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Cartilage-like mechanical properties of poly (ethylene glycol)-diacrylate hydrogels

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ABSTRACT

Hydrogels prepared from poly-(ethylene glycol) (PEG) have been used in a variety of studies of cartilage tissue engineering. Such hydrogels may also be useful as a tunable mechanical material for cartilage repair. Previous studies have characterized the chemical and mechanical properties of PEG-based hydrogels, as modulated by precursor molecular weight and concentration. Cartilage mechanical properties vary substantially, with maturation, with depth from the articular surface, in health and disease, and in compression and tension. We hypothesized that PEG hydrogels could mimic a broad range of the compressive and tensile mechanical properties of articular cartilage. The objective of this study was to characterize the mechanical properties of PEG hydrogels over a broad range and with reference to articular cartilage. In particular, we assessed the effects of PEG precursor molecular weight (508 Da, 3.4 kDa, 6 kDa, and 10 kDa) and concentration (10–40%) on swelling property, equilibrium confined compressive modulus (H_{A0}), compressive dynamic stiffness, and hydraulic permeability (k_{p0}) of PEG hydrogels in static/dynamic confined compression tests, and equilibrium tensile modulus (E_{ten}) in tension tests. As molecular weight of PEG decreased and concentration increased, hydrogels exhibited a decrease in swelling ratio (31.5–2.2), an increase in H_{A0} (0.01–2.46 MPa) and E_{ten} (0.02–3.5 MPa), an increase in dynamic compressive stiffness (0.055–42.9 MPa), and a decrease in k_{p0} (1.2×10^{-15} to 8.5×10^{-15} $m^2/(Pa\ s)$). The frequency-dependence of dynamic compressive stiffness amplitude and phase, as well as the strain-dependence of permeability, were typical of the time- and strain-dependent mechanical behavior of articular cartilage. H_{A0} and E_{ten} were positively correlated with the final PEG concentration, accounting for swelling. These results indicate that PEG hydrogels can be prepared to mimic many of the static and dynamic mechanical properties of articular cartilage.

1. Introduction

The ability of hydrogels to provide mechanical support and mechanical cues is particularly important for tissue engineering with cell types that are normally subjected to load. Poly (ethylene glycol) (PEG) hydrogels have been used extensively for *in vivo* and *in vitro* tissue engineering of cartilage, which normally bears both compressive and tensile load. PEG hydrogels provide a three-dimensional environment, sufficiently resembling that of native cartilaginous tissues to maintain differentiated cells in a chondrogenic phenotype [1–3] and to examine chondrogenic differentiation, for example, by mesenchymal stem cells [3–6]. PEG hydrogels are able to maintain cells viable and synthesizing cartilaginous matrix [1–8].

PEG hydrogels are fluid-filled crosslinked three-dimensional networks, consisting of covalently bonded PEG chains, and can be formed from multifunctional PEG precursors. PEG hydrogels can be fabricated by photopolymerization of PEG precursors modified with either acrylate or methacrylate moieties in the presence of photoinitiators [9]. Upon exposure to UV light, photoinitiators are fragmented to yield free radicals. These radicals attack carbon–carbon double bonds present in the acrylate groups, initiating polymerization to form a hydrogel network. When exposed to aqueous solvents, the crosslinked network swells until the retractive (elastic) forces of the polymer chain are balanced by swelling forces of the network [10]. A more tightly crosslinked hydrogel will have larger retractive forces, resulting in less water being imbibed within the network [11].

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The mechanical properties of articular cartilage have been characterized extensively and vary substantially during growth and in adults, as well as in health and disease [12–22]. The stiffness of articular cartilage varies markedly with frequency and test conditions. Such mechanical behavior can be described well by intrinsic elastic material properties and strain-dependent hydraulic permeability [13,15–20,22], with consideration of structural dimensions and physical boundary conditions. The compressive modulus and permeability of cartilage vary with depth from the articular surface. The equilibrium confined compression modulus (H_{A0}) of cartilage ranges from 0.08 to 2.1 MPa from superficial to deep layers of adult bovine cartilage [17] and increases with maturation [15]. The dynamic compressive stiffness of articular cartilage increases substantially with frequency and strain rate in the confined configuration [13,15,16]. The equilibrium tensile modulus (E_{ten}) of mature adult cartilage is higher than the compressive modulus, varying in human articular cartilage from 25 MPa in the superficial layer to 4.8 MPa in the deep layer [21] and increasing with maturation [12]. The hydraulic permeability (k_p), a measure of the ease with which fluid flows through the tissue when driven by a pressure gradient [13,22], is strain-dependent and can be inferred from dynamic compression tests. The k_p of cartilage varies with depth from the articular surface [13,22] as well as with compressive strain [18], ranging from 0.3×10^{-17} to 4.6×10^{-15} $m^2/(Pa\ s)$ in adult bovine articular cartilage [13,15].

The structure and swelling properties of PEG hydrogels are affected by molecular weight and concentration of the precursors [23–27]. Mesh size (ξ), the average distance between adjacent crosslinks, is a measure of the space available between PEG chains. Mesh size increases with molecular weight, for example, doubling from 7.6 nm to 16 nm when the molecular weight of PEG increases from 860 Da to 10 kDa [23]. In contrast, ξ decreases as PEG concentration increases, for example, halving from 14–16 to 6–8 nm as the concentration of 3 kDa PEG increases from 10 to 20% w/v [24,26]. PEG molecular weight and concentration have similar effects on the average molecular weight between crosslinks (M_c), a measure of the degree of crosslinking of PEG hydrogels [23,24]. Concomitantly, the volumetric swelling ratio, the volume of hydrogel relative to the volume of polymer, increases with PEG molecular weight [23,25] and decreases with PEG concentration [24,26,27].

A variety of mechanical properties of PEG hydrogels are also modulated by molecular weight and concentration of PEG precursors, over the ranges studied previously (Table 1, Fig. 1) [1,8,23–32]. PEG hydrogels with higher concentration have higher compressive modulus as assessed by a constant rate compression test [1,24,28,31,32] and higher tensile modulus as assessed by constant rate extension test [23,25]. At similar PEG concentration, hydrogels with low molecular weight are more brittle, as indicated by tensile failure at lower strain [8,23–25,27–29,31,32]. For example, hydrogels fabricated from PEG with low molecular weight (1 kDa) had higher tensile ramp modulus (90 kPa) and lower fracture strain (30%) than hydrogels formed with 4 or 10 kDa PEG [23]. In those studies, mechanical properties of PEG hydrogels have been assessed by a compression test with a constant rate (strain or stress) until failure. The ramp modulus was determined as the slope of the linear region of the resulted stress–strain curve [23–25,27–30,33]; however, this property is generally greater than the intrinsic (equilibrium) material elastic modulus. Although the results from such studies have provided useful information on rate-dependent structural mechanical properties, a more comprehensive mechanical characterization of the intrinsic material properties and viscoelastic mechanical properties of PEG hydrogels would be useful; such information would guide the selection and design of appropriate scaffolds for tissue engineering applications, both for macroscopic load-bearing properties and for mechanical cues transmitted to cells by matrix stiffness [34] in the absence or presence of external loads. In addition, since certain types of external loads are periodic, assessment of dynamic properties over a range of frequencies is also of interest.

We hypothesized that the cartilaginous properties of PEG hydrogels could be modulated by varying the molecular weight and

Table 1
Mechanical properties of PEG-based hydrogels in compression and tension [8,23–25,27–32]. Abbreviations: PEG-diacrylate (PEG-DA), PEG-dimethacrylate (PEG-DM), oligo-(PEG)-fumarate (O-PEG-F), PEG poly (lactic acid) (PEG-b-PLA), PEG-urethane dimethacrylate (PEG-UDM).

PEG formulation	Concentration [%]	Molecular weight [Da]	Methods	Mechanical property determined	Results
[1] PEG-DM	10	3000	15% unconfined compression at constant rate of 0.2; oscillatory compression of 15%, 1 Hz	Tangent modulus, maximum stress from dynamic compression	0.06 MPa, 0.0084 MPa
	20	3000			0.67 MPa, 0.12 MPa
[23] O-PEG-F (OPF)	75	1000	Constant extension at 10 (lk and 4k) or 25 mm/min (10k) until failure	Tensile modulus, stress and strain at fracture	0.09 MPa, 0.025 MPa, 0.31
	75	4000			0.023 MPa, 0.013 MPa, 0.52
	75	10,000			0.016 MPa, 0.013 MPa, 0.77
[25] PEG-DA and $PDMS_{star}$	10	3400	Constant extension at 1 mm/min	Tensile modulus (E)	0.09 MPa
	10	6000			0.07 MPa
[26] PEG-DM	10	3400	Unconfined compression at constant rate of 40 mN/min	Compressive modulus	0.034 MPa
	20	3400			0.36 MPa
	30	3400			0.94 MPa
	40	3400			1.37 MPa
[27] PEG-DA	20	3000	Constant extension at 0.15/min until failure	Quasi-static modulus, ultimate stress and strain	0.4 MPa, 0.2 MPa, 0.37
	65	508			22 MPa, 2.2 MPa, 0.12
	80	508			27 MPa, 1.9 MPa, 0.1
[28] PEG-DM and PEG-LA	10	3000	Unconfined compression at a constant rate of 40–100 mN/min	Compressive modulus	0.06 MPa
	15	3000			0.17 MPa
	20	3000			0.49 MPa
[30] PEG-DA	15	2000	Unconfined compression at constant rate of 0.0005 mm/s until failure	Shear modulus, Young's modulus, stress and strain at failure	0.01 MPa (G), 0.036 MPa (E),0.36 MPa, 0.71
[31] PEG-b-PLA	25	4600	Unconfined compression at constant rate of 400 mN/min	Compressive modulus	0.25 MPa
	50	4600			0.7 MPa
	70	4600			0.9 MPa
[32] PEG-DM	10	4600	Equilibrium unconfined compression at 5–20%; oscillatory compression of 1%, 0.01–10 Hz at 10% offset	Equilibrium compressive modulus and storage modulus	0.05 MPa, 0.04–0.05 MPa
	15	4600			0.19 MPa, 0.15–0.19 MPa
	20	4600			0.27 MPa, 0.25–0.55 MPa