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ORIGINAL PAPER

Viscoelastic properties of cross-linked polyvinyl alcohol and surface-oxidized cellulose whisker hydrogels

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Abstract Reinforcement of polyvinyl alcohol (PVA) hydrogels was achieved by direct chemical cross-linking of surface modified microcrystalline cellulose (MCC) whiskers with PVA. In order to produce hydrogels, the MCC whiskers were first obtained by TEMPO-mediated oxidation of the cellulose substrate and ultrasonication followed by direct cross-linking to PVA (Mw 98,000) via forming acetal bonds and freeze–thawing. The viscoelastic properties of the produced hydrogels were clearly improved following the chemical cross-linking, featuring values for viscous and elastic moduli G′ and G″ on the order of 10 kPa, which is particularly interesting for biomedical orthopedic applications.

Keywords Microcrystalline cellulose · Whiskers · Polyvinyl alcohol · Cross-linking · Cryogels

Abbreviations

DMA	Dynamic mechanical analysis
DMSO	Dimethyl sulfoxide
ESEM	Environmental scanning electron microscopy
MFC	Microfibrillated cellulose
MCC	Microcrystalline cellulose
NCC	Nanocrystalline cellulose
PEG	Polyethylene glycol
PEI	Polyethelene imine
PVA	Polyvinyl alcohol
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl

Background

Soft tissue (e.g., cartilage, nucleus pulposus, dura mater, synovial fluid, collagen–proteoglycan matrix, etc.) is rich in water and constitutes a significant part of human body. Therefore, from the point of tissue engineering, hydrogels of various types of polymers which could mimic the properties of the soft tissue are interesting. The viscoelastic properties of the soft tissue vary greatly within the body with complex shear moduli |G*| spanning from 1 to 100 kPa for e.g., vitreous humor and cartilage (Iatridis et al. 1996), respectively. Therefore, characterizing the viscoelastic properties of biocompatibile polymer hydrogels is important. It should, however, be stressed that the choice of the polymers is determined not only by the mechanical properties that these polymers may feature but also is inherently limited by their toxicity and

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biodegradability. The latter is the reason why there are still very few known polymers which are suitable for replacing the native soft tissue.

Polyvinyl alcohol (PVA) is one of the few synthetic polymers featured with excellent biocompatibility (Nakamura et al. 2001). PVA is further attractive as it features a highly useful property of forming macroporous physically cross-linked hydrogels upon repeated freezing and thawing, i.e., the so-called cryogels (Inoue 1972; Peppas and Stauffer 1991). The water in the system acts as a porogen during freezing: As water freezes, the local solubility of PVA is changed, and polymer-rich as well as polymer-lean regions are formed, eventually resulting in local crystallization of PVA chains in the polymer-rich regions (Ricciardi et al. 2005). Recent studies reveal that the size of the crystallites is around 7 nm and their periodicity is about 180–200 nm (Kanaya et al. 2012). The properties of the cryogels are first of all determined by the number of the freeze–thaw cycles, polymer concentration, Mw of the polymer, degree of acetylation, and tacticity (Lozinsky 1998). Furthermore, co-mixtures of water with other solvents which are miscible with water, e.g., DMSO, ethanol, glycerine, PEG, etc., can produce hydrogels of varying mechanical and optical properties (Alves et al. 2011; Hoshino et al. 1996; Hyon et al. 1989). The early work on the characterization of the viscoelastic properties of PVA hydrogels was done by Watase and Nishinari (1983, 1988), who observed an increase in the elastic modulus of the PVA hydrogels with concentration. It was observed that the dynamic storage modulus of the gel derived from syndiotactic-rich PVA was remarkably higher than that of the atactic PVA gel (Fukae et al. 2011). The ease of manufacturing and wide availability of different grades of PVA have attracted the interest in using these cryogels in many fields, e.g., for making contact lenses, drug delivery vehicles, cell immobilization in biotechnology, reinforcement of thawed soils and grounds for eco-engineering, creation of solid nutritional media in microbiology, artificial baits for fishing, protective covers for frozen meat or fish in food industry, development of biomimetic actuators, etc. (Hyon et al. 1989; Nakamura et al. 2001; Cascone et al. 1995; Janssen et al. 1992; Kobayashi et al. 2005; Kuriaki et al. 1989; Lozinsky and Plieva 1998; Steckler 1984). Especially interesting are the orthopedic applications of PVA hydrogels for replacement of soft tissue thanks to their excellent biomechanical, wear, and biocompatibility properties (Baker et al. 2012).

Most of the hydrogels with high water content, including PVA hydrogels, are mechanically weak (Cha et al. 1992; Watase and Nishinari 1988). Various aspects of improving PVA hydrogel properties with respect to their biomedical applications have been reviewed (Alves et al. 2011). An obvious way to increase the mechanical strength of the hydrogels would be to use PVA with high Mw at high concentrations. However, this approach is not feasible since solutions of high Mw PVA at high concentrations become viscous and hard to dissolve. Alternative strategies have been reported in the literature to increase the mechanical strength of PVA hydrogels. The viscoelastic properties of photo-cross-linked glycidyl-modified PVA to produce hydrogels for nucleus pulposus replacement were investigated (Bader and Rochefort 2008). Park et al. (2001) investigated the viscoeleastic properties of chemically cross-linked PVA with glutaraldehyde. Cascone et al. (1995) investigated the viscoelastic properties of PVA hydrogels from DMSO–water solutions for tissue engineering. Kuriaki et al. (1989) described a method of annealing in ethanol–water solutions to produce transparent contact lenses. To produce artificial cartilage, a somewhat modified approach for annealing PVA hydrogels with water–ethanol mixtures followed by heat treatment was also reported (Kobayashi et al. 2005).

The common theme of the above mentioned strategies is to increase the density of cross-linking between PVA chains either chemically or physically. The physical methods of PVA annealing are aimed at decreasing the local solubility of PVA, which will favor the crystallite formation. The latter can be achieved by direct dehydration via evaporation (Otsuka and Suzuki 2009) or osmosis, e.g., saturated salt solutions (Choi et al. 2007), using competitor solvents which interrupt water–PVA interactions, e.g., annealing solvent mixtures (Bao 1998), or coagulants, e.g., 7.5 % KOH + 1 M Na2SO4 (Liu et al. 2009). A radically different approach to improve the mechanical strength of PVA hydrogels includes production of composites with other biocompatible and non-toxic polymers. Nanocellulose in this respect is highly appealing due to its availability and absence of toxicity (Peresin et al. 2010). Abitbol et al. (2011) reported a cryogel of PVA with NCC. Wang discloses a patent on hydrogels of bacterial cellulose with PVA which is claimed to be useful for replacing dura mater

of brain (Wang 2007). Similarly, Wan and Millon (2005) disclose a patent for reinforcing PVA hydrogels with bacterial cellulose in tissue engineering applications. These are examples wherein the composites were produced by co-mixing without any additional cross-linking between cellulose nanocrystals/nanofibers and PVA. Whereas significant progress in surface-modifications of cellulose nanocrystals has been recorded during the past decade (Klemm et al. 2011), the potential of direct chemical cross-linking between cellulose nanocrystals and PVA to produce hydrogels suitable for replacing soft tissue has not been fully explored yet.

TEMPO-mediated surface oxidation of cellulose fibers has become increasingly popular ever since it was introduced in mid 1990s (Chang and Robyt 1996; de Nooy et al. 1996; Isogai and Kato 1998). The oxidation is regioselective to O(6) hydroxyls on the surface of the cellulose fibers, and, if conducted under carefully controlled conditions, does not result in dissolution of fibers or changes in the degree of crystallinity, although some decrease in degree of polymerization may be observed (Saito and Isogai 2004). As a result of surface limited oxidation, both carboxylic groups and aldehydes are introduced (Habibi et al. 2006; Saito and Isogai 2006, 2007). Interestingly, the possibility of cross-linking TEMPO oxidized cellulose nanofibers through aldehyde chemistry to imines, e.g., polyethyleneimine (PEI), has been reported (Syverud et al. 2011). It should be noted that the aldehyde groups are highly reactive not only with respect to imines but also readily form acetals with PVA at acidic pH. Apart from TEMPO oxidation, there are alternative methods of introducing aldehyde groups on the surface of cellulose, e.g., periodate oxidation. However, these will not be considered in the present work.

Thus, the aim of the present work was to investigate the feasibility of direct chemical cross-linking of microcrystalline cellulose whiskers with PVA as a novel route of mechanical reinforcement of PVA hydrogels. The viscoelastic properties of the obtained hydrogels were then investigated using dynamic mechanical analysis (DMA).

Materials and methods

Microcrystalline cellulose was Avicel PH102, FMC Corp. USA. PVA Mw = 98,000, TEMPO, sodium bromide, sodium hypochlorite, sodium hydroxide, sodium chloride, and sulfuric acid were received from Sigma Aldrich.

TEMPO-mediated oxidation and whisker gel formation

About 0.3 g of microcrystalline cellulose was dispersed in 10 ml of distilled water. To the dispersion was added 100 ml solution containing 5 mg of TEMPO and 58 mg of sodium bromide. The pH of the obtained solution was then adjusted to pH $\sim$10 with 0.1 M sodium hydroxide solution under stirring. To the mixture 1 ml of 10 % sodium hypochlorite solution was added to initiate the oxidation. The pH of the mixture was maintained at around pH = 10.5 using 0.1 M sodium hydroxide solution, and the reaction was allowed to proceed for 1 h before it was quenched with 10 ml of ethanol. The suspension was then repeatedly centrifuged and redispersed with fresh distilled water to remove the reactants and then dialyzed against deionized water for 48 h. After dialysis the sample was sonicated using Vibracell VC1500 (1,500 W; 20 kHz) at the amplitude of 40 % for 3 min to form a thick gel. The solids content of the gel was 3.88 % weight as measured gravimetrically by drying the sample to a constant weight at 105 °C.

Cryogel formation

In 10 ml of the 3.88 % of cellulose sample, 1 g of PVA was dissolved in a beaker with stopper under stirring at 90 °C in a water bath. To initiate the cross-linking catalytic amounts of 0.5 M sulfuric acid were added and the pH adjusted to pH $\sim$2. The mixture was continued to be stirred at 60 °C for 30 min. Upon addition of sulfuric acid the viscosity of the mixture visibly increased. The viscous mass was then poured in cylindrical forms and stored in a freezer at −18 °C overnight after which the samples were thawed. Only 1 freeze–thaw cycle was implemented. No additional reinforcement with dehydrating–rehydrating agents was performed.

Scanning electron microscopy

The MCC whiskers were examined using an environmental scanning electron microscope (Philips XL30

SEM) in the hi-vac mode. The gel sample was dried and sputtered with Au/Pd prior to microscopy.

Polarized light microscopy

The samples were investigated with polarized light microscopy (Nikon Eclipse LV100POL) at 10× magnification.

Determination of aldehyde content

The aldehyde groups were converted to oximes by Schiff base reaction with hydroxylamine NH_2OH (Kim et al. 2000). The reagent (0.0125 mol) was dissolved in 100 ml of pH 4.5 acetate buffer (0.1 M) and added to 10 ml of 3.88 % MCC whisker gel. The mixture was stirred at 20 °C for 24 h, and the product was recovered and washed by repeated centrifugation. The elemental CHN composition was determined by atomic absorption spectroscopy.

Dynamic mechanical analysis

The rheological measurements were carried out in the dynamic oscillation mode using an Anton Paar instrument (Modular Compact Rheometer MCR 302). The measuring system was that of a plate–plate geometry (Ø = 25 mm). The measurements were conducted between 0.1 and 100 Hz at 25 °C unless otherwise specified in duplicates. The applied strain γ was 5 %, and the force at the contact between the plate and the sample was set to 1 N. The gel properties were described in terms of two dynamic mechanical properties: the elastic (storage) modulus G' (also known as the dynamic rigidity), reflecting the reversibly stored energy of the system, and the viscous (loss) modulus G'', reflecting the irreversible energy loss. When plotted against frequency, a pronounced plateau is present in the G' modulus spectrum for rigid gel structures, whilst the G'' modulus should be considerably smaller than G' in the plateau region (Mihranyan et al. 2007). The damping factor tan δ was defined as the ratio between G'' and G':

$$\tan\delta = \frac{G''}{G'}. \quad (1)$$

Typically, the values tan $\delta < 1$ correspond to true gels.

Results and discussion

In this study, the TEMPO-mediated oxidation of MCC enabled to readily defibrillate of MCC particles as evidenced by the formation of a thick jelly mass following a brief ultrasonic treatment of the TEMPO-oxidized particles as pictured in Fig. 1. As it is seen in Fig. 1, the gel was so thick that a wooden straw could be held firmly inside the jelly mass without leaning to the sides of the jar, and the jelly product would not flow under gravity even when placed up-side down. It should be mentioned that recently a method of producing cellulose whiskers directly from MCC was described, which does not involve chemical surface modification (Li et al. 2012). However, this method required prolonged treatment of MCC using ultra-high ultrasonic energy (1,500 W). As it has been discussed above, the TEMPO-mediated oxidation of cellulose fibers leads to the formation of aldehyde groups as well as negatively charged carboxylic groups along the surface of cellulose crystallites (Habibi et al. 2006; Saito and Isogai 2004), which in turn greatly facilitate the defibrillation of cellulose fibers into elementary fibrils with only limited energy input (Saito et al. 2006).

Modified microcrystalline cellulose is a pharmaceutical purity grade cellulose material produced by hydrolysis of cellulose with mineral acid to a level-off DP (typically around DP = 200–500). Therefore, unlike its MFC analogue, the product of MCC defibrillation is expected to consist of cellulose whiskers rather than long nanofibers featuring large aspect ratio. The latter was confirmed with polarized light microscopy analysis. Figure 2a shows the polarized light microscopy images of original MCC particles featuring large rod-like fragments. Figure 2b shows the polarized light microscopy image of TEMPO-oxidized, defibrillated MCC at the same magnification. As it is clearly seen in the Fig. 2b, the large rod-like particles are no longer present and are replaced by whiskers. The morphology of the MCC whiskers was further affirmed using ESEM imaging (Fig. 2c).

In order to quantify the surface aldehyde group content, the latter were converted to oximes with NH_2OH to form Schiff's base, and the CHN elemental analysis was then performed. The elemental CHN-analysis revealed relatively high N content, viz. 3.2 wt%, corresponding to 2.3 mmol/g aldehyde

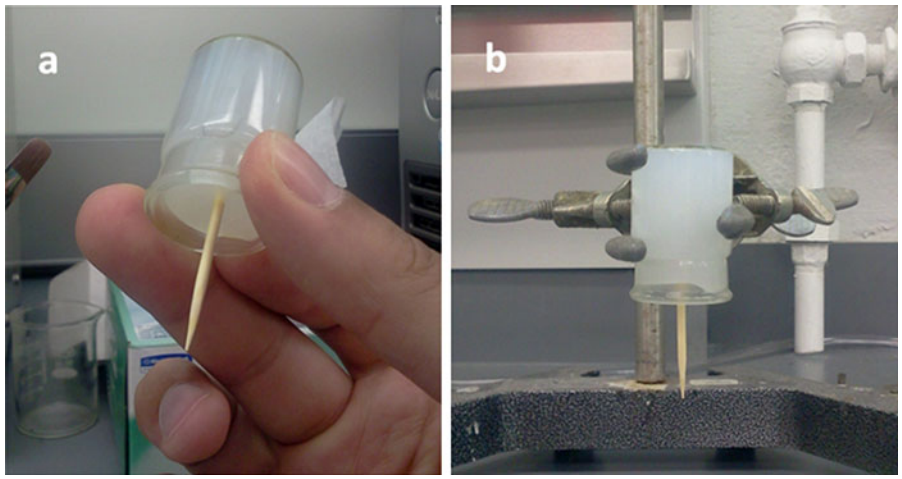

Fig. 1 TEMPO-oxidized MCC gel (3.88 wt%) following the ultrasonic dispersion

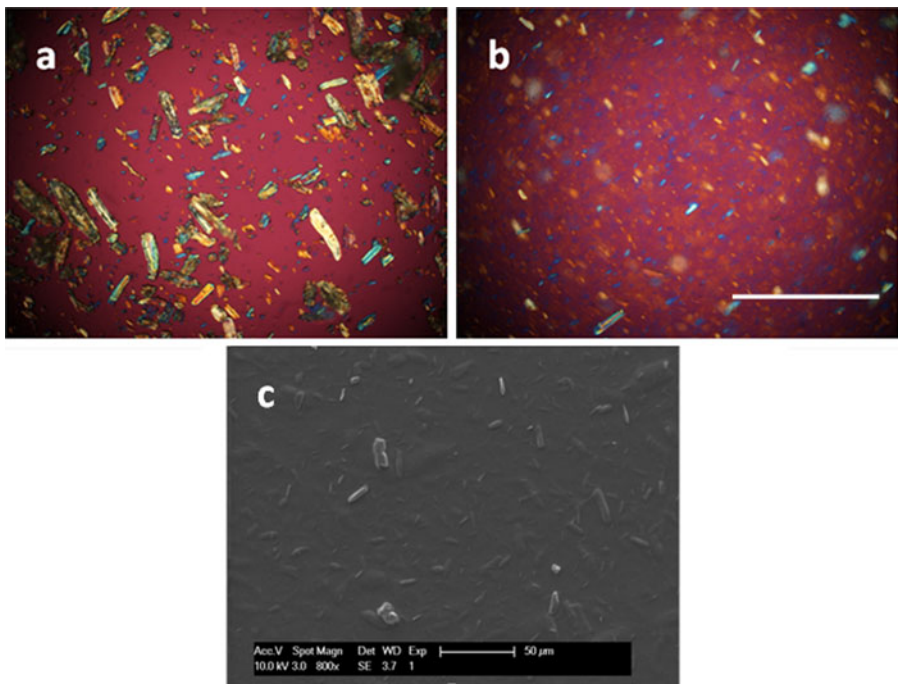

Fig. 2 Polarized light microscopy images of **a** microcrystalline cellulose original particles and **b** TEMPO-oxidized microcrystalline cellulose whiskers following ultrasonic dispersion (*scale bar* corresponds to 100 µm) as well as a SEM image **c** of TEMPO-oxidized microcrystalline cellulose

content. The aldehyde content values obtained with CHN analysis are higher than those normally reported with conductimetric titration, i.e., ca. 0.2–0.3 mmol/g (Saito and Isogai 2006, 2007), which is probably related to the higher sensitivity of CHN analysis, which is a direct (i.e., based on specific binding to aldehyde), non-bulk method unlike the conductimetric titration which is an indirect, bulk method estimating the aldehyde content from the differences in carboxylate content before and after chlorite treatment. The aldehyde group containing product of TEMPO-oxidation was then used to cross-link PVA with MCC whiskers and make cryogels. During the reaction, upon addition of acid, the viscosity of the system

visibly increased, producing paste-like texture. The samples were then frozen over-night and subsequently thawed, and the viscoelastic properties of the produced PVA-MCC cryogels were then characterized. Figure 3 shows schematically the cross-linking of cellulose whiskers with PVA.

Figure 4 shows the viscoelastic properties of the TEMPO-oxidized MCC–PVA hydrogels compared to those of MCC–PVA hydrogels without TEMPO treatment. It should be mentioned that addition of MCC particles to the PVA hydrogels may in itself improve the mechanical properties of PVA hydrogels since the MCC particles act as inert fillers and thereby increase the solidity of the system.

It is clearly seen from Fig. 4 that the hydrogels of PVA cross-linked with TEMPO oxidized MCC whiskers were significantly more rigid than those of PVA with MCC without cross-linking as evidenced by the higher values for both G′ and G″. It is also worth to notice that the variability in the results was somewhat higher for the MCC–PVA hydrogels which were generally softer than their cross-linked counterpart.

Figure 5 shows the frequency dependence of the damping factor tan δ of the TEMPO-oxidized MCC–PVA cross-linked hydrogels as compared to the PVA–MCC hydrogels without cross-linking. It is seen that both samples undergo some shear thinning under applied dynamic load as evidenced by the increase in the numerical value of damping factor tan δ. However, there appears a shift to higher frequencies (1–10 Hz) for the TEMPO-oxidized MCC sample as compared to the reference MCC–PVA sample.

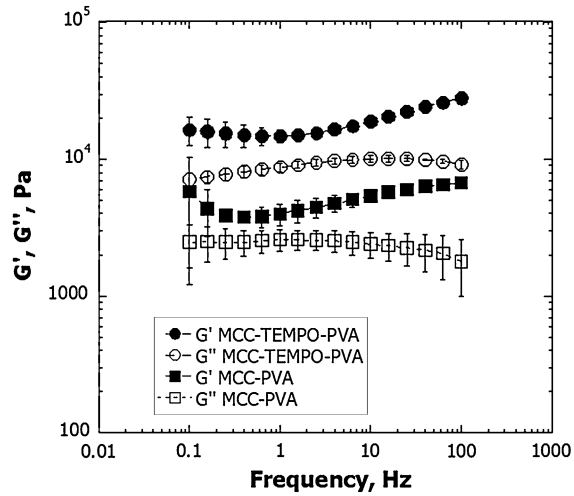

Fig. 4 Frequency dependence of the elastic (storage) modulus G′ and viscous (loss) modulus G″ of 3.8 wt% MCC–PVA hydrogels

The temperature dependence of the damping factor tan δ at 1 Hz is presented in Fig. 6. It is seen in this graph that both samples exhibit the same tendency for changes in their viscoeleastic properties, although the cross-linked sample exhibits in general lower tan δ values. As the temperature is increased, the numerical value for the damping factor tan δ increases which indicates a transition to a more fluid-like behavior. At around 60 °C it is seen that the hydrogels break, which is characteristic for PVA hydrogels (Fukae et al. 2011). In the region between 60 and 74 °C, a plateau is

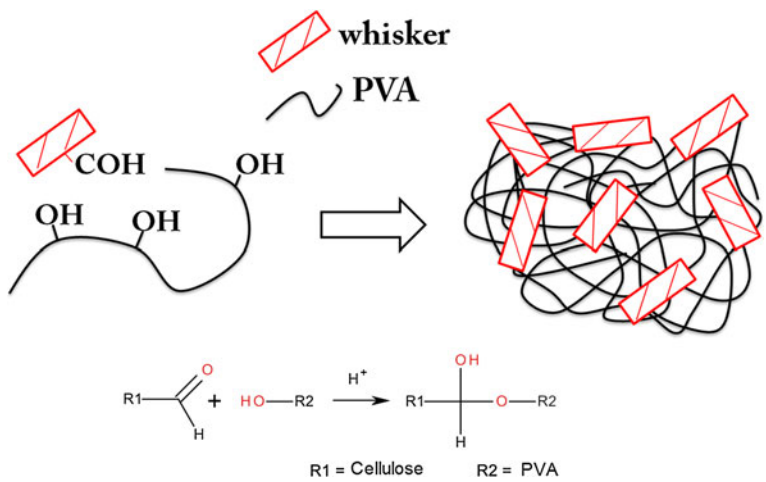

Fig. 3 Schematic *drawing* of chemical cross-linking between surface-modified cellulose whiskers and PVA polymer chains

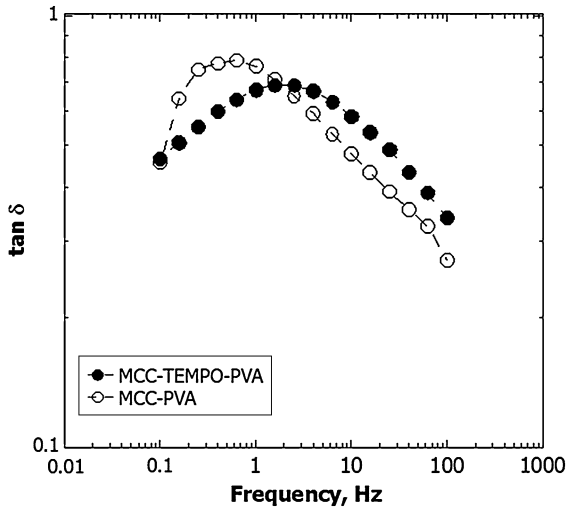

Fig. 5 Frequency dependence of the damping factor tan δ of 3.8 wt% MCC-PVA hydrogels

visible for the TEMPO-oxidized MCC sample suggesting that some of the PVA chains are still restrained, probably due to bonding to MCC whiskers. Although the effect of chemical cross-linking is clearly detectable, the viscoelastic properties of the hydrogels still seem to be largely dominated by the crystallization of PVA during freeze-thawing.

The values for G′ and G″ observed in this study were on the order of 10 kPa after single freeze-thaw cycle, whereas the PVA hydrogels suitable for orthopedic applications reported earlier required repeated freeze-thawing (Baker et al. 2012). In this respect, the strategy of reinforcing PVA hydrogels via cross-linking with MCC whiskers is appealing for biomedical applications, such as orthopedic soft tissue engineering.

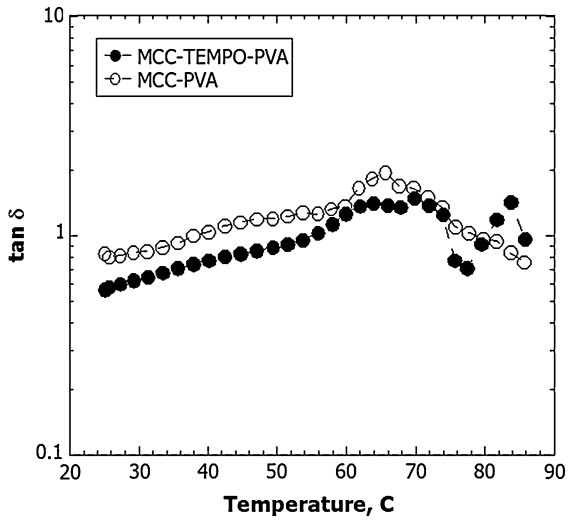

Fig. 6 Temperature dependence of the damping factor tan δ of 3.8 wt% MCC–PVA hydrogels at 1 Hz

Conclusion

In this work it was shown that cross-linking of surface modified cellulose whiskers is an appealing strategy to reinforce PVA hydrogels, which are potentially useful to substitute soft tissues in biomedical applications. Future work should include long-term biomechanical strength and wear studies as well as biocompatibility tests.

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