] These methods typically have high failure rates (25–50% at 10 years), prolonged rehabilitation times (>12 months), and show decreasing efficacy in patients older than 40–50 years.[2,6] Focal joint resurfacing with traditional orthopedic materials (e.g., cobalt–chromium alloy, ultrahigh-molecular-weight polyethylene) is being explored as an alternative strategy, but due to their high stiffness, these implants may ultimately contribute to joint degeneration through abnormal stress and wear.[11,12] The "holy grail" of cartilage restoration is a cost-effective procedure that can immediately and durably restore the mechanical function of cartilage.

Hydrogels have been extensively explored as a cartilage substitute because, like cartilage, they mostly consist of water and have a low permeability, giving them a very low coefficient of friction (COF). However, current hydrogels do not have sufficient mechanical strength and durability under cyclic loading and wear conditions to serve as a load-bearing cartilage replacement. For example, **Figure 1**A shows that no previously reported gel achieved both the tensile and compressive strength of cartilage (see Table S1 in the Supporting Information for the data and references). If a synthetic hydrogel is to be used for replacement of cartilage, it should have at least the strength of cartilage so that it does not fail during a return to normal activities. A hydrogel replacement for cartilage should also have the same time-dependent mechanical properties as cartilage to ensure a normal stress-distribution, as well as a fatigue strength and wear resistance the same as or better than cartilage to ensure durability.

This paper describes a biomimetic approach to create the first hydrogel that has the strength and modulus of cartilage in both tension and compression (see Figure 1A,B). This hydrogel consists of bacterial cellulose (BC), poly(vinyl alcohol) (PVA), and poly(2-acrylamido-2-methyl-1-propanesulfonic acid sodium salt) (PAMPS), so we refer to it as the BC–PVA–PAMPS hydrogel. As demonstrated in Figure 1C–D, a cylindrical sample of BC–PVA–PAMPS hydrogel (59% water) with a diameter of 20 mm exhibited <5% strain under a 100 lb. weight (a compressive stress of 1.43 MPa). To put this into context, a 200 lb (890 N) human will have a peak force of 3000 N on the knee

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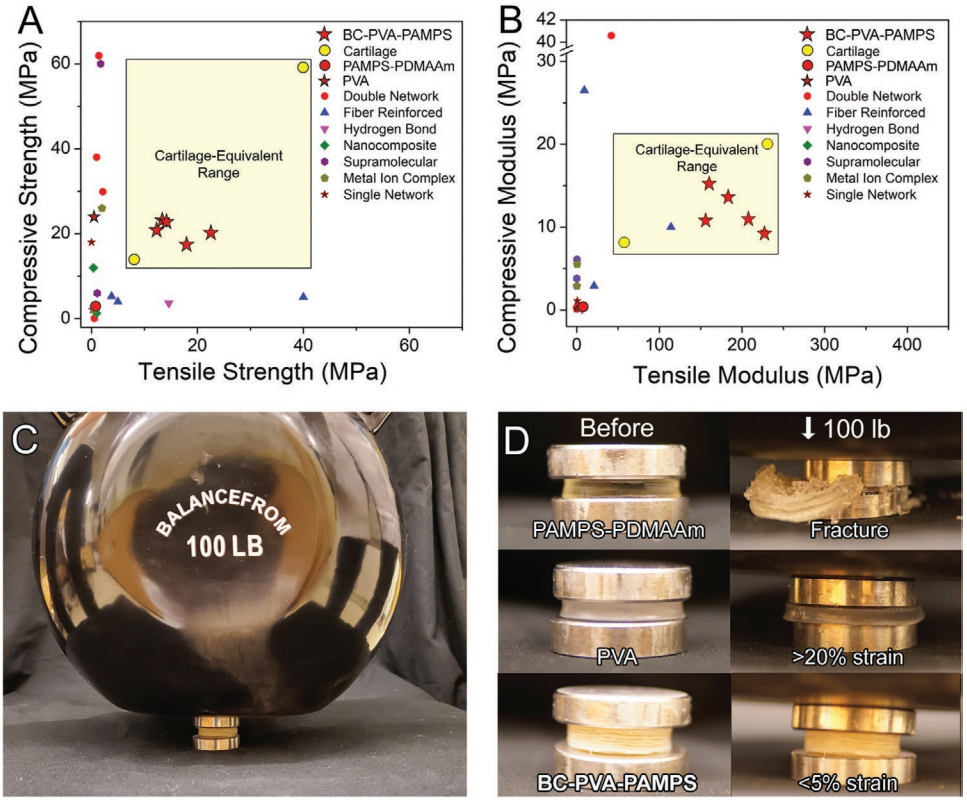

Figure 1. A,B) Plots of the compressive versus tensile strength and modulus for BC–PVA–PAMPS (this work) and other strong hydrogels (see Table S1 in the Supporting Information for data and references).[13–35] The multiple data points for BC–PVA–PAMPS are for different compositions. C) BC–PVA–PAMPS easily bears the weight of a 100 lb. kettlebell. D) Cylinders of PAMPS–PDMAAm, PVA, and BC–PVA–PAMPS hydrogel before and after compression with 100 lbs.

during walking, corresponding to a peak contact stress of 2.5 MPa.[36] In comparison, a double network hydrogel consisting of PAMPS and polydimethylacrylamide (PAMPS–PDMAAm) of the same diameter fractured under the 100 lb load even though it has been reported to exhibit a compressive strength of 3.1 MPa.[17] Although the PAMPS–PDMAAm hydrogel has been extensively studied for treatment of cartilage defects,[37,38] it is too weak to be used in the human knee. A comparison with a PVA hydrogel was also made as it has received FDA approval to treat arthritis of the first metatarsophalangeal (MTP) joint.[39] A PVA hydrogel exhibited significant deformation (>20%) due to its low compressive modulus (0.31–0.8 MPa).[16] Such a large deformation means that PVA alone would transfer stress to the surrounding cartilage and bone if used as synthetic cartilage in the knee. In contrast, the BC–PVA–PAMPS hydrogel has the compressive strength and modulus necessary to serve as a weight-bearing replacement for cartilage.

2. Results and Discussion

2.1. Design of the BC–PVA–PAMPS Hydrogel

Cartilage-equivalent properties were achieved in the BC–PVA–PAMPS hydrogel by mimicking the structure of cartilage. Articular cartilage principally consists of water (60–85% by weight), collagen fibers (15–22%) with diameters of ≈100 nm, and negatively charged aggrecan (4–7%).[40–42] The collagen fiber network gives cartilage its high tensile strength.[40] Aggrecan is a brush-like molecule with a negative charge that comes from sulfate groups on the glycosaminoglycan chains attached to a protein core.[43,44] Aggrecan forms large aggregates with hyaluronan that are trapped within the collagen network, leading to an osmotic pressure that resists compressive loads.[41–43,45–50]

Collagen cannot be used in a synthetic replacement for cartilage because it degrades in the human body, as is demonstrated by the high failure rate of decellularized allografts.[51] BC was chosen as the nanofiber network to mimic collagen due to its biocompatibility, high tensile strength, and because the human body lacks the enzymes necessary to degrade cellulose.[52–55] The second network consisting of a PVA hydrogel was infiltrated into the BC network to provide an elastic restoring force, provide viscoelastic energy dissipation,[56–58] and to increase the tensile strength by allowing BC fibers to share load in the composite framework.[21,59,60] As shown in **Figure 2**A, a BC-PAMPS hydrogel had a tensile strength of 4.6 MPa, lower than the 8.1 MPa required to be in the cartilage-equivalent range. In contrast, a BC–PVA hydrogel has a cartilage-equivalent tensile strength of 12.3 MPa.

A PAMPS network was added to the hydrogel to provide it with a fixed negative charge from the sulfate groups on the PAMPS molecules, thereby mimicking the role of the

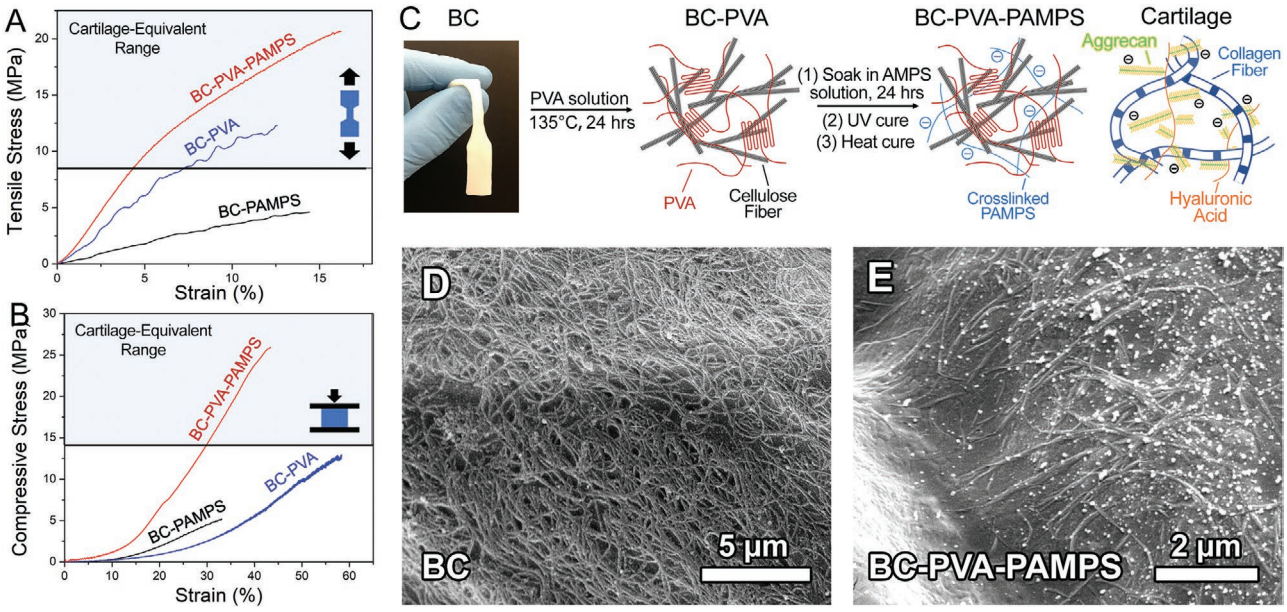

Figure 2. A,B) Tensile and compressive stress–strain curves for BC–PVA, BC–PAMPS, and BC–PVA–PAMPS hydrogels; C) illustration of the BC–PVA–PAMPS hydrogel fabrication process; D,E) Cryo-SEM images of the BC and the BC–PVA–PAMPS hydrogel.

chondroitin sulfate and keratan sulfate components that give aggrecan its negative charge.[45,61] This negative charge results in an osmotic pressure that swells cartilage and contributes to its compressive strength. As shown in Figure 2B, neither the BC–PAMPS nor the BC–PVA hydrogel had sufficient strength to be considered cartilage-equivalent. By adding the PAMPS network into the BC–PVA hydrogel, we increased both the compressive modulus (23 MPa) and strength (10.8 MPa) to within the cartilage-equivalent range.

We note that although the introduction of the BC into a PVA–PAMPS hydrogel increases the tensile strength from 1.06 to 20.6 MPa, it decreases the strain at failure from 66% to 17% (see Figure S1 in the Supporting Information). This is due to the fact that the BC films themselves have fracture strains less than 25%, and the prestraining and alignment caused by compression of the films will decrease this further.[62,63] Cartilage has a tensile strain at failure in the range of 20–30%, only slightly greater than the strain at failure of the BC–PVA–PAMPS hydrogel.[64] For comparison, the strain at failure for human tendons is ≈8%.[65]

2.2. Fabrication Process

Figure 2C provides an illustration of the fabrication process for the BC–PVA–PAMPS hydrogel. First, a piece of BC was pressed to a controlled thickness, typically 0.5 mm, by using spacers between 2 metal plates. A cryogenic scanning electron microscopy (cryo-SEM) image (Figure 2D) shows the nanofibrous nature of the BC. Next, the pressed BC was soaked in an aqueous solution of 40 wt% PVA at 135 °C for 24 h to diffuse the PVA solution into the BC. The BC–PVA gel was then frozen at –78 °C for 30 min and thawed to room temperature to physically crosslink the PVA network.[60] The BC–PVA hydrogel was then soaked in a solution of 30 wt% AMPS, 60×10^{-3} M MBAA, 50×10^{-3} M I2959, and 0.5 mg mL^{-1} potassium persulfate (KPS) solution for 24 h. The hydrogel was cured with a UV transilluminator (VWR) for 15 min on each side, and then heat cured in an oven at 60 °C for 8 h to ensure even and complete curing. The resulting BC–PVA–PAMPS hydrogel was stored in 0.15 M phosphate buffered saline (PBS) solution for at least 24 h before further characterization. Figure 2E shows a cryo-SEM image of the surface of the BC–PVA–PAMPS hydrogel.

2.3. Effect of Composition on Strength and Modulus

Thirty mechanical tests were performed on BC–PVA–PAMPS hydrogels with different molecular weights of PVA (fully hydrolyzed), and different concentrations of BC, PVA, AMPS, and MBAA crosslinker to determine the sensitivity of the hydrogel's mechanical properties to these parameters. The results are shown in **Figure 3**. Unless otherwise stated, the composition of the hydrogel selected for subsequent testing in the paper was 22.1 wt% BC, 40 wt% PVA (molecular weight: 146 000 g mol^{-1}, fully hydrolyzed), 30 wt% PAMPS, and 60×10^{-3} M MBAA. A list of the hydrogel compositions, including their water content and swelling ratios, is provided in Table S2 (Supporting Information).

A BC wt% of 13.9%, 22.1%, or 49.8% resulted in a cartilage-equivalent tensile and compressive strength, but only the intermediate value of 22.1% resulted in a hydrogel with a cartilage-equivalent tensile modulus. For the PVA network, molecular weights of 77 000, 146 000, and 202 000 g mol^{-1} were tested. Increasing the PVA molecular weight from 77 000 to 146 000 g mol^{-1} increased the tensile and compressive strength of the hydrogel from below to within the cartilage-equivalent range. This increased strength may be attributed to increased hydrogen bonding and entanglement between the polymer chains.[60,66] However, increasing the molecular weight further to 202 000 g mol^{-1}

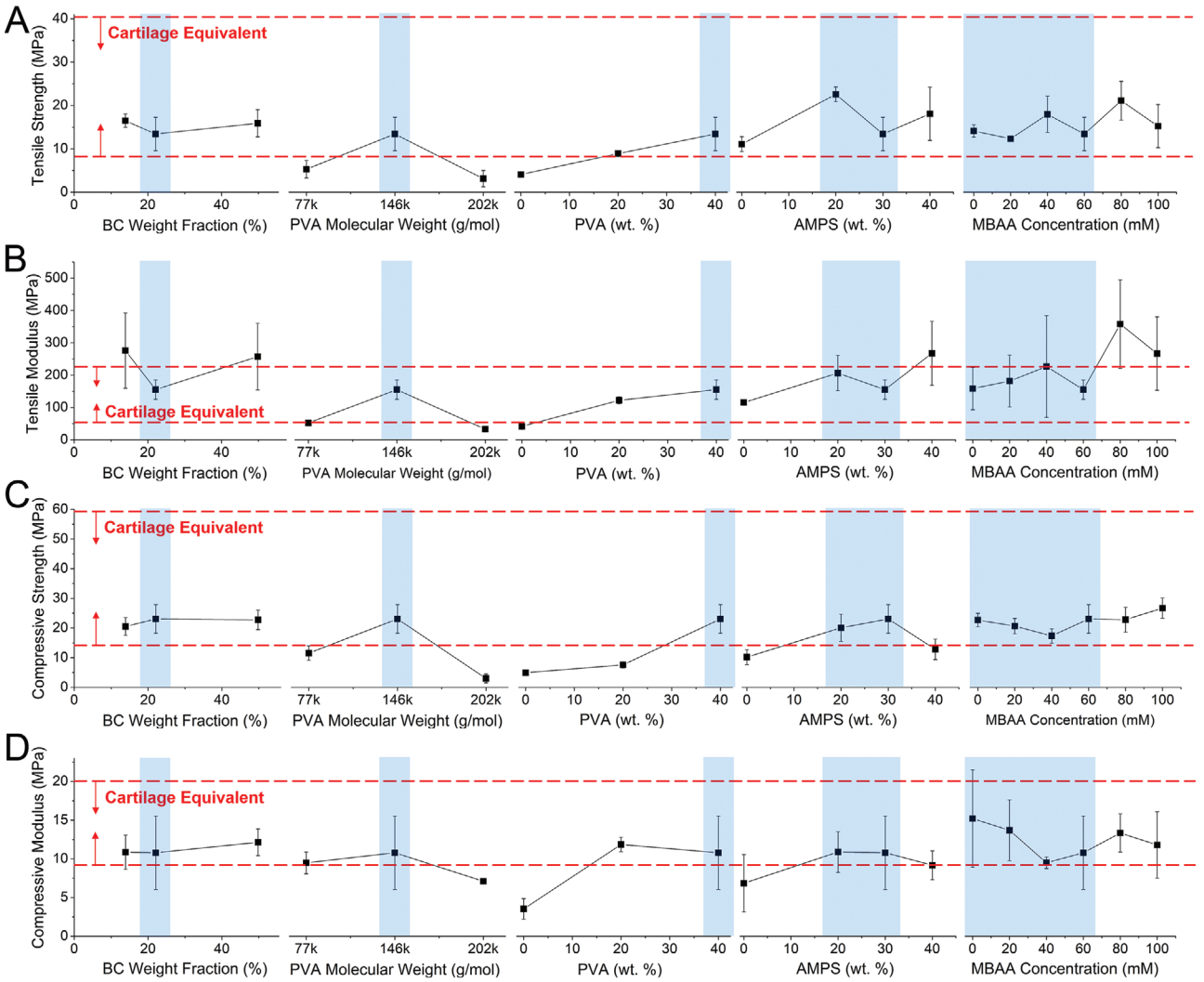

Figure 3. A) Tensile strength, B) tensile modulus, C) compressive strength, and D) compressive modulus of BC–PVA–PAMPS hydrogels with different formulations. The concentrations of BC, PVA, PAMPS, MBAA are 20, 40, 30 wt% and 60×10^{-3} M and the molecular weight of PVA was 146 000 g mol^{-1} unless otherwise indicated. The range of compositions that corresponds to cartilage-equivalent hydrogels are denoted with blue shading.

lead to a decrease in strength outside of the cartilage-equivalent range because the higher molecular weight polymer did not fully dissolve during the infiltration processes. Compositions with PVA below 40 wt% were not cartilage equivalent, while higher concentrations did not fully dissolve during infiltration.

PAMPS by itself forms a relatively stiff, brittle hydrogel. Thus, increasing the AMPS concentration increased the tensile and compressive moduli. The addition of an intermediate range of AMPS (20–30 wt%) provided cartilage-equivalent mechanical properties. Further increasing the AMPS wt% (e.g., 40 wt%) made the hydrogel brittle under compression, decreasing its compressive strength below the cartilage-equivalent range.

MBAA crosslinks the PAMPS network. Interestingly, MBAA was not necessary to provide cartilage-equivalent mechanical properties. The MBAA concentration had a relatively minor effect on the mechanical properties of the hydrogel, but an MBAA concentration of 80×10^{-3} M or higher increased the tensile modulus to outside the cartilage-equivalent range. Therefore, a range of 0–60×10^{-3} M of MBAA provided cartilage-equivalent mechanical properties.

Given the numerous studies of strong hydrogels based on polyacrylamide (PAAm, see Table S1 in the Supporting Information, for examples), we also attempted to make cartilage-equivalent hydrogels composed of BC, PAMPS, and PAAm. Similar concentrations of BC and PAMPS were used to compare with the BC–PVA–PAMPS hydrogel. Although several of the compositions tested achieved a cartilage-equivalent compression strength (see Table S3 in the Supporting Information), none of the compositions tested achieved a cartilage-equivalent tensile strength. We attribute this difference to the lower strength of the PAAm hydrogel relative to PVA.

2.4. Creep under Confined Compression

A cartilage-equivalent hydrogel should ideally not only mimic the strength and modulus of cartilage, but also its

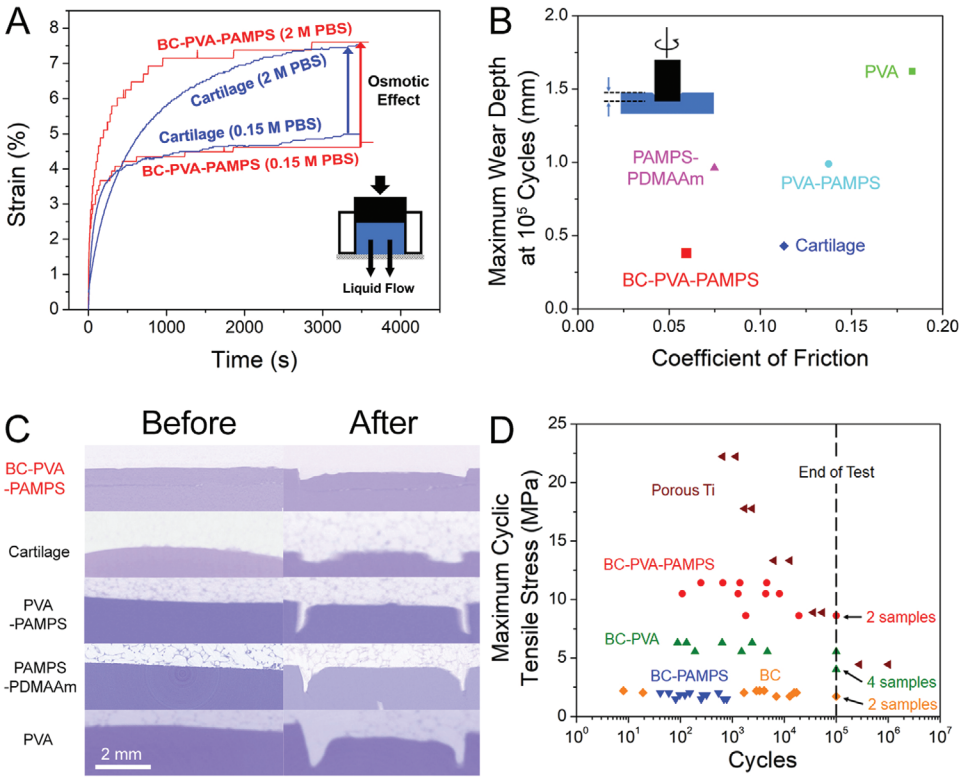

Figure 4. A) Strain versus time for confined, uniaxial creep tests on BC–PVA–PAMPS hydrogel and cartilage under 0.04 MPa. B) Comparison of the coefficient of friction and wear depth of porcine cartilage and the BC–PVA–PAMPS hydrogel. C) MicroCT images of the BC–PVA–PAMPS hydrogel, porcine cartilage, PVA–PAMPS hydrogel, PAMPS–PDMAAm hydrogel and PVA hydrogel before and after wear testing of 100 000 rotations at 100 mm s^{-1} in PBS. D) Maximum cyclic tensile stress applied versus the number of cycles before fracture. Eight samples indicated by arrows did not fail after 100 000 cycles.

time-dependent mechanical properties. **Figure 4**A shows plots of compressive strain versus time for BC–PVA–PAMPS and porcine femoral cartilage under confined compression with a constant pressure of 0.04 MPa (see Figure S2 in the Supporting Information for the experimental setup). The pressure of 0.04 MPa was chosen to keep the strain of the sample in a small range (<10%), as was done in previous work.[67] Tests were performed in 0.15 M PBS to mimic the salt concentration in the physiological environment. The creep curve for the BC–PVA–PAMPS hydrogel is similar to porcine cartilage. The aggregate moduli for these samples were determined by fitting the slope of the stress–equilibrium strain curve over the range of 0.04–0.1 MPa (shown in Figure S3 of the Supporting Information). This analysis produced an aggregate modulus of 0.78 MPa for both the BC–PVA–PAMPS hydrogel and porcine cartilage, which is consistent with the range of values reported in the literature for human femoral cartilage (0.46–1.43 MPa).[68] The permeability of the hydrogel was also determined as described in the supporting information. The permeability of BC–PVA–PAMPS hydrogel (3.2×10^{-15} m^4 N^{-1} s^{-1}) is also in the range of values reported for human cartilage ($1.2–9.2 \times 10^{-15}$ m^4 N^{-1} s^{-1}),[68,69] indicating that the time-dependent deformation of the BC–PVA–PAMPS hydrogel should match that of surrounding cartilage if it is implanted into a patient's knee.

Given the large amount of literature citing the important contribution of osmotic pressure to the compressive strength of cartilage,[41,48–50,70–72] we were curious to see if there was a similar osmotic effect for the BC–PVA–PAMPS hydrogel. Such an osmotic effect was previously deduced from a decrease in the aggregate modulus at a higher salt concentration.[45,61] We found that indeed the aggregate modulus of the BC–PVA–PAMPS decreased to nearly the same value (0.50 MPa) as porcine cartilage (0.49 MPa) when the PBS concentration was increased to 2.0 M (Figure 4A). Thus, a component of the compressive strength and modulus of the BC–PVA–PAMPS hydrogel can be attributed to the osmotic pressure resulting from the large fixed negative charge density provided by PAMPS.

2.5. Coefficient of Friction

Any replacement for cartilage should have a similarly low COF and resistance to wear to ensure that the synthetic replacement is durable and generates minimal wear debris in vivo.[73,74] A low COF is also desirable to minimize wear of the opposing cartilage surface.[74–76] The COF of BC–PVA–PAMPS, PVA, PAMPS–PDMAAm, PVA–PAMPS, and cartilage samples were tested with a rotating pin-on-disk configuration (shown in Figure S5 of the Supporting Information). As shown in Figure 4B, the COF of BC–PVA–PAMPS (0.06) was not only the lowest among the hydrogels previously studied for cartilage replacement (0.17 for PVA, 0.08 for PAMPS–PDAAm, 0.13 for PVA–PAMPS), it was also lower than that of porcine articular cartilage (0.11).

We attribute the low COF to the negative charge of the PAMPS network and the role of BC in reducing the swelling of the hydrogel during soaking in AMPS. The charged surface of the PAMPS hydrogel network can increase the thickness of the water lubrication layer between the gel and the opposing surface, and thereby decrease the COF.[77,78] Both the PVA–PAMPS and PAMPS–PDMAAm hydrogels have a lower COF than PVA, providing further support for the importance of the negative charge for minimizing the COF. The reason why the BC–PVA–PAMPS hydrogel has a lower COF than PVA–PAMPS is likely because the BC network decreases the volumetric swelling ratio of the hydrogel after being soaked in PBS (132% for BC–PVA–PAMPS hydrogel vs 310% for PVA–PAMPS), thus increasing the fixed charge density. The relationship between COF and the sliding speed of PVA, PVA–PAMPS, porcine cartilage, PAMPS–PDMAAm, and BC–PVA–PAMPS are shown in Figure S6 (Supporting Information).

2.6. Wear Resistance

The wear resistance of the hydrogels was tested by rotating a 304 stainless-steel pin on top of the samples in 0.15 M PBS for 10^5 cycles under a pressure of 1 MPa. As shown in Figures 4B and 4C, the maximum wear depth of BC–PVA–PAMPS hydrogel (370 μm) was 2.6–4.4 times smaller than the other hydrogels (1620, 962, and 989 μm for PVA, PAMPS–PDMAAm and PVA–PAMPS hydrogels, respectively). The wear depth for the BC–PVA–PAMPS is even 14% smaller than that of porcine cartilage (429 μm). We attribute this excellent wear resistance to the low COF, high modulus and high strength of the BC–PVA–PAMPS hydrogel.[79] Traditional, more wear-resistant orthopedic materials like cobalt-chromium alloy (CoCr) or ultra-high-molecular-weight polyethylene have a much higher COF (CoCr against cartilage: 0.1–0.2; BC–PVA–PAMPS against cartilage: 0.03)[80] which can lead to wear to the opposing cartilage surface.[80–82]

We also measured the wear of PVA and the BC–PVA–PAMPS hydrogel against cartilage in bovine serum to determine what amount of wear might be expected under these more physiologically relevant conditions. A cartilage pin was rotated on top of a BC–PVA–PAMPS disk and a PVA disk for 1 million cycles with 1 MPa of pressure.[16,76] As shown in Figure S7 (Supporting Information), the wear of the BC–PVA–PAMPS hydrogel was undetectable under MicroCT, which means that the maximum wear depth was smaller than the resolution of the MicroCT (25 μm) after 1 million cycles (see Figure S7 in the Supporting Information). On the other hand, the PVA sample was completely worn through (3.5 mm) after 200 000 cycles under the same testing conditions. These results indicate the amount of wear that will occur for the BC–PVA–PAMPS hydrogel in vivo should be negligible.

2.7. Fatigue Resistance

Cartilage experiences cyclic stress in vivo, so it is important to characterize the fatigue properties of materials that have the potential to be used for cartilage replacement.[83–85] We focused on tensile fatigue because tensile fatigue failure of collagen may play a role in the mechanical failure of cartilage,[85,87–90] and failure in tension is more clearly defined than failure in compression for cartilage-like materials.[14] To ensure the hydrogel did not change over the course of the fatigue experiments, we stored hydrogel samples in PBS solution for up to 12 days and measured their thickness and tensile strength. Figure S8 (Supporting Information) shows the tensile strength and thickness of the hydrogel remained constant over 12 days. Cyclic tests were conducted at 2.5 Hz, so that a 100 000 cycle test took 11.1 h, and samples with a higher strength experienced a higher stress rate (see Table S4 in the Supporting Information for testing conditions). The first five loading–unloading cycles for the BC–PVA–PAMPS fatigue test and the associated hysteresis energies are shown in Figure S9 (Supporting Information).

Figure 4D shows the results from cyclic tensile testing for the BC–PVA–PAMPS hydrogel, its components in different combinations, as well as porous titanium for comparison.[86] The BC–PVA–PAMPS hydrogel exhibited a remarkably high fatigue strength of 8.62 MPa at 10^5 cycles, which is comparable to 85% porous 3D-printed titanium.[86] Addition of PAMPS to BC decreased its resistance to fatigue due to the brittle nature of PAMPS.[91] The addition of PVA to BC increased fatigue resistance due to the toughness of PVA;[56–58] all four BC–PVA samples were free of damage at 10^5 cycles. BC–PVA–PAMPS exhibited a higher fatigue strength than BC–PAMPS due to the ability of PVA to act as a toughening agent and cancel out the poor fatigue properties of PAMPS. The fatigue strength of BC–PVA–PAMPS is the same as the fatigue strength of cartilage in middle-aged adults.[85]

2.8. Biocompatibility

To test for biocompatibility, a sample of the BC–PVA–PAMPS hydrogel was submitted to NAMSA (North American Science Association, LLC), a medical research organization, to test the in vitro cytotoxicity of the gel to mammalian cells with the elution method (ISO 10993-5). The resulting report is included in the Supporting Information. No signs of cell cytotoxicity or lysis were observed after incubating L-929 mouse fibroblast cells with an extract of the hydrogel for 48 h. This result is not surprising given the components of the hydrogel have already been independently demonstrated to be biocompatible.[52,92] The lack of adverse cell response indicates that this hydrogel may be suitable for use as a cartilage replacement in vivo, but further animal testing is necessary to confirm the biocompatibility of the hydrogel over longer time periods.

3. Conclusion

In summary, a biomimetic approach was used to create the first hydrogel with the same strength and modulus as human articular cartilage in compression and tension. Bacterial cellulose nanofibers provided the hydrogel with a source of tensile strength in a manner analogous to collagen nanofibers in cartilage. PVA provided an elastic restoring force, viscoelastic energy dissipation, and prevented stress concentration on individual

BC fibers. PAMPS provided the hydrogel with a source of fixed negative charge and osmotic restoring force similar to the role of aggrecan in cartilage. The BC–PVA–PAMPS hydrogel has an aggregate modulus (0.78 MPa) and permeability (3.2×10^{-15} m^4 N^{-1} s^{-1}) that give it the same time-dependent mechanical response as cartilage under confined compression. The BC–PVA–PAMPS hydrogel exhibited a coefficient of friction (0.06) about half that of cartilage, was 4.4 times more resistant to wear than PVA, and exhibited cartilage-equivalent fatigue strength at 100 000 cycles. BC–PVA–PAMPS was not cytotoxic and is comprised of materials that have been previously demonstrated to be biocompatible. Taken together, these properties make the BC–PVA–PAMPS hydrogel an excellent candidate material for use in the repair of cartilage lesions.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

bacterial cellulose, cartilage, hydrogel, polyvinyl alcohol

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