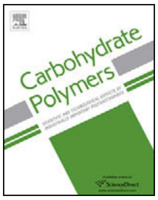
Carbohydrate Polymers 151 (2016) 392–400

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol



Physically and chemically cross-linked cellulose cryogels: Structure, properties and application for controlled release

Diana Ciolacu[a,*], Cyrielle Rudaz[b], Mihai Vasilescu[c], Tatiana Budtova[b,*]

[a] "Petru Poni" Institute of Macromolecular Chemistry, Department of Physical Chemistry of Polymers, 41A Grigore Ghica Voda Alley, 700487 Iasi, Romania
[b] MINES ParisTech, PSL Research University, CEMEF—Centre de Mise en Forme des Matériaux, CNRS UMR 7635, CS 10207 rue Claude Daunesse, 06904 Sophia Antipolis, France
[c] "Babes-Bolyai" University, Faculty of Physics, Mihail Kogalniceanu, 1, 3400 Cluj-Napoca, Romania

ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form 9 May 2016
Accepted 23 May 2016
Available online 24 May 2016

Keywords:
Cellulose
Cross-linking
Cryogel
Hydrogel
Swelling
Controlled release

ABSTRACT

Porous cellulose matrices were prepared via cellulose dissolution in 8 wt% NaOH-water, physical gelation and chemical cross-linking with epichlorohydrin (ECH), coagulation in water and lyophilisation. Cellulose and cross-linker concentration were varied. The behaviour of gels upon coagulation and the swelling of cryogels in water were analysed. An anomalous high swelling at cross-linker concentration around stoichiometric molar ratio with cellulose was observed. Cellulose cryogel morphology, crystallinity and density were studied. The influence of chemical cross-linking on cellulose swelling was explained by suggesting that ECH acts as a spacer preventing cellulose chains tight packing during coagulation. Cellulose was loaded with a model drug, procaine hydrochloride, and the kinetics of its release was investigated.

1. Introduction

Cellulose is a versatile polymer which exists in various forms, can be functionalized and is used to make different materials. For example, native cellulose reinforces plant cell walls, and natural fibres can be used to reinforce plastics; man-made cellulose materials are fibres, films, sponges and aerogels; cellulose esters can be thermoplastic and ethers can be water-soluble (Klemm, Heubletin, Fink, & Bohn, 2005; Ciolacu & Popa, 2010; Qiu & Hu, 2013). So-called cellulose hydrogels is a special class of cellulose wet materials which can be based either on cellulose I (case of bacterial or nano/microfibrillated cellulose) (Klemm et al., 2011; Saito, Uematsu, Kimura, Enomaea, & Isogai, 2011) or cellulose II (when prepared via cellulose dissolution followed by coagulation in water) (Sannino, Demitri, & Madaghiele, 2009; Chang & Zhang, 2011; Chang, Duan, Cai, & Zhang, 2010). Both types show high water retention, from several hundred to several thousand percent.

Hydrogels, by definition, are the networks that are swollen in aqueous media. They are widely applied in medicine and pharmacology, food, cosmetics, engineering and hygienic applications. The classical examples of synthetic polymers that are used for synthesizing hydrogels are poly(hydroxyethyl methacrylate), polyvinyl alcohol, polyacrylamides, polyacrylates, etc. Cellulose ethers carrying methyl-, carboxymethyl-, hydroxypropyl- or hydroxyethyl groups or their various combinations and which are water-soluble can also form hydrogels (Ahmed, 2015). The main principle is that aqueous medium is a solvent for the matter constituting the gel whatever is gelation mechanism and the nature of the bonds which "keep together" the macromolecules: physical (hydrogen, hydrophobic or van der Waals) or chemical (covalent or ionic). It should be noted that because water is cellulose anti-solvent, the term "hydrogel" is, strictly speaking, not applicable for cellulose I and II. However, we shall use it in the following for simplicity. Cellulose and cellulose derivatives' based hydrogels are very attractive materials for bio-medical applications (as matrices for drug delivery, for tissue engineering, scaffolds) due to their biocompatibility and biodegradability (Chang, Duan et al., 2010; Klemm et al., 2011; Peng, Dhar, Liu, & Tam, 2011; Bhattacharya et al., 2012; Qiu & Hu, 2013).

In this work we shall focus on cellulose II based hydrogels. They are obtained as an inevitable step during cellulose processing, i.e. cellulose coagulation into water from any solution. One of the oldest examples is cellulose hydrogels obtained during cellulose regeneration from viscose (Ando & Konishi, 2000; Saito, Sakurai, Sakakibara, & Saga, 2003). Cellulose II hydrogels can also

---

* Corresponding authors.
E-mail addresses: dciolacu@icmpp.ro (D. Ciolacu), Tatiana.Budtova@mines-paristech.fr (T. Budtova).

http://dx.doi.org/10.1016/j.carbpol.2016.05.084
0144-8617/

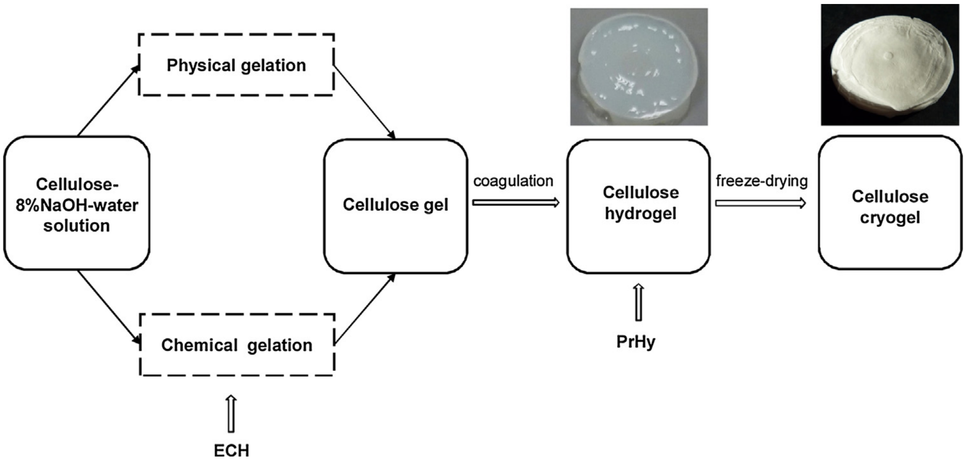


Fig. 1. Schematic presentation of physically and chemically cross-linked cellulose cryogels loaded with PrHy.

be obtained when coagulating cellulose from solution in direct solvents: NMMO monohydrate (Chang & Zhang, 2011), LiCl/DMAc (de Oliveira & Glasser, 1996; Xia, Patchan, Maranchi, & Trexler, 2015), ionic liquids (Turner, Spear, Holbrey, & Rogers, 2004; Sescousse, Gavillon, & Budtova, 2011a) and 6–10 wt% NaOH-water based solvent (Gavillon & Budtova, 2008; Sescousse, Gavillon, & Budtova, 2011b; Luo & Zhang, 2013). In the latter solvent, cellulose solutions are gelling forming a physical gel (Budtova & Navard, 2016). Using a cross-linker such as epichlorhydrin (ECH), it is also possible to obtain cellulose chemical gel (Zhou, Chang, Zhang, & Zhang, 2007; Chang, Zhang, Zhou, Zhang, & Kennedy, 2010; Ciolacu, Oprea, Anghel, Cazacu, & Cazacu, 2012; Qin, Lu, & Zhang, 2013).

Various properties of cellulose II hydrogels prepared from NaOH-based solvent had already been studied. It was shown that after being freeze-dried, cellulose is re-swelling in water at room temperature up to 3000–6000% (Zhou et al., 2007). The increase of cellulose and ECH concentration leads to the decrease of swelling (Qin et al., 2013): for example, for hydrogels prepared from 5 wt% cellulose solution, the degree of swelling decreased from 2300 to 1400% for ECH content from 5 to 15%. The compressive modulus of hydrogels increased with the increase of ECH concentration. Light transmittance of visible light can reach 90% for hydrogels prepared from 2 wt% cellulose solution (Chang, Zhang et al., 2010).

Cellulose and cellulose-lignin hydrogels, synthesized by dissolving cellulose in 8 wt% NaOH-water, followed by the chemical cross-linking with epichlorohydrin, were further used as a matrix for controlled release of polyphenols obtained by extraction from grapes seeds of *Chambourcin* type (Ciolacu et al., 2012). The swelling capacity of hydrogels increased from 1145 to 3061 wt% with the increase of lignin content.

The aim of this paper was to advance in the understanding of the physical properties of cellulose II based hydrogels prepared from cellulose-8% NaOH-water solutions and the influence of ECH concentration. The reason was our discovery of an anomalous swelling of cellulose hydrogels: we found an increase of hydrogel swelling degree with the increase of ECH concentration, with maximum swelling being at approximately cellulose:ECH stoichiometric ratio. In this work we focused on the differences induced by physical (without ECH) and chemical (ECH-induced) gelation on cellulose hydrogels' swelling in water after synthesis and after freeze drying (cryogels), and on cryogels' structure, morphology and density. Furthermore, the ability of freeze-dried cellulose hydrogels to function as drug delivery systems was studied. Cellulose hydrogels were loaded with procaine hydrochloride (PrHy) and the kinetics of its release in water was investigated.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose Avicel PH-101 DP of 180 as given by the manufacturer was purchased from Sigma-Aldrich. Sodium hydroxide (NaOH) in pellets with a purity ≥97% was supplied by Merck. Epichlorohydrin (ECH), b.p. 115–117 °C and purity >98% (Fluka), was used without further purification. Procaine hydrochloride (PrHy) with m.p. 155–156 °C and purity ≥97% were supplied by Sigma-Aldrich.

2.2. Methods

2.2.1. Preparation of neat cellulose cryogels and their drug-loaded counterparts

Cellulose–8 wt% NaOH-water solutions were prepared according to a standard procedure (Egal, Budtova, & Navard, 2007; Gavillon & Budtova, 2008; Sescousse & Budtova, 2009). Briefly, cellulose was swollen in distilled water for 2 h at 5 °C, 18 wt% NaOH aqueous solution was added to reach 8 wt% solvent concentration and the whole was mixed at −6 °C with an overhead mixer at 800 rpm for 2 h. Two cellulose concentrations were prepared, 5 and 7 wt%.

Two types of samples were synthesized: physically and chemically cross-linked cellulose (Fig. 1). To prepare physically cross-linked samples, solutions were poured into moulds and kept at room temperature for 24 h. In these conditions cellulose-NaOH solutions undergo physical gelation (Roy, Budtova, & Navard, 2003). Cross-linked cellulose was synthesised by adding ECH dropwise into a fresh cellulose-8% NaOH solution, stirring vigorously for 15–20 min, rapidly pouring into moulds and keeping the system for 24 h at room temperature. Samples after physical or chemical gelation will be called "gels" (each time the gelation mode will be specified). Epichlorohydrin concentration was varied to reach different molar ratios of ECH (*n mol ECH*) to anhydroglucose units, AGU (*n mol AGU*):

$$R = nmolECH/nmolAGU \quad (1)$$

The gels were then immersed in a non-solvent bath (water) and washed many times to coagulate cellulose and remove NaOH, resulting in cellulose "hydrogels".

Loading of cellulose with procaine was performed as follows: hydrogels (cross-linked and not) were placed in 50 mL procaine hydrochloride (PrHy) solution of different concentrations (hydrogels from 5 wt% cellulose solution in 2, 4 and 8 g/L PrHy and from