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Review

Extremely strong and tough hydrogels as prospective candidates for tissue repair – A review

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ABSTRACT

Ideal candidates for the repair of robust biological tissues should exhibit diverse features such as biocompatibility, strength, toughness, self-healing ability and a well-defined structure. Among the available biomaterials, hydrogels, as highly hydrated 3D-crosslinked polymeric networks, are promising for Tissue Engineering purposes as result of their high resemblance with native extracellular matrix. However, these polymeric structures often exhibit a poor mechanical behavior, hampering their use in load-bearing applications. During the last years, several efforts have been made to create new strategies and concepts to fabricate strong and tough hydrogels. Although it is already possible to shape the mechanical properties of artificial hydrogels to mimic biotissues, critical issues regarding, for instance, their biocompatibility and hierarchical structure are often neglected. Therefore, this review covers the structural and mechanical characteristics of the developed methodologies to toughen hydrogels, highlighting some pioneering efforts employed to combine the aforementioned properties in natural-based hydrogels.

Contents

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1. Introduction

Soft structural tissues such as cartilage, blood vessels and tendons are characterized by a high water content, load bearing ability (i.e. strength), fracture resistance (i.e. toughness) and softness (i.e. low modulus) [1]. For instance, cartilage, which contains about 75 wt% of water, is able to undertake a remarkable compressive stress of several MPa [2] without fracture, exhibits a toughness of more than 1000 J m^{-2} and a nominal compressive modulus of 0.1–1.0 MPa [3]. This extraordinary mechanical behavior have been ascribed to a plethora of molecular and structural events occurring in biological tissues [4].

An optimal device for the repair of robust biological soft tissues either based on regeneration or replacement strategies should meet several criteria such as, (i) strength to sustain the applied force, (ii) biocompatibility resorting, for instance, to natural polymers, (iii) a well-defined structure from the molecular to the macroscopic levels and (iv) recoverability to reversibly deform without fracture [1,5–8]. In the last years, many groups have been focusing their efforts in order to create these multifunctional systems combining the aforementioned properties [9]. One class of such materials are hydrogels, which consist of three-dimensional solid networks made from crosslinked hydrophilic polymer chains [10]. Owing to their outstanding characteristics such as water absorption and retention ability, biocompatibility and tunable physical, chemical and biological properties, these polymeric networks are excellent candidates for a broad range of biomedical applications [11], which include scaffolds for Tissue Engineering (TE) [12–14], carriers for drug delivery [11,15–18], molecular filters in biological science [19–21], superabsorbent devices in disposable diapers [22] and valves for microfluidics [23–25]. Furthermore, when exposed to an environmental signal such as temperature and pH, some sensitive hydrogels are able to respond and translate this stimulus into a macroscopic event, allowing their application as sensors and/or actuators and smart drug release devices [9,26–32]. But, perhaps, the most interesting feature about these 3D networks is their high resemblance, in terms of structure and physical properties, with the native extracellular matrix (ECM), highlighting their potential for TE and biomedical purposes [11,33–37]. However, their use in stress-bearing applications is often hindered since hydrogels, when highly swollen, often lack of mechanical properties such as strength, toughness, elongation and recoverability [20,38,39]. This poor mechanical performance is in high contrast with native structural hydrogels such as cartilage and may result in unintended failure *in vivo* [40]. Considering the aforementioned drawback, hydrogels were classified as mechanical weak materials, and hence, little attention was paid to them as artificial substitutes of load-bearing soft tissues. Nevertheless, in the last few years, new strategies and concepts have been developed to toughen hydrogels including double networks [41], topological [42] and nanocomposite hydrogels [43]; allowing the application of these 3D structures, for instance, as artificial substitutes of native tissues with structural properties similar to hydrogels such as skin [44], heart valves [45], spinal disks [46], cartilage [8], muscles and nerves [47,48].

In particular, natural-origin polymers are good candidates for biomedical applications as a result of their biocompatibility [49], low cost and easiness to process into hydrogels [50]. Although the chemical structure of synthetic polymers is easily controlled when comparing with natural polymers, they often lack of cell-signaling and cell-interactive motifs which are difficult to mimic in laboratory and are extremely important for the material integration with the surrounding tissues [51,52]. Several natural-based polymers have been investigated for this purpose [53] including proteins such as collagen [54] and gelatin [55]; and polysaccharides such as cellulose [56], chitosan [57], hyaluronan [58] and chondroitin sulfate [59]. However, the brittleness of these hydrogels is in great contrast with the toughness of biological tissues, showing fracture energies of about 0.1–10 J m^{-2} [60,61], tensile moduli ranging from 10 to 10^4 Pa [62] and compressive fracture stresses lower