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Dialdehyde cellulose crosslinked poly(vinyl alcohol) hydrogels: Influence of catalyst and crosslinker shelf life

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ABSTRACT

Dialdehyde cellulose (DAC) derived from α-cellulose by periodate oxidation was solubilized and utilized as a suitable crosslinking agent for poly(vinyl alcohol) (PVA). The crosslinking occurs between reactive aldehyde groups of DAC on the C2 and C3 carbons of anhydroglucose unit and hydroxyl groups on PVA backbone in the presence of acidic catalyst. Two catalyst systems based on diluted hydrochloric or sulfuric acid were tested. Their influence on the PVA/DAC network has been investigated by solid-state ^{13}C NMR, XRD analysis and in the terms of network parameters and mechanical properties. Because DAC undergoes structural changes and decays with time, the role of DAC solution age (1, 14 and 28 days old) on material properties of formed PVA/DAC samples was studied as well. Outlined, even after 28 days after solution preparation, DAC exhibited the capability to act as an efficient crosslinker for PVA. The resulting material properties of PVA/DAC hydrogels were found to be dependent on the molecular weight of solubilized DAC closely related to its age and the choice of catalyst system. Furthermore, the DAC potential for PVA crosslinking was investigated in a broad concentration range. Besides, the DAC crosslinking efficiency was also compared to that of common crosslinking agent glutaraldehyde. The results showed different network topology of prepared hydrogels and exceptional crosslinking potential of DAC in comparison to glutaraldehyde, which is most likely related to DAC macromolecular character.

1. Introduction

Cellulose is an abundant natural polymer, which exhibits valuable properties such as biocompatibility, good chemical modifiability and hydrophilicity beneficial for a plethora of applications in many different fields (Thomas et al., 2013). Standing alone, compounded with synthetic polymer or used in small concentrations as additives, they demonstrate water retention capability which is one of the key properties of hydrogels. The water retention capability of hydrogels arises due to the presence of three-dimensional network of crosslinked macromolecules containing hydrophilic groups (Wichterle & Lím, 1960). Crosslinked hydrogel matrix should contain (i) covalently bonded macromolecules of at least one polymeric substance, and/or (ii) physically crosslinked units constituted of macromolecular entanglements, (iii) hydrogen bonds or strong van der Waals interactions between chains, or (iv) at least two macromolecular chains joined in crystallites (Peppas, 2000).

Biopolymer-based hydrogels are particularly favourable for applications in the field of biomedical sciences as they are able to mimic the structure of a living tissue (Chen & Hunt, 2007; Ma, 2008; Tibbitt & Anseth, 2009), to introduce new functional groups for enhanced performance or to modify the biodegradability profile (Liu, Kost, Yan, & Spiro, 2012). In pharmaceutical sector, the hybrid biopolymer-based hydrogels find utilization as dressing materials containing active substance for wounds healing, drug delivery systems with variable release profiles dependent on external stimuli (pH, temperature), scaffolds for improved tissue regeneration, various body implants (i.e. cartilages) or as biosensors for specific molecules (Baker, Walsh, Schwartz, & Boyan, 2012; Carpi, 2011; Kamoun, Chen, Mohy Eldin, & Kenawy, 2015; Qiu & Park, 2001).

One of the synthetic polymers suitable for the formation of hydrogels is poly(vinyl alcohol), PVA. The PVA-based hydrogels can be prepared using different routes, directly determining the nature of formed network and physico-chemical properties. These include (i) physical route of crosslinking by cyclical freezing and thawing or high temperature/energy treatment (Bolto, Tran, Hoang, & Xie, 2009) and (ii) chemical route utilizing crosslinking agents such as epichlorhydrine, various aldehydes (formaldehyde, glutaraldehyde, benzaldehyde etc.), anhydrides (EDTA dianhydride) or boric acid (Bolto et al., 2009; Lee & Mooney, 2001, p. 2; Miyazaki et al., 2010; Thomas et al., 2013). The

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first approach has undeniable advantage in the absence of any kind of additive, although the crosslinking process has relatively poor definition in the exact terms of chemical reaction mechanism. The low molecular weight crosslinkers used in the second approach have typical set of features such as synthetic origin (except boric acid) and relatively high toxicity. The small size of molecules enables them to penetrate readily through various portals of entry into a living organism.

Therefore, for medical applications, it is more desirable to utilize crosslinking agents derived from naturally available biopolymers, which have a potential to become lower-toxicity alternative to common toxic low-molecular weight crosslinkers. In this manner, Genipin (substance extractable from the fruits of *Gardenia Jasminoides*) was introduced as a low toxicity natural crosslinker (Bispo et al., 2010). However, limited availability and related high cost restricts its use on larger scale. This issue can be overcome by the choice of abundant, easily available and modifiable biopolymers as an original material for polymer analogue reaction imparting the product functional crosslinking side groups. One of the most accessible biopolymers is cellulose and its derivatives such as dialdehyde cellulose (DAC). In the recent study of Kim et al., solubilized DAC was utilized as a crosslinking agent for chitosan (Kim, Lee et al., 2017). Besides its crosslinking capability, the cytotoxicity of DAC was shown to be 6–12x lower than commonly used crosslinking agent glutaraldehyde.

In this study, DAC prepared from α-cellulose by sodium periodate oxidation of hydroxyl groups on C2 and C3 to aldehydes (see Fig. S1) was investigated as a crosslinking agent for PVA. In order to utilize DAC in solution-based processes, it has to be solubilized using prolonged heating procedure (Kim, Wada, & Kuga, 2004). As has been shown in our recent study, solubilization step of DAC cannot be considered just as a simple dissolution as it leads to significant loss of molecular weight of final solubilized DAC product (Münster et al., 2017). Nevertheless, recent studies have shown potential of solubilized DAC towards the purpose of crosslinking (Kim, Lee et al., 2017; Kim, Kim, Choi, Kimura, & Wada, 2017). To obtain crosslinked PVA/DAC hybrid hydrogel, acidic catalyst must be added to initiate crosslinking reactions between aldehyde groups of DAC and hydroxyl groups of PVA. Two catalyst systems based on (i) hydrochloric acid or on (ii) sulfuric acid were introduced in this study and their effects on xerogel/hydrogel characteristics were investigated. These catalysts represent common systems used for crosslinking process employing reactions of aldehyde moiety (Jamnongkan, Wattanakornsiri, Wachirawongsakorn, & Kaewpirom, 2014; Kim, Lee, & Han, 1994; Saallah et al., 2016; Tang, Saquing, Harding, & Khan, 2010; Yeom & Lee, 1996). Moreover, the influence of aging of solubilized DAC (1, 14 and 28 days old) on properties of prepared xerogels and hydrogels was studied. The investigation of DAC solution shelf life is particularly important, because DAC in solution is known to be highly reactive and to undergo aging rapidly in terms of reactive aldehyde content loss and progressive molecular weight decrease (Kim, Kuga, Wada, Okano, & Kondo, 2000, 2004), and it is normally recommended to use always freshly made solutions (Sirviö, Liimatainen, Visanko, & Niinimäki, 2014). However, according to our recent work dedicated to characterization of the DAC solution composition in time (Münster et al., 2017), considerable stabilization of aldehyde content for extended period of time was observed, when DAC solutions were kept at low pH (3.0–3.5). It was shown that low pH reduces the degradation processes and slows down the reaction kinetics of β-elimination. Possible applicability of older (14+ days old) DAC solutions as crosslinking agents was also suggested. Therefore, crosslinking capabilities of the acidic DAC solutions of different age combined with the two catalyst systems were investigated in current study of PVA/DAC blends. Besides the evaluation of crosslinking capability of DAC during its aging, it is important to compare the crosslinking potential of this novel crosslinker to the most commonly used crosslinking agent. Thus, comparative study focusing on crosslinking of PVA by DAC or by glutaraldehyde including use of different concentrations of crosslinking agents was conducted.

2. Experimental

2.1. Materials

Mowiflex TC 232 (Kuraray Specialities Europe GmbH) was used as source of poly(vinyl alcohol) (PVA), density $\rho_p = 1.3\ g/cm^3$, number average molecular weight $\overline{M}_n = 23\ 500\ g/mol$ (estimated by GPC). Dialdehyde cellulose (DAC) was prepared by periodate oxidation of α-cellulose (Sigma Aldrich Co.) by sodium periodate ($NaIO_4$) (PENTA, Czech Republic). Oxidation reaction was terminated by addition of ethylene glycol (PENTA Czech Republic). The degree of oxidation was estimated by conversion of DAC to oxime by reaction with hydroxylamine hydrochloride (Sigma Aldrich Co.) and subsequent consumption sodium hydroxide (PENTA, Czech Republic). All chemicals used in crosslinking reaction including 35% hydrochloric acid (HCl), 96% sulfuric acid (H_2SO_4), 99.8% methanol (CH_3OH) (PENTA, Czech Republic), 99.8% acetic acid (CH_3COOH) and 50% water solution of glutaraldehyde (Sigma Aldrich Co.), were of analytical purity (p.a.) and used as received without further purification. Demineralized water was used throughout the experiment.

2.2. Preparation of crosslinked PVA/DAC and PVA/GA hydrogels

In the first step, periodate oxidation of α-cellulose was carried out. Detailed preparation and properties DAC solutions and dried samples are presented elsewhere (Münster et al., 2017). In brief, 10 g of α-cellulose was suspended in 250 mL of water containing 16.5 g of $NaIO_4$ and stirred in dark for 72 h. Oxidation was stopped by adding of excess of ethylene glycol. Never-dried product was flushed on filter and then solubilized at 80 °C for 7 h under reflux, purified by centrifugation and filtration to remove residual solids and diluted to 200 mL with water. The pH of the solution was kept between 3.2 ± 0.1 all the time. Solubilized DAC was analysed in the terms of reactive aldehyde group content over 28 days. This was achieved by the oxime reaction of prepared solubilized DAC of different age with hydroxylamine hydrochloride. Typically, sample solution containing 0.1 g of solubilized DAC was diluted to fixed volume by demineralized water and pH was set to 4.00 using 0.1 M HCl. Next, 20 ml of solution containing 0.43 g of hydroxylamine hydrochloride was adjusted to pH 4.00 by 0.1 M NaOH. These two solutions were mixed together and stirred for 24 h at 150 RPM in closed containers. The reactive aldehyde group content was determined by the consumption of 0.1 N NaOH (Kim et al., 2004; Veelaert, de Wit, Gotlieb, & Verhé, 1997).

The second step involved preparation of PVA crosslinked samples using DAC of various age. PVA/DAC mixtures were prepared by dissolution of 4.95 g PVA in 70 mL of water and addition of defined volume of fresh (1 day old) DAC solution containing 0.05 g (1 wt%) of solubilized DAC. To form a crosslinked network, acidic catalyst was introduced. Two acidic catalyst systems were chosen giving rise to two types of PVA/DAC blends (referred as type or series A and B in further text). In type A, 1.5 mL of 1.33 M HCl solution served as the catalyst and pH buffer. In B type, 0.25 mL of 10%vol H_2SO_4 was used as the catalyst, together with 0.75 mL of 10 vol% solution of CH_3COOH (pH buffer) and 0.5 mL of 10 vol% CH_3OH (quencher). Whole process was repeated using two- and four-weeks old DAC solution.

In the comparative crosslinking study, fresh DAC and conventional crosslinking agent glutaraldehyde (GA) was utilized for PVA crosslinking in the set of chosen concentrations. The concentration range of used DAC crosslinker was from 0.0625 to 5 wt%. For example, PVA/DAC blend crosslinked using 1 wt% DAC contained 0.05 g of solubilized DAC. Since the fresh DAC was estimated to have content of reactive aldehyde groups 11.7 ± 0.3 mmol/g, the particular amount of reactive aldehyde groups used for crosslinking of this sample was 585 ± 13 μmol. To achieve comparable crosslinking of PVA, the volume of GA crosslinking solution containing equal amount of reactive aldehyde groups per sample was used. Content of reactive aldehyde