



Improving the mechanical and thermal properties of gelatin hydrogels cross-linked by cellulose nanowhiskers

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ABSTRACT

This study demonstrates the preparation of a renewable and biocompatible hydrogel with superior mechanical properties consisting of a gelatin matrix cross-linked with oxidized cellulose nanowhiskers. We found an increased degree of chemical cross-linking (0.14–17%) between gelatin and nanowhiskers with the increased amount of aldehyde contents (0.062–0.230 mmol g⁻¹). ¹H nuclear magnetic resonance (NMR) *T*₂ relaxation experiments on D₂O swollen hydrogels demonstrated systems consisting of both gelatin and cellulose nanowhiskers displayed a higher percentage of “ridge” protons, attributed in part to increasing chemical cross-linking junction points between gelatin and nanowhiskers. This increase in hydrogel rigidity not only modified local chain dynamics but also influenced gel swelling, showing relatively reduced water uptake ability than that of the neat gelatin. Rheological measurements confirmed a 150% improvement in storage modulus (*G'*) of the cross-linked hydrogels compared to neat gelatin. Chemical cross-linking also increased the resistance of the gels towards thermal degradation above the melting temperature of gelatin as observed by thermal scanning experiments.

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1. Introduction

Hydrogels represent an interesting class of polymer networks, which have received a substantial amount of interest in pharmaceutical and biomedical applications including contact lens materials, artificial tendons, matrices for tissue engineering and drug delivery systems. Development of hydrogels is a rapidly growing research arena and a number of synthetic, as well as, naturally derived materials have been studied and reported in the literature to form well-characterized hydrogels (Jagur-Grodzinski, 2010; Van Vlierberghe, Dubruel, & Schacht, 2011). Among those, gelatin is a widely used material to form hydrogels for numerous biomedical applications such as wound dressing, plasma expander, adhesive and adsorbent material, vascular prostheses and in drug delivery as hard or soft capsules, hydrogels, or microspheres due to its high water content capacity, biocompatibility, biodegradability and non-immunogenicity (Chen, Leu, Fang, Chen, & Fang, 2011; Dragusin et al., 2011; Huang & Fu, 2010; Silva, Mano, & Reis, 2010).

Gelatin is a protein obtained by de-naturing the triple-helix structure of collagen into single strain molecules. Upon cooling the aqueous solution of gelatin below 35 °C, it forms physical thermo-reversible gels due to partial recovery of collagen triple-helix structure by disorder–order rearrangement (Bode, da Silva,

Drake, Ross-Murphy, & Dreiss, 2011; Liao, Zhang, & Chen, 2009; Pena, de la Caba, Eceiza, Ruseckaite, & Mondragon, 2010). However, the application of gelatin is typically limited at higher temperature (above 35 °C), where breaking of the secondary bonding structure destroys the physical network. This leads to poor thermal and mechanical properties, and has thus far limited gelatin, a readily available and relative inexpensive material from further application. Therefore, chemical cross-links between the protein chains of gelatin are used to stabilize these gels, often refer to a chemical gelatin gels (Draye, Delaey, Van de Voorde, Van Den Bulcke, Bogdanov, et al., 1998). Various cross-linking agents including carbodiimide (Kuijpers et al., 1999), formaldehyde (de Carvalho & Grosso, 2004), glutaraldehyde (Leo, Vandelli, Camerini, & Forni, 1997; Liu, De Yao, Wang, & Li, 2000), oxidized polysaccharides such as dextran (Draye, Delaey, Van de Voorde, Van Den Bulcke, Bogdanov, et al., 1998; Draye, Delaey, Van de Voorde, Van Den Bulcke, De Reu, et al., 1998) chondroitin sulfate (Dawlee, Sugandhi, Balakrishnan, Labarre, & Jayakrishnan, 2005; Kuijpers et al., 2000), and starch (Mu et al., 2010) have been used to chemically cross-link gelatin chains in order to improve the gel stability, increasing the resistance to thermal degradation and improving mechanical properties.

Recently, rod-like polysaccharide nanoparticles known as cellulose nanowhiskers, have gained considerable interest as a promising biomaterial due to their outstanding properties such as high surface area, high mechanical property, hydrophilicity, biocompatibility, and biodegradability (Eichhorn, 2011; Eichhorn et al., 2010). Cellulose nanowhiskers are usually obtained by the

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controlled acid hydrolysis of native cellulose fibers, where the size and mechanical characteristics of the resulting nanowhiskers depend on the source and hydrolysis conditions of cellulose fibers. The typical dimension of wood-based nanowhiskers is 5–10 nm in width and 100–300 nm in length (Habibi, Lucia, & Rojas, 2010; Peng, Dhar, Liu, & Tam, 2011; Siqueira, Bras, & Dufresne, 2009). Because of their unique characteristics, cellulose nanowhiskers have been incorporated as fillers in several polymeric hydrogel matrices. For instance, supramolecular hydrogels based on cyclodextrin/polymer inclusion was prepared by Zhang et al. (2010) and it was shown that incorporation of cellulose nanowhiskers into these hydrogels enhance gelation, mechanical strength and facilitates sustained release of drugs. Goetz, Mathew, Oksman, Gatenholm, and Ragauskas (2009) synthesized hydrogels by co-cross-linking a poly(methyl vinyl ether co maleic acid) (PMVEMA)–polyethylene glycol (PEG) matrix with cellulose nanowhiskers, again resulting in a significant improvement in mechanical and swelling properties. Other examples of composite hydrogels include CNW-reinforced with various polymer matrices such as agarose (Osorio-Madrado et al., 2012), regenerated cellulose (Wang & Chen, 2011), poly(acrylamide-co-acrylate) (Spagnol, Rodrigues, Neto, et al., 2012; Spagnol, Rodrigues, Pereira, et al., 2012), hemicellulose (Karaaslan, Tshabalala, Yelle, & Buschle-Diller, 2011) and chitosan-graft-poly(acrylic acid) copolymer (Spagnol, Rodrigues, Pereira, et al., 2012). Nevertheless, there has been no attempt so far on the employment of cellulose nanowhisker as a renewable, non-toxic and inexpensive cross-linker in gelatin matrix to enhance the material's hydrogel properties.

In presence of periodic acid, cellulose nanowhiskers undergo oxidative cleavage at the C₂–C₃ glycol bond resulting in dialdehyde groups at the respective carbon atoms. These aldehyde groups could act as a potential cross-linker since they will react with free amine groups of gelatin through Schiff's base formation. In this study, we present chemical cross-linking of gelatin by periodate oxidized nanowhiskers containing different amounts of aldehyde groups. To investigate the effect of cross-linking on the gel properties, physicochemical, thermal and mechanical properties of the formulated hydrogels were studied using a variety of advanced techniques. We observed a significant improvement in mechanical and thermal properties of the cross-linked gels compared to neat gelatin gels, which could broaden the use of gelatin hydrogels in various biomedical applications.

2. Materials

A fully bleached commercial softwood Kraft pulp was used as a source for cellulose nanowhiskers. Gelatin (type A, Bloom 300) and all chemicals and solvents were purchased from VWR International.

3. Experimental

3.1. Preparation of cellulose nanowhiskers

Cellulose nanowhiskers were prepared by sulfuric acid hydrolysis of a bleached softwood pulp based on a literature procedure (Bondeson, Mathew, & Oksman, 2006). In brief, 60.00 g (oven dried weight) of the pulp was mixed with H₂SO₄ solution (64%, w/w, 1:10 g/mL) with continuous stirring at 45 °C for 45 min. The hydrolysis reaction was stopped by adding excess (10-fold) of distilled water followed by the removal of acidic solution by successive centrifugation at 12,000 rpm for 10 min until the supernatant became turbid. The sediment was collected and dialyzed (MWCO: 12–14,000) against tap water until the solution pH became neutral. After dialysis, the content was sonicated for 10 min and centrifuged for 5 min at 10,000 rpm. The cloudy supernatant,

containing nanowhiskers, was collected and the remaining sediment was again mixed with water, sonicated and centrifuged to obtain additional nanowhiskers; this procedure was repeated till the supernatant was clear. Cellulose nanowhiskers were obtained in 20–30% yield.

3.2. Sodium periodate oxidation of cellulose nanowhiskers

An aqueous mixture of cellulose nanowhiskers (100.00 mL, 1.74 wt.%, w/v) and sodium periodate (0.17 g, 0.79 mmol) was stirred for 2 days in absence of light at room temperature. The product was then placed into dialysis membranes (MWCO: 12–14,000) and dialyzed against DI water for 2 days to remove the spent oxidant, and then freeze-dried providing a gravimetric yield of 98%. The same procedure was then repeated using 2.44, 4.07 and 5.70 mmol of sodium periodate. These samples were named as DAC1, DAC2, DAC3 and DAC4, where DAC, dialdehyde cellulose and 1, 2, 3, and 4 corresponds to 0.1, 0.3, 0.5 and 0.7, weight ratio of sodium periodate to nanowhiskers, respectively.

3.3. Synthesis of cross-linked hydrogels

A solution was prepared by adding gelatin (4.708 g) to water at 40 °C with slow stirring and the solution was kept at this condition for 3–4 days to remove all entrained air-bubbles. The oxidized nanowhisker suspension (30 mL, 1.74 wt.%, 0.523 g) was degassed to get rid of any bubbles using a water aspirator. Then the nanowhisker suspension was warmed to 40 °C and slowly added to gelatin solution and mixed for 20 min under constant stirring. The mixed gel was poured onto a Teflon mold at room temperature and after drying for 24 h at room temperature the gels were stored at 4 °C for 10 days. The gels were punched into samples of 14 mm diameter and 2 mm thickness for further characterization. The same procedure was followed to prepare cross-linked gels with four different levels of oxidized nanowhiskers.

3.4. Determination of carbonyl groups by copper titration

The carbonyl group content of the starting and oxidized whiskers was determined following Tappi standard method T430 (Tappi Standard T430). Briefly, DAC nanowhiskers (1.00 g) were treated with an aqueous CuSO₄ solution (3.50 mL, 0.40 N) and a carbonate–bicarbonate solution (63.5 mL, 2.40 N, 1.04 N). The mixture was heated to 100.00 °C for 3 h, cooled, filtered, and washed with 5% aqueous Na₂CO₃ solution (70.00 mL, w/v) and hot water (150.00 mL). The whiskers along with the filter paper were dispersed in 5% phosphomolybdic acid (16.60 mL, w/v), stirred, filtered, and then washed thoroughly with water. The filtrate was diluted with deionized water (450.00 mL) followed by the titration with 0.05 N KMnO₄ to a faint pink end point. A blank test was also performed following the same procedure. For each sample, the experiment was repeated three times to obtain the copper number and the data were reported with an error of less than ±3.0%. The copper number and carbonyl group content was calculated by following the expressions (Rohrling et al., 2002).

$$\text{Copper number (Cu\#)} = \frac{6.36(V - B)N}{W}$$

$$\text{Carbonyl group content (mmol/100 g)} = \frac{\text{Cu\#} - 0.07}{0.6}$$

V is the volume of KMnO₄ solution to titrate the filtrate from the specimen, mL; *B* is the volume of KMnO₄ solution to titrate the blank filtrate, mL; *N* is the normality of KMnO₄, 0.05 N, *W* is the weight of the CNWs, g.

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