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Nanocellulose nanocomposite hydrogels: technological and environmental issues

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Over the last decade, nanocellulose-based nanocomposite hydrogels have emerged as promising materials in different fields of application such as medicine, food, and agriculture. The present review addresses the advances in the synthesis methods and technological applications of these hydrogels. Different chemical and physical cross-linking methods used for the design of cellulose nanocrystals, cellulose nanofibrils, and bacterial cellulose hydrogels are discussed in detail. Nanocomposite hydrogels based on nanocellulose or reinforced with nanocellulose have good mechanical properties, biocompatibility, and biodegradability and allow the incorporation of several molecules or solutes, which can provide a slow and controlled release profile. The major advances exploring these hydrogels in biomedicine, food, and agriculture are reviewed. Finally, challenges and environmental issues related to their production are briefly discussed.

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Introduction

Nanocellulose has received much attention over the last two decades due to its renewable nature and unusual properties. These include high elastic modulus, high specific surface area, low density, non-abrasive nature, easy surface functionalization, biodegradability, and biocompatibility. Nanocellulose can be generally classified into three types: cellulose nanocrystals (CNCs), cellulose nanofibrils (CNFs), and bacterial nano-



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cellulose (BNC). The term nanomaterial is used to describe materials with a scale ranging from one billionth of a meter (10^{-9} m) to one millionth of a meter (10^{-6} m) which has properties not observed when organized on a large scale. For example, colloidal suspensions of CNCs with 5 nm in diameter may form iridescent films by maintaining their chiral nematic structure when dried slowly.¹ The presented color patterns come from the reflection of certain wavelengths on the surface of the film, while the cellulose fibers present in plants reflect all the wavelengths belonging to the visible light range.

The discovery of the excellent ability of mechanical reinforcement by Favier *et al.*² initiated a wave of promising applications of CNCs for composites,³ packaging,⁴ catalysis,⁵ nanoelectronics,⁶ sensors and energy storage,⁷ and biomedicine.^{8,9} Many of these applications explore the high moisture absorption and wettability with hydrophilic polymers of nanocellulose to get hydrogels with good mechanical properties, biocompatibility, and biodegradability.

Since the first work with poly(2-hydroxyethyl methacrylate) (PHEMA) and ethylene glycol dimethacrylate (EGDMA) for contact lens applications in the 1960s,¹⁰ notable progress has been achieved in the synthesis, characterization, and application of hydrogels. Hydrogels can be formed using natural, synthetic polymers or a combination of both, denominated as semi-synthetic. Hydrogels present a hydrophilic three-dimensional (3D) structure with a great capacity to absorb and retain water without dissolving.¹¹ The water absorption of hydrogels is affected by capillarity, osmotic force, hydration capacity, and the elastic retractive force of the polymer network. The solubility depends on the cross-linking density and interlacement of the polymer chains. Some hydrogels may exhibit responsive behavior to external stimuli, such as (1) pH; (2) temperature; (3) ionic strength, (4) light; (5) electric field, (6) magnetic field; and (7) solvent composition.¹² The incorporation of nanostructures can improve the properties of the hydro-

gels. In this context, nanocellulose has been used to get nanocomposite hydrogels with new properties and functions.

Nanocellulose has high dispersion in aqueous media and it can be prone to surface chemical modifications that can be exploited in the manufacture of hydrogels. As previously reported, nanocellulose is a good reinforcing agent, has good interaction with hydrophilic polymers, and is biodegradable, biocompatible, renewable, and generally regarded as an eco-friendly material. Recent advances in the large-scale production of nanocellulose,^{13–15} the understanding of its physical and chemical properties^{16–19} and its wide range of applications have driven interest in the production of nanocomposites based on nanocellulose. In this sense, the popularity of nanocellulose as a component in the formulation of hydrogels tends to grow even more in the coming years.

Thus, in this review, we discussed the recent and important advances in nanocellulose hydrogels. It addresses the production, characterization, and applications of nanocomposite hydrogels containing CNC, CNF, and BNC. We gave a special emphasis on the hydrogel production and sustainable development.

Based on the current literature, only the review by De France *et al.*²⁰ on obtaining biodegradable and non-biodegradable hydrogels and aerogels with CNC and CNF produced from plants was related to this question. In the present review, recent advances in the field of research and applications of nanocellulose-containing biodegradable hydrogels are deeply discussed. The present review covers the main processes for the production of CNC, CNF, and BNC, and hydrogels by clean processes. So, its purpose was to highlight the relevant aspects of these hydrogels as medical, food and agricultural materials. Thus, we shed light on the current trends and future prospect with a special emphasis on environmental issues. It is expected that this review will forge new directions for the design, synthesis and wider application of nanocellulose-containing biodegradable hydrogels and functional materials.



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Nanoscale nature of cellulose

The science of cellulose started in 1837 with the discovery by Anselme Payen of the existence of a fibrous substance present in all plants. In 1839, the French academy attributed the name of cellulose to this substance.²¹ Almost a century later, it was discovered that certain bacteria can produce an identical substance to the cellulose of plants.²² Since its discovery, it was believed that cellulose was an aggregate of some glucose or cellobiose molecules like micelles. Only between the 1920s and 1940s, the idea that cellulose is a polymer formed by molecules of glucose bounded by covalent bonds gained strength.

The interest in the polymeric nature of cellulose boosted many studies about its supramolecular organization. For example, Wuhrmann *et al.*²³ observed the presence of nanofibers 6–7 nm in diameter attached to ramie, hemp, and cotton fibers after ultrasonic treatment. In 1950, Ranby and Ribi²⁴ reported the first transmission electron microscopy images of micellar cellulose particles produced by hydrolysis with dilute sulfuric acid. Today, we know that the observed particles were CNCs.

The description of the method for obtaining a suspension of cellulose nanofibrils occurred only in 1983 by Turbak *et al.*²⁵ and Herrick *et al.*²⁶ The liquid-crystalline property of CNCs dispersed in water was first studied by Marchessault *et al.*²⁷ in 1959, but the formation mechanism of the chiral nematic liquid-crystalline phase in CNC films was only reported in 1992.¹

Years later, in 1995, Favier *et al.*² reported the first attempt to reinforce a polymer with CNCs. Since then, nanocellulose materials have been mixed or dispersed in a variety of polymer matrices and used for different applications. Thus, the discovery of nanocellulose has enabled a revolution in different fields of research and entered the long history of cellulose as a nanomaterial of great modern industrial interest.

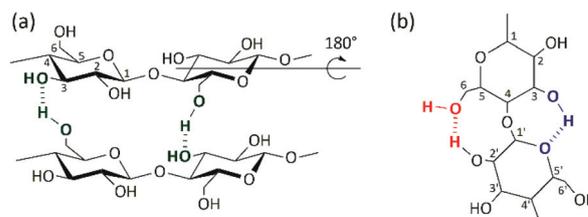


Fig. 1 Chemical structure of cellulose. (a) Inter- and (b) intramolecular hydrogen bonds.

Overview of the structure of cellulose

Cellulose is the most abundant natural polymer on the planet, with an annual production estimated at 10^{12} tons.²⁸ Cellulose is found in plants, with approximately 15–30% of the dry mass in the primary cell wall and more than 40% in the secondary cell wall.²⁹ The formation of the primary cell wall occurs in the early stages of cellulose biosynthesis near the middle lamella. The secondary cell wall is the thickest layer and the most important for the mechanical properties of the plant.

The secondary wall layers differ in chemical composition, orientation of cellulose microfibrils and thickness. In the S2 layer, the cellulose chains are nearly parallel to the longitudinal axis of the cell, whereas, in S1 and S3 layers, the chains are nearly perpendicular to the longitudinal axis.³⁰ The junction of 18 cellulose chains gives rise to aggregates called microfibrils.³¹ The cellulose microfibrils are embedded in a matrix composed of hemicelluloses and lignin to form a natural composite.

Cellulose consists of β -D-glucopyranosyl-(1 \rightarrow 4)- β -D-glucopyranose (cellobiose) units, formed by the β (1 \rightarrow 4) glycosidic bond between two molecules of β -D-glucopyranose ($C_6H_{12}O_6$) in 4C1 chair conformation with the second unit rotated 180° around the molecular axis (Fig. 1).



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Fauze A. Aouada licensed in chemistry from the State University of Maringá (2003), and received a Master's degree in Chemistry from the State University of Maringá (2005) and PhD in Chemistry at the Federal University of São Carlos. His research goal focuses on the development of nanocomposites for slow/controlled release in agriculture and interactions of inorganic nanoparticles with plants and soil.



Judith P. A. Feitosa

Graduate in Chemical Engineering from the Federal University of Ceara, and holds a doctorate in Chemistry obtained from São Paulo University. She has been a full professor at the Department of Organic and Inorganic Chemistry since 1999, where she founded the Laboratory of Polymer Chemistry. She has experience in a broad range of topics one of the most important of which is the characterization, derivatization and application of natural polymers obtained from the diverse biota of Brazil, in particular polysaccharides. Other major interests include the production and application of hydrogels and aerogels.

The degree of polymerization (DP) is in the range of about 10 000 units of β -D-glucopyranose.³² In general, the DP depends on the source and the method of isolation used to separate the cellulose from the cell wall.

Cellulose is synthesized at the plasma membrane–cell wall interface by synthase proteins (CesA). These proteins form a hexameric rosette structure called the cellulose synthase complex (CSC).³³ During the natural synthesis of cellulose, each CSC produces 18 cellulose chains that crystallize forming crystals with 3–5 nm in diameter, composing the microfibrils.³⁴ This structure is a result of the strong tendency of the hydroxyl groups (–OH) to form intra (O6...H–O2' and O3–H...O5') and intermolecular (O3...H–O6) hydrogen bonds. The most common crystalline form of cellulose is native cellulose or cellulose I, which presents unitary triclinic and monoclinic cells, called cellulose I α and I β , respectively.²⁸

Besides the formation of crystalline domains, intramolecular and intermolecular hydrogen bonds govern the solubility and the mechanical properties of cellulose. Cellulose chains separation minimizes the hydrogen bond influence, favoring the dissolution of cellulose. As an example, the addition of charges in the cellulose chains increases their solubility due to microfibril swelling.³⁵ The leverage effect on the O3–H...O5' bond governs the high axial elastic modulus of cellulose.³⁶ During stretching, the alignment of the zig-zag conformation occurs around the C–O–C glycosidic bond. A detachment occurs in the hydrogen bond between the O3–H...O5', while the distance between the hydrogen bond O6...H–O2' does not change. Thus, a slight deformation of the glycosidic bond prevents the compression of the O6...H–O2' bond, and amplifies the O3–H...O5' bond effect on cellulose stiffness.

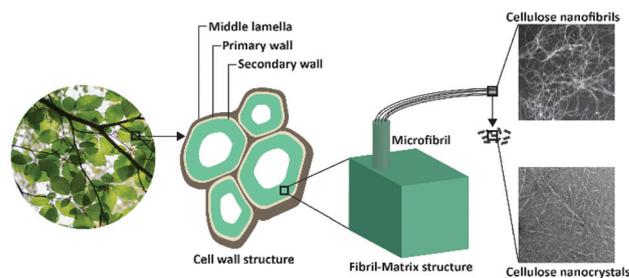


Fig. 2 Schematic representation of nanocellulose obtained from plants.

Fundamentals of nanocellulose

Nanocellulose is obtained from renewable sources using theoretical–experimental approaches called top-down and bottom-up. The top-down method produces nanometer scale blocks by shattering from bulk cellulose, while the bottom-up method uses individual molecules or atoms to construct nanometer scale blocks. Acid hydrolysis and disk milling are examples of the top-down method, while production by bacteria is an example of a bottom-up method. Fig. 2 shows a representation of CNCs and CNFs from the cell wall. CNCs are rod-like crystalline fragments of cellulose obtained by the selective removal of the amorphous regions. CNFs are filamentous fragments with a cross-section on the order of a few nanometers containing both amorphous and crystalline domains.

Nanocellulose has been used to improve the performance of products and develop materials with unique characteristics. It can be used as a mechanical reinforcing agent, thickening agent, rheological modifier, emulsion stabilizer, low-calorie



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Morsyleide de Freitas Rosa obtained her PhD in the Technology of Chemical and Biochemical Processes at Federal University of Rio de Janeiro in 1997. Since 1995, she has worked at the Brazilian Agricultural Research Corporation (EMBRAPA). Her research is focused on the development of biobased products within the context of biorefining, whereby biomass is disassembled to create value-added

products such as nanocellulose, bionanocomposites, hydrogels and aerogels.



Alain Dufresne

Alain Dufresne received his Ph.D. in 1991 from INSA Toulouse (Electronics) and was Post-doc at Polytechnique Montreal, and Lecturer at INSA Lyon. He was appointed as Associate Professor in 1993, and then Professor in 2001, at Grenoble University. Since 2003 he has been Professor at Grenoble INP. He was visiting Professor at UFRJ and Embrapa Fortaleza (Brazil), and UKM (Malaysia). His research interests are the processing and character-

ization of renewable nanocomposites. He has published +270 peer-reviewed papers. He received the 2016 International Nanotechnology Division Award and FiberLean® Technologies Prize awarded by TAPPI and is among the 2016 top 300 most cited researchers in materials science and engineering/Elsevier Scopus Data.

food additive, hydrogel, aerogel, liquid crystal, support for catalysis and immobilization of enzymes, scaffold, carrier vehicle for system controlled release, biosensor, bioimaging agent, pharmaceutical binder, *etc.*¹⁶

Nanocellulose displays a good dispersal ability in water, and for this reason, nanocomposites with nanocellulose were initially prepared by mixing this aqueous dispersion with aqueous solutions of water-soluble polymers or aqueous dispersions of polymers (latexes). Upon drying, the intercalation of polymer chains between well-dispersed nanocellulose prevents its aggregation and promotes the formation of a homogeneous mixture between the nanoparticle and the matrix.

The high aspect ratio and stiffness of nanocellulose contribute to the formation of nanocomposites with improved mechanical properties compared to the neat matrix. Another advantage is its ability to increase the tortuosity (or pathway) in the diffusion of gases and water vapor molecules through the polymer matrix, improving the polymer barrier property. Both properties depend on the degree of dispersion of nanocellulose in the polymer matrix and the nature of interfacial interactions.

Cellulose is an attractive substrate for several reactions due to its simple structure. The addition of specific functional groups on cellulose changes its reactivity, solubility, and dispersibility in hydrophobic media or polymer matrices.³⁷ These changes increase the range of applications for nanocellulose. Modification is generally achieved through derivatization reactions such as acetylation, silanization, cationization, carbamation, amidation, oxidation, grafting from, grafting onto, Diels-Alder, thiol-ene, and Huisgen cycloaddition (Fig. 3).

The toxicity of CNCs and CNFs was the object of several studies pointing to a good perspective for the clinical use of these nanostructures.^{38,39} When taking into account all characteristics, properties, and applications, nanocellulose is at the forefront of new and attractive materials that combine technical and environmental aspects.⁴⁰

Cellulose nanocrystals

The Technical Association of the Pulp and Paper Industry (TAPPI) has proposed a new TAPPI standard (WI 3021) to describe nanocellulose materials. As per the proposed, CNCs present a pure crystalline structure and dimensions of 3–10 nm

in width and an aspect ratio (ratio of the largest to the smallest dimension) greater than 5 and usually less than 50.

The preparation of CNCs was first reported by Rånby in 1949.^{24,41,42} The main material used for the production of CNCs is wood. But, they can also be produced from non-wood plants, tunicates, certain species of bacteria, and algae. The length (L) and diameter (D) of CNCs depend on the cellulose source and extraction conditions. In general, CNCs extracted from plants, such as cotton linters, coconuts, palm oil, sugarcane bagasse, sisal, *etc.*, have lower length than CNCs isolated from tunicates.

The acid hydrolysis of glycosidic bonds is the most popular method for CNC extraction. This process causes the separation of the crystalline domains and the degradation of amorphous regions. The parameters involved for obtaining CNCs can change their geometry, crystallinity index, and aspect ratio.

The most commonly used acids are sulfuric, hydrochloric, phosphoric and hydrobromic acids or a mixture of inorganic and organic acids.³² However, H_2SO_4 has been and continues to be the most used acid to extract nanocrystals from the biomass. This choice stems from the formation of crystals with a good dispersibility ability in aqueous medium. The CNC suspension is stabilized by electrostatic repulsion interaction between anionic groups ($-SO_3^-$) on the surface of the crystals.

Despite these advantages, H_2SO_4 can result in handling risks and high costs in the acid residue treatment.⁴³ To avoid these problems, many researchers have studied alternative processes to obtain CNCs. Among them, we can highlight enzymatic hydrolysis,^{44,45} enzymatic hydrolysis followed by acid hydrolysis,⁴⁶ ultrasonically assisted hydrolysis without⁴⁷ and with weak organic acids,⁴⁸ hydrolysis with oxidizing agents,⁴⁹ hydrolysis in subcritical water⁵⁰ and hydrolysis mediated by ionic liquids.⁵¹

Cellulose nanofibrils

According to TAPPI WI3021, CNFs present both crystalline and amorphous regions, with dimensions of 5–30 nm in width and an aspect ratio usually greater than 50.

The first work related to cellulose defibrillation was reported in 1983 by Turbak *et al.*²⁵ and Herrick *et al.*,²⁶ both researchers at the ITT Rayonier Eastern Researchers Division Laboratory in Whippany, New Jersey, USA. These researchers produced CNFs by passing a 2 wt% refined cellulose suspension through a Manton-Gaulin homogenizer. But, as pointed out by Eriksen *et al.*⁵² the main disadvantage of this process is its high energy consumption. This negative energy balance limited the commercial use of this material after its discovery.

Two decades later, Taniguchi and Okamura⁵³ innovated the pulp production process using a Supermasscolloider (Masuko Sangyo Co. Ltd, Japan). The pulp was passed between one static disk and one rotating disk in parallel, defibrillating the cellulose by high shearing forces.

The next instrumental advance occurred in 2004, when Zimmermann *et al.*⁵⁴ reported the disintegration of cellulose fibers to produce CNFs using a microfluidizer. Other techniques have been explored for the production of CNFs such as

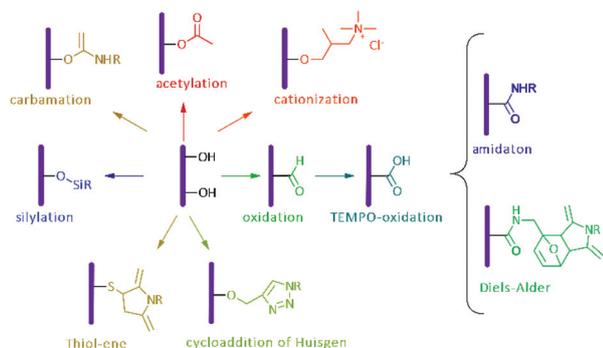


Fig. 3 Possible chemical modifications that can be conducted to cellulose.

ultrasound,⁵⁵ high-speed industrial blending,⁵⁶ and extrusion.⁵⁷ However, the predominant techniques are still homogenization (homogenizer and microfluidizer) and grinding with disks.

To reduce the energy cost for CNF production, biological or chemical treatments have been applied before the chosen shear stage. The biological pretreatment consists of using enzymes to promote the partial hydrolysis of cellulose.^{58,59} The chemical pretreatment introduces functional groups on the surface of cellulose. The functional groups generate repulsion points between the fibrils. For example, oxidation with the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)/NaBr/NaClO system promotes electrostatic repulsions between the cellulose fibrils that help the shear and dispersion of the nanofibrils. When compared to the H₂SO₄ hydrolysis, TEMPO-mediated oxidation adds negative charges to the cellulose surface without causing degradation of the amorphous region.⁶⁰ This method converts part of the -O(6)H groups into carboxylic groups which can be used for the introduction of different functions. The nanofibril yield is influenced but the degree of oxidation is significantly dependent on the reaction conditions.

Saito *et al.*⁶¹ and Saito and Isogai⁶² were the pioneers in the studies using TEMPO oxidation for the production of CNFs. The discovery of the Isogai's group led to a veritable explosion of scientific work.

Bacterial nanocellulose

BNC is formed from the conversion of glucose molecules into cellulose nanofibrils by different bacterial species, such as *Acetobacter*, *Agrobacterium*, *Achromobacter*, *Aerobacter*, *Azotobacter*, *Sarcina ventriculi*, *Salmonella*, *Escherichia*, *Gluconobacter*, *Komagataeibacter* (formerly classified as *Gluconacetobacter*), and *Rhizobium* (Fig. 4).⁶³ The synthesis of cellulose occurs within the cells. The cellulose comes in the form of an interlaced ribbon with a diameter of 100 nm and a few micrometers in length.⁶⁴

The first description of BNC was reported in 1886 by Brown.⁶⁵ Brown observed that some microorganisms produced a gelatinous membrane on the surface of beer samples.

Microbial cellulose is obtained from a substrate rich in mono- and oligosaccharides at different pH values and incubation times. Thus, the formation of cellulose occurs by the fermentation of the culture medium. Cellulose is isolated through a treatment with NaOH.⁶⁴ Its production follows a bottom-up model, which allows standardization and control of the properties (size, crystallinity, shape, aspect ratio, *etc.*) during its production.

The absence of lignin, hemicelluloses and pectin makes this material attractive for applications in the medical field.

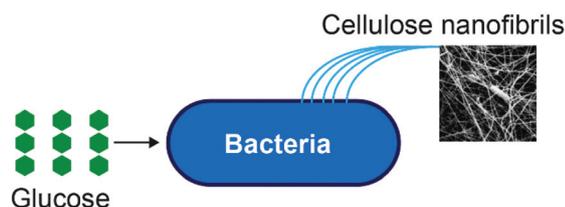


Fig. 4 Schematic image of bacterial cellulose production.

Hydrogels: theoretical concepts and properties

Since their discovery in 1960s by Wichterle and Lim,¹⁰ hydrogels have generated great interest. In the following two decades, considerable attention has been directed towards the synthesis of hydrogels, contact lens production, and drug delivery. Currently, hydrogels are used in hygiene products, soil conditioners, artificial snow, food additives, wound healing, cell growth, among other applications.¹¹

Hydrogels are heterogeneous mixtures of two (or more) phases. The dispersed phase is water and the solid phase is a solid three-dimensional network (Fig. 5).⁶⁶ They consist of a 3D polymer network filled by water. Water retention occurs due to the formation of hydrogen bonds between hydrophilic groups. The hydration process leads to the deformation of the polymer chains to compensate for the stress created inside their structure. Water absorption ends when these opposing forces reach equilibrium. The absorption process, also called swelling, may still be dependent on the cross-linking density, flexibility, presence of polymer chain charges, changes in pH, ionic strength, and temperature.

The interactions that govern the formation of hydrogels can be: (1) electrostatic interactions, (2) ionic gelification, (3) host-guest interactions, (4) hydrogen bonds, (5) van der Waals forces, (6) hydrophobic interactions, (7) interlacing of the chains and (8) covalent bonds between a cross-linking agent (multifunctional monomer) and the polymer chains.⁶⁷

The electrostatic interaction is the attraction between oppositely charged groups on different polymers (Fig. 6a). Ionic gelification is promoted by the chelate formation due to the interaction of functional groups present in the polymer chain with metal ions (Fig. 6b).

Hydrogel formation can still be governed only by local self-assembly. This hydrogel is the result of multiple weak interactions, including host-guest interactions, hydrogen bonds, van der Waals forces, hydrophobic interactions, *etc.* In this system, the association between the molecules could not be maintained only by individual interactions (Fig. 6c). For example, it has been recently demonstrated that methylcellulose (MC) polymer chains in water are able to form nanostructured fibrils (14 nm in diameter) under heating.^{68,69} The

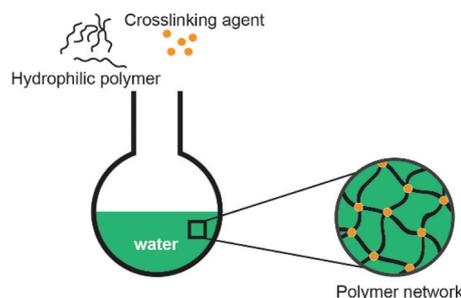


Fig. 5 Three-dimensional network formation.

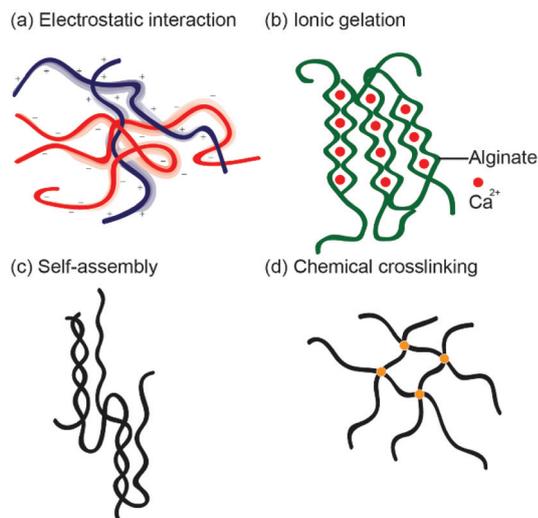


Fig. 6 (a) Electrostatic interaction, (b) ionic gelation, (c) molecular self-assembly and (d) chemical cross-linking.

MC chains adopt a ring-like conformation at higher temperature, and then these ring structures self-assemble into fibrils. The collapse is driven by strong intermolecular interaction from MC monomers.⁷⁰ These nanoscale fibrils then form networks owing to the hydrophobic attraction, forming a fibrillar gel.

Physical hydrogels are not permanent and may dissolve when the interactions between the polymers collapse. Chemical hydrogels are formed by permanent structures in which the atoms are bonded by covalent bonds in a continuous network extending throughout the material (Fig. 6d). Some examples of approaches used for the formation of chemical hydrogels are radical polymerization, Schiff base formation reactions, addition and condensation reactions, UV irradiation and enzymatic action.⁷¹

The formation of an elastic network immersed in a liquid has been described by DLVO,⁷² fractal⁷³ or bound percolation theories.⁷⁴ The DLVO (Derjaguin–Landau–Verwey–Overbeek) theory considers that the stability of a colloidal dispersion is determined by the balance of attractive van der Waals forces and the electrical double layer forces. Thus, in solutions with a high concentration of counterions or near the isoelectric point, the thickness of the double layer is very thin and the van der Waals forces of attractive character predominate. Polymerization or cross-linking reactions are aggregation processes similar to those used for forming colloidal gels.⁷⁵ The fractal model assumes that the hydrogel structure is formed by fractal aggregates. The initial step for gel formation is the aggregation of some particles to form fractal aggregates. These aggregates grow until they occupy the total volume of the liquid. As a consequence, the viscosity tends to infinity and the system behaves like a gel. The formation of the fractal structure suggests that in any volumetric fraction the properties of the hydrogel will be the same.⁷³

The percolation theory is a nonlinear probabilistic model used to describe statistical processes. The model assumes the

existence of an abrupt phase transition between two well-defined states.⁷⁶ According to this theory, the gel point is interpreted as an infinite and continuous sequence of interactions joining the individual aggregates until reaching the percolation threshold. The percolation threshold is a critical point where above this point the percolation occurs and below it does not occur. Near this point, even a small change in one parameter produces an abrupt change in another. Thus, the percolation model allows deriving a power-law for the evolution of parameters such as viscosity and elastic modulus.

Hydrogels can be synthesized from synthetic polymers, such as polyacrylamide, polyacrylic acid, among others, or from natural polymers such as cellulose, chitosan, and starch. This last class has been the subject of many investigations due to their renewable and biodegradable properties.⁷⁷

The mechanical properties of hydrogels are a topic of great interest for industry. Many applications need that the hydrogel maintains its shape for long periods of time or deforms without the occurrence of fractures. For example, when using a hydrogel for the replacement of an articular cartilage, it is necessary that the material presents high stiffness (Young's modulus of 1 MPa), high toughness (1000 J m⁻²) and high water content (60–80%).⁷⁸ However, conventional hydrogels obtained by the chemical reaction of a mixture of monomers and cross-linkers have a low stiffness (<10 kPa),⁷⁹ low tensile strength (<100 kPa),⁷⁹ low tensile strength, and low toughness (<100 J m⁻²).⁶⁷ In general, chemical cross-linking promotes the formation of an inhomogeneous polymer network.⁸⁰ This network possesses defects, like loops, dangling ends, and heterogeneity in cross-link density (Fig. 7). Thus, the failure crack propagates preferably along these irregularities.

Recent studies have mostly focused on new strategies for the formation of hydrogels with enhanced mechanical properties. Okumura and Ito⁸¹ reported the incorporation of a polymer chain into a cyclic cross-linker that can move throughout the length of the straight chain. Under stress, the energy is dissipated by sliding the cross-linker through the polymer matrix. Gong *et al.*⁸² have developed a new class of hydrogels with two polymer networks linked by many cross-linking mechanisms (double-network). During mechanical stretching, the polymer network bundles dissipate some of the energy, while the other network remains intact. Sakai *et al.*⁸³ reported

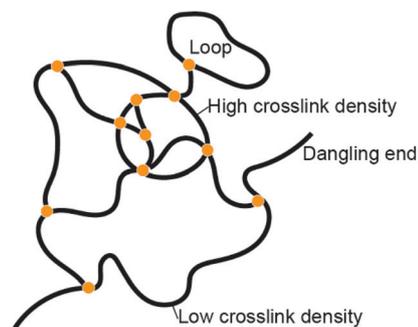


Fig. 7 Hydrogel network defects.

a polymer network obtained by the coupling of polyethylene glycol-tetra-amino and polyethinoglycol-tetra-*N*-hydroxy-succinamide glutarate of the same size. This strategy consists of the formation of a homogeneous polymer network that can be more resistant to fracture. Haraguchi and Takeshita⁸⁴ have developed a new class of hydrogels reinforced with nanoparticles. Nanocomposite hydrogels are nanomaterial-filled hydrogels that exhibit higher elasticity and strength compared to traditional hydrogels. When the polymer network is stretched, the filler-polymer interaction is switched-off, and the hydrogel can swell several times its mass. Thus, the energy dissipation generated during elastic deformation is caused by the energetically favorable synergy between chain entropy and polymer-filler interaction enthalpy.

Nanocellulose-reinforced “green” hydrogels

Biodegradable polymers or polymers obtained from renewable resources have gained much attention in the last few decades due to the increase of public pressure on environmental issues. To make these polymers more competitive against the usual (non-renewable) polymers, the incorporation of reinforcing agents has been studied as one way to improve their properties. In this context, many researchers have focused on the use of nanocellulose as an alternative to inorganic reinforcing agents for the production of fully “green” composites.⁴⁰ Hydrogels entirely made of biopolymers and reinforced with nanocellulose can be classified as “green” nanocomposite materials because of their renewable and biodegradable design. The production of these “green” materials combines and creates new and attractive properties that can be explored in the fields of biomedicine, food, agriculture, *etc.*

The incorporation of nanocellulose into the hydrogel formulation promotes improvements in properties and a significant expansion in the range of applications. For example, the mechanical properties are improved as a function of the particle-particle and particle-polymer interactions. The interactions between adjacent nanoparticles can be classified as “on” or “off”. In the “on” state, the formation of a percolation network occurs, promoting an increase in the particle-polymer interactions. In the “off” state, the percolation network is not formed due to the weakening of the particle-particle interactions, which also hampers the particle-polymer interactions. Thus, when a load is applied in the “on” state, a reversible rearrangement occurs between the reinforcement and the matrix. For this reason, the energy is dissipated and the fracture resistance increases. On the other hand, a high concentration of the reinforcement may cause an increase in the viscosity of the system and a reduction in the mobility of the polymer chains, favoring the formation of a non-homogeneous polymer network during cross-linking.

In general, the nanocellulose-hydrogel interactions may be physical, chemical or a combination of both. Nanocellulose may be the major component or only be dispersed within the

hydrogel structure. The synthesis of the hydrogel may involve only a single step, as simultaneous polymerization and cross-linking, or several steps, as chemical modification of nanocellulose followed by cross-linking. In the following sections, we will review the main strategies used for the construction of “green” nanocomposite hydrogels with natural polymers and synthetic biodegradable polymers containing nanocellulose.

Alginate

Sodium alginate or alginic acid is an anionic polysaccharide found naturally in the cell wall of algae, and it is formed by (1-4)-linked β -D-mannuronic and α -L-guluronic acids. Alginate forms hydrogels in the presence of divalent cations such as Ca^{2+} . The interaction between guluronic residues and divalent ions promotes the ionic gelation of alginate in the form of egg-box structures.

Due to this property, alginate is commonly used to produce beads and physical polymer networks. For example, Mohammed *et al.*^{85,86} fabricated alginate/CNC beads with CaCl_2 . The spherical hydrogels showed an increase in the absorption of the methylene blue dye with the increase of the CNC concentration. Park *et al.*⁸⁷ used the same strategy to prepare beads with BNC oxidized *via* TEMPO and alginate. They observed an increased compressive strength, chemical stability and cell proliferation when compared to pure alginate beads. Laurén *et al.*⁸⁸ coated suture lines with CNFs and alginate cross-linked with CaCl_2 and BaCl_2 . The results showed a cell viability around 100% over the two-week incubation period.

Lin *et al.*⁸⁹ reported the synthesis of double layer beads with an inner layer formed from cationic alginate/CNCs and an outer layer containing only alginate cross-linked with CaCl_2 . The hydrogel presented a complex controlled release mechanism involving two distinct release rates for each hydrogel layer.

Martínez Ávila *et al.*⁹⁰ developed double layer BNC/alginate hydrogels with a macroporous layer of BNC/alginate on the top of a dense layer of regenerated BNC. The dense layer promoted good mechanical stability, while the macroporous layer favored chondrocyte adhesion and proliferation.

Aarstad *et al.*⁹¹ prepared CaCO_3/D -glucono- δ -lactone modified alginate hydrogels containing CNFs and cross-linked with CaCl_2 that showed a high elastic modulus value. Naseri *et al.*⁹² developed double-network hydrogels with alginate and gelatin also containing 50% CNCs. The hydrogel presented an elastic modulus value of 0.5 GPa, a mechanical strength of 14.4 MPa and a deformation of 15.2%. Anirudhan *et al.*⁹³ reported the synthesis of a hydrogel containing TEMPO oxidized CNCs and chitosan cross-linked with *N*-ethyl-*N'*-(3-(dimethylamino) propyl) carbodiimide/*N*-hydroxysuccinimide (EDC/NHS), alginate coated and then grafted with 2-hydroxyethyl methacrylate-co-methacrylic acid *via* radical polymerization. The second coating with the copolymer added responsive pH behavior to the hydrogel and allowed two different drugs to be incorporated into the controlled release system. The release of the first drug was pH dependent, while the release of the second drug

was controlled by the combined effect of the polymer degradation with the hydrogel swelling. Yue *et al.*⁹⁴ reported the production of a hydrogel with a core containing CNF/poly(vinyl alcohol) (PVA)/glutaraldehyde (GA) and a shell formed from alginate/CaSO₄/Na₂HPO₄. The hydrogel had 3.2 times greater compressive strength than the hydrogel without the incorporation of CNFs.

Recently, 3D printing technology has been exploited for the production of alginate nanocomposite hydrogels containing nanocellulose.^{95–97} For example, Markstedt *et al.*⁹⁷ reported the printing of different pieces using a viscous CNF/alginate dispersion. After printing, the molds were immersed in a solution of CaCl₂. Complex three-dimensional structures with high storage modulus, shear modulus and compressive strength were printed using a mixture of 80% CNF and 20% alginate as printable biotin (Fig. 8).

Cellulose and cellulose derivatives

Cellulose and its derivatives, such as carboxymethylcellulose (CMC), hydroxyethylcellulose (HEC) and MC have been used in many industrial applications (particularly in food and pharmaceutical industries) as foam and emulsion stabilizers, thickeners, binding agents, *etc.*, due to their biodegradability and non-toxicity. Moreover, their low price makes them popular in the market. However, the mechanical properties of swollen hydrogels are inadequate for more demanding applications.

Dai and Kadla⁹⁸ are pioneers in the study of hydrogels reinforced with nanocellulose. The authors used TEMPO-oxidized CNCs as a reinforcing agent for CMC/HEC hydrogels cross-linked with divinyl sulfone (DVS). The incorporation of CNCs increased the compression modulus of the pure hydro-

gel when compared with hydrogels reinforced with Cloisite Na⁺ nanoclay. Araki *et al.*⁹⁹ found similar results using CNCs as a reinforcing agent for CMC/HEC hydrogels. McKee *et al.*¹⁰⁰ reported the formation of a hydrogel after dissolution of MC at 60 °C in the presence of CNCs with a storage modulus of 900 Pa. According to the authors, due to the structural similarity, MC has a strong interaction with nanocrystals, forming cross-links and, hence, the gels (Fig. 9).

Another strategy that has been explored is obtaining “all-cellulose nanocomposites”, when the composites are prepared using cellulose as both a matrix and reinforcement.^{101–103} In general, this method consists of mixing nanocellulose with a pre-dissolved cellulose solution in a specific solvent to induce the formation of a hydrogel and eliminate chemical incompatibilities between the matrix and the reinforcement.¹⁰¹ Lourdin *et al.*¹⁰³ added a mixture of type I CNCs and lyophilized type II cellulose in a solution of microcrystalline cellulose dissolved in 1-butyl-3-methylimidazolium chloride and dimethylsulfoxide. The type I CNCs acted as a rigid structure and promoted the co-crystallization of type II CNCs in the regenerated cellulose matrix. This effect favored the production of more rigid hydrogels due to the formation of a percolation network capable of avoiding the conversion of type I CNCs into type II.

Collagen

Collagen is the most abundant protein in the human body and is widely used in *in vitro* and *in vivo* tissue engineering applications. Li *et al.*¹⁰⁴ reported the production of a porous collagen/CNC scaffold with gelatin microspheres containing basic fibroblast growth factor (bFGF) as a platform for release and formation of blood vessels (angiogenesis). For compositions with up to 5% CNC, the authors observed an increase in the degree of swelling. *In vitro* and *in vivo* results indicate that the scaffold was biocompatible and biodegradable and significantly increased the formation of new blood vessels.

Zhu *et al.*¹⁰⁵ and Guo *et al.*¹⁰⁶ used a similar strategy for controlled release of gentamicin sulfate and curcumin, respectively. *In vitro* tests indicated that the scaffold for release

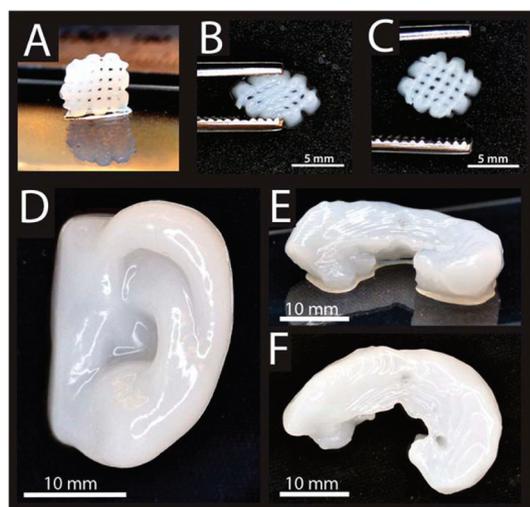


Fig. 8 (a) 3D printed small grids (7.2 × 7.2 mm²) with 80% CNF and 20% alginate after cross-linking. (b) The shape of the grid deforms while squeezing, and (c) it is restored after squeezing. (d) 3D printed human ear and (e and f) sheep meniscus with 80% CNF and 20% alginate. Side view (e) and top view (f) of the meniscus.⁹⁷ Copyright 2015, American Chemical Society.

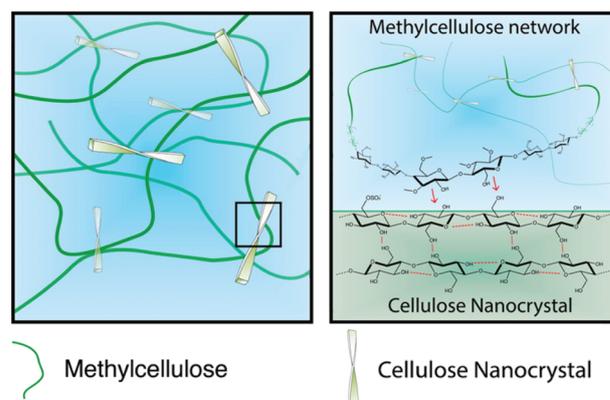


Fig. 9 Schematic representation of the nanocomposite hydrogel. The suggested adsorption of MC on CNCs is indicated by red arrows.¹⁰⁰ Copyright 2014, American Chemical Society.

of gentamicin sulfate was biocompatible with NIH-3T3 cells and showed antimicrobial activity against *E. coli* and *S. aureus*. *In vivo* tests in rats indicated that the scaffold for curcumin release had anti-inflammatory activity and accelerated the regeneration of the dermis.

Saska *et al.*¹⁰⁷ prepared BNC based nanocomposite hydrogels esterified with glycine and cross-linked *via* EDC/NHS cross-linking. The hydrogels exhibited a lower degree of swelling, stability and mechanical resistance when compared to control gels containing only BNC. The formation of a Schiff base between BNC with aldehyde groups and collagen was explored by Wen *et al.*¹⁰⁸ for the release of collagen peptides. The hydrogel showed good cell adhesion and proliferation of Westar rat fibroblast cells cultured *in vitro*.

Gelatin

Gelatin is a protein produced from the denaturation of collagen and it is widely used in the development of systems for controlled release and artificial organic tissues. Wang *et al.*¹⁰⁹ explored the hydrogel properties of CNF-enhanced gelatin. The authors observed that the CNF percolation limit was reached after the addition of 10% of reinforcement.

Dash *et al.*¹¹⁰ investigated the influence of the amount of aldehyde groups of the IO_4^- oxidized CNC on the manufacture of gelatin hydrogels. When increasing the proportion of aldehyde groups from 0.062 to 0.230 mmol g^{-1} , the degree of swelling of the hydrogel decreased from 92.5% to about 87.5%. For the hydrogel with a degree of swelling of 90% (CNC, 0.114 mmol g^{-1}), the authors observed that the storage modulus of the hydrogel was 150% greater than for pure hydrogels. In addition, the storage modulus (G') remained stable even above the melting temperature of gelatin.

Zheng *et al.*¹¹¹ used the same strategy for preparing gelatin hydrogels with CNFs. The compressive strength improved with the increasing amount of CNFs containing 0.015 mmol g^{-1} of aldehyde groups and with the amount of aldehyde groups (0.008–0.017 mmol g^{-1}) for a given concentration of CNFs. The compressive strength of the nanocomposite hydrogel was 41 and 38 times higher than for the pure gelatin hydrogel and the gelatin hydrogel with non-oxidized CNFs, respectively. The degree of swelling was significantly higher when compared to the gelatin hydrogel and gelatin/non-oxidized CNFs.

Yang *et al.*¹¹² explored the electro-fenton oxidative electrochemical process to oxidize BNC and prepare hydrogels of gelatin/oxidized BNC and hydroxyapatite. During the electro-fenton process, the hydroxyl radical (OH^\bullet) is generated *in situ* by the cathodic reduction of hydrogen peroxide in a three-electrode cell. The *in situ* formation of the radical avoids hazards associated with its storage and handling. The tensile strength decreased from 0.72 to 0.3 MPa when compared to the pure BNC hydrogel. The gelatin/oxidized BNC and hydroxyapatite hydrogels were completely degraded in 90 days.

Ooi *et al.*^{113,114} prepared gelatin and CNC hydrogels cross-linked with GA to release theophylline. They found that after 4 h the hydrogel containing 25% CNC released only 40% of the drug at pH 1.2. Release of the drug after 4 h from the CNC-

free hydrogel was approximately 70%. The drug release behavior was attributed to the lower degree of swelling of the hydrogels containing CNCs.

Chen *et al.*¹¹⁵ used a culture medium containing gelatin molecules for the production of physical BNC/gelatin hydrogels. Chemical cross-linking was promoted by immersing the hydrogel in a solution of GA at different concentrations. Increasing the degree of cross-linking decreased the crystallinity, the degree of swelling and the tensile strength, and increased the compressive strength and tensile strength, as expected.

Ran *et al.*¹¹⁶ prepared double-network hydrogels with BNC and gelatin by immersing the hydroxyapatite-coated BNC in a solution of gelatin at 45 °C for 7 days (Fig. 10). The hydrogel showed an elastic modulus value of 0.27 MPa in the swelling equilibrium state and 177 MPa in the dry state. The hydrogel also showed higher adhesion, proliferation and differentiation of mesenchymal stem cells derived from the bone marrow of rats (rBMSCs) cultured *in vitro* than the control hydrogel without hydroxyapatite.

Recently, García-Astrain *et al.*¹¹⁷ prepared hydrogels containing CNCs, gelatin and chondroitin sulfate A. The hydrogel was doubly cross-linked by the Diels–Alder reaction between CNCs functionalized with maleimide groups and gelatin functionalized with furan groups, and by the reaction with EDC/NHS between gelatin and chondroitin sulfate A. The formation of the gelatin/CNC network decreased the swellability index of the hydrogel from 3220% to approximately 2200% when compared to the CNC-containing gelatin hydrogel cross-linked

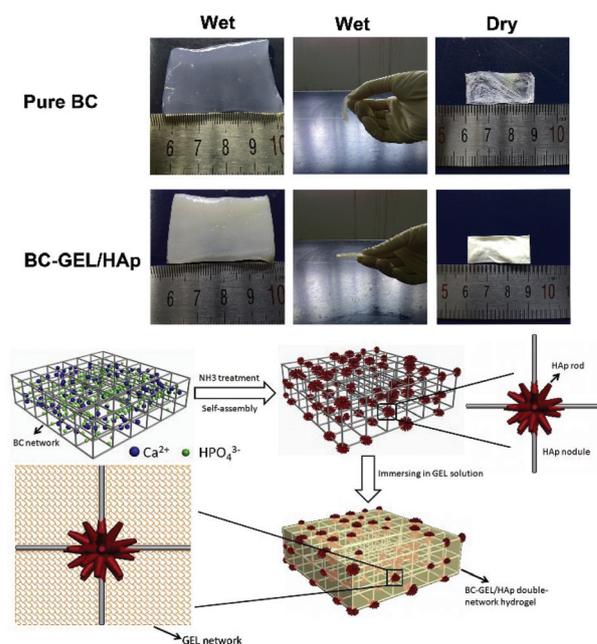


Fig. 10 (Above) Digital photographs of the bacterial cellulose and bacterial cellulose/gelatin/hydroxyapatite composites in wet and dry states; (Below) schematic diagrams of the self-assembly of hydroxyapatite into the bacterial cellulose network and the preparation process of the double-network hydrogel.¹¹⁶ Copyright 2017, Elsevier.

with chondroitin sulfate; while the presence of CNCs increased the degree of swelling when compared to the gelatin hydrogel cross-linked with chondroitin sulfate (2463%). The storage modulus (G') increased progressively with the increase of chemical cross-links. The results indicated that the formation of cross-links between gelatin and CNC blocked the effect of the hydrophilic nature of the CNC on the water absorption of the hydrogel.

Shin *et al.*¹¹⁸ investigated the use of CNFs as a viscosity modifier and mechanical reinforcement in biotins of gelatin modified with methacrylamide groups containing fibroblast cells (Fig. 11). The mixture was subjected to radical polymerization with ammonium persulfate and tetramethylethylenediamine. The addition of CNFs increased the viscosity of the modified gelatin solution. The mechanical properties increased with increasing CNF concentration and the *in vitro* tests showed that the hydrogels were biocompatible and had high cell viability.

Poly(vinyl alcohol) (PVA)

PVA is a water-soluble polymer that has been extensively investigated because of its good biocompatibility and mechanical properties. PVA solutions can form rigid hydrogels through freeze–thaw cycles. During freezing, the PVA chains interact with each other to form crystallites which act as physical cross-links, maintaining the insolubility of the material in water.

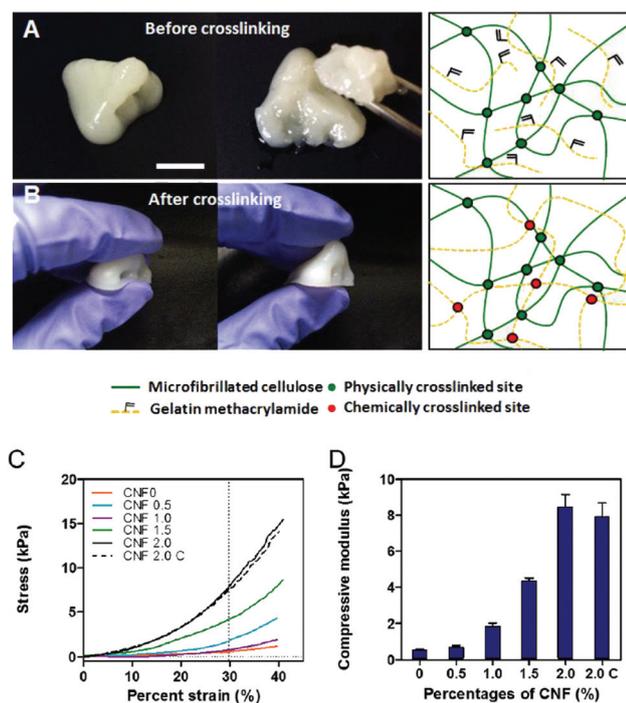


Fig. 11 (a) 3D printed human nose structure before chemical cross-linking of gelatin methacrylamide (scale bar: 1 cm); (b) compressive test of a printed nose structure after cross-linking of gelatin methacrylamide; (c) compressive stress–strain curves and (d) compressive modulus of gelatin methacrylamide/CNF concentration composite hydrogels as a function of CNF concentrations.¹¹⁸

Abitbol *et al.*¹¹⁹ prepared PVA hydrogels containing CNCs by direct dispersion of the nanocrystals in an aqueous PVA solution. The PVA/CNC suspension was subjected to freeze–thaw cycles at -20 °C. The decrease in the crystallinity of CNC reinforced PVA was compensated by the strong interaction and miscibility between the components. The strength of the gels increased in the order of 1.5 wt% > 0.75 wt% ~ 3.0 wt% > pure PVA. The authors suggest that the CNC reinforcing effect was superimposed by the increase of failures in the hydrogel containing 3.0 wt% CNCs.

On the other hand, Gonzalez *et al.*¹²⁰ and Lam *et al.*¹²¹ observed an increase in tensile strength and compression modulus, respectively, with the CNC concentration for PVA hydrogels subjected to freeze–thaw cycles. Butylina *et al.*¹²² reported that increasing the number of freeze/heating cycles from 3 to 5 did not show significant differences in the properties of the CNC-containing PVA hydrogel.

Millon and Wan¹²³ produced a PVA hydrogel reinforced with BNC with mechanical properties similar to cardiovascular tissues. Tang *et al.*¹²⁴ produced BNC hydrogels impregnated with PVA in the form of tubes for the replacement of veins and arteries. BNC was obtained by static culture and then immersed in a solution of PVA. Castro *et al.*¹²⁵ percolated BNC nanofibrils with PVA *in situ* using a static culture medium containing PVA molecules. The BNC-PVA systems were subjected to the freeze–thaw technique to promote the physical cross-linking of PVA. Recently, Li *et al.*¹²⁶ investigated the effect of the amount of freezable bound water on the compression module of double-network hydrogels of BNC and physically cross-linked PVA. The authors observed a significant increase in the amount of freezable bound water in hydrogels with more than 20% PVA. In this state, the water molecules were more strongly attached to the hydrogel, which hindered the loss of water and crack formation under compression.

Tanpichai and Oskman¹²⁷ used CNCs as a reinforcement in GA cross-linked PVA hydrogels. The incorporation of 1% CNC increased the compressive strength from 17.5 kPa to 53 kPa, an increase of 303%. The presence of CNCs did not appear to affect the thermal properties and the degree of swelling of the hydrogel. Chen *et al.*¹²⁸ manufactured PVA/BNC hydrogels containing a small amount of PEG (0.5%) and cross-linked with GA. The thermal stability and the degree of swelling increased with the BNC concentration. The hydrogel showed a modulus of elasticity of 933.3 MPa, a mechanical strength of 123.8 MPa and a deformation of 22.6%. The modulus of elasticity of the hydrogel was 19 times greater than for the pure PVA hydrogel. The hydrogel presented higher biocompatibility than pure BNC.

Han *et al.*¹²⁹ studied the mechanical and optical properties of borax cross-linked PVA hydrogels containing 1% of CNCs with I and II crystalline allomorphs as well as cellulose I nanofibers (CNF I). The type of nanocellulose affected the compressive strength in the order of CNF I > CNC I > CNC II > pure PVA. The compressive strength of CNF I reinforced PVA-borax was 21 times greater than for pure PVA hydrogels. The mechanical properties increased with increasing aspect ratio of the

reinforcement. The transparency of the gels increased in the reverse order. Spoljaric *et al.*¹³⁰ have shown that borax-cross-linked PVA hydrogels reinforced with different amounts of CNFs have self-healing properties. Recently, Lu *et al.*¹³¹ reported a simple and intermediate reagent-free strategy for the synthesis of borax cross-linked and CNF-reinforced PVA nanocomposite hydrogels (Fig. 12). The authors explored a one-pot tandem-type methodology, which consisted of a combination of different processes, simultaneous or sequential, in just one operation. The bamboo pulp solution was sheared in a ball mill and immediately dispersed in a solution containing borax and PVA at 90 °C. The obtained hydrogels showed a pH-responsive behavior, self-healing and good mechanical properties. The high costs of production and the yield loss due to insulation and purification can be avoided using this methodology.

McKee *et al.*¹³² synthesized a PVA/CNC hydrogel *via* a host-guest interaction with cucurbit[8]uril. CNCs were functionalized by surface-initiated atom transfer radical polymerization (ATRP) to yield a dense set of methacrylate polymer brushes bearing naphthyl units. The complexation reaction between functionalized CNCs and PVA containing pending viologen units and cucurbit[8]uril resulted in a material with 85% water, a high storage modulus ($G' > 10$ kPa), a rapid sol-gel transition (<6 s) and a self-healing property. In addition, its viscoelastic properties have been completely restored even when keeping their pieces separated for many months.

Poly(ethylene glycol) (PEG) and pluronic

PEG, a neutral, water-soluble and non-toxic polymer, has been widely used in biomedical applications. PEG has been approved by the Food and Drug Administration (FDA) for domestic consumption in a variety of personal care products, cosmetics, food and pharmaceuticals.

Nair *et al.*⁷⁷ made CNF-containing hydrogels cross-linked with poly(methyl-vinyl-ether-*co*-maleic acid) and poly(ethylene

glycol) with good thermal stability, tear resistance and elastic modulus. The degree of swelling decreased with increasing CNF concentration, while the thermal stability, elastic modulus, fracture toughness and strength increased when compared to the hydrogel containing only the two synthetic polymers.

Yang *et al.*^{133,134} investigated the mechanical properties of CNC-containing polyethylene glycol and pluronic F127 diacrylates. The hydrogels were formed from solutions irradiated with UV light at 365 nm. The results indicated an increase in elastic modulus, fracture strength and resistance to deformation with increasing CNC concentration. Recently, Yin and Yang¹³⁵ reported the formation of a hydrogel involving double cross-linking *via* electrostatic interactions between CNFs oxidized *via* TEMPO and polyethylene glycol with terminal amine groups (PEG-NH₂) and radical polymerization with polyethylene glycol diacrylates. In an acidic environment, the formation of the coordination structure did not occur and chemical cross-linking predominated. In an alkaline environment, two types of cross-linking occurred, *viz.* covalent and non-covalent.

Shao *et al.*¹³⁶ reported the synthesis of self-healing nanocomposite hydrogels formed from the Diels-Alder click reaction between CNFs modified with furan groups and maleimide-functionalized PEG (Fig. 13). The lower the degree of substitution of the CNC functionalized with the furan group and the ratio between the furan and maleimide groups, the higher the degree of swelling at equilibrium. The inverse tendency was observed for the mechanical properties. The

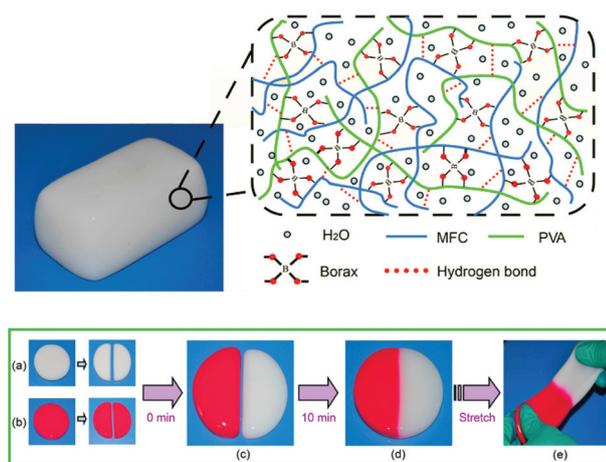


Fig. 12 (Above) Schematic illustration of the PVA/borax/CNF network and (Below) demonstration of the self-healing ability for PVA/borax/CNF at room temperature.¹³¹ Copyright 2017, American Chemical Society.

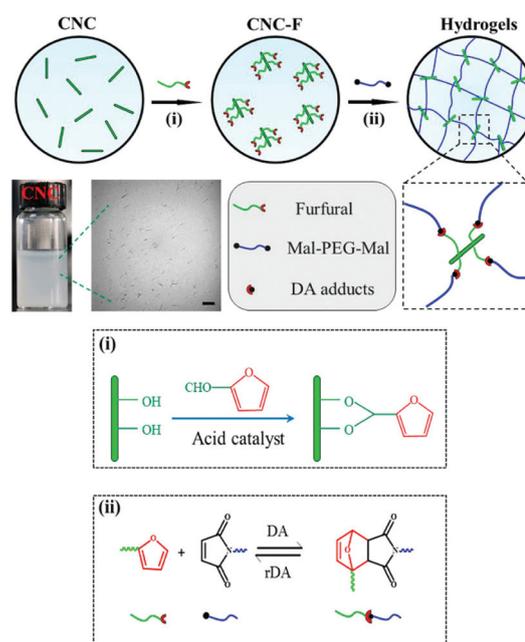


Fig. 13 Synthesis route to self-healing CNC-PEG nanocomposite hydrogels. Inserted images are the CNC aqueous solution and its TEM images, bar = 500 nm. (i) CNCs were modified with furfural by applying a well-known acetalization reaction in the presence of a solid acid catalyst. (ii) Reversible DA reaction between individual furyl and maleimide groups.¹³⁵ Copyright 2017, American Chemical Society.

increased occurrence of furan groups on the CNC surface increased the cross-link density, limiting the expansion of the polymer chains during the swelling process and increasing the resistance to fracture of the hydrogel. The authors reported a degree of swelling of up to 50 g g^{-1} , and a tensile and compression strength of 160 kPa and 300 kPa, respectively. Due to the reversible nature of the covalent bond formed by the Diels–Alder reaction, the nanocomposite hydrogels exhibited a stable and cyclic stress–strain behavior, characterized by the formation of coincident hysteresis loops.

Lin and Dufresne¹³⁷ synthesized hydrogels *via* a host–guest interaction between CNCs functionalized with β -cyclodextrin and pluronic for controlled release of doxorubicin. The results demonstrated that the presence of CNCs extended drug release due to the synergy between tortuosity and the formation of a percolation network that hinders the diffusion of the drug through the hydrogel. Thus, CNCs extended the doxorubicin release effect over 96 h.

Nanocellulose-based hydrogels with inorganic nanoparticles

Nanocellulose can also be used as a substrate for the incorporation of inorganic nanoparticles, such as carbon nanotubes, graphene and graphene oxide to obtain hydrogels with antibacterial, antiviral, antifungal, magnetic, electrical and mechanical properties.

Hydroxyapatite-reinforced BNC hydrogels have been exploited for bone recovery. For instance, Ahn *et al.*¹³⁸ reported the production of hydroxyapatite-coated BNC hydrogels by immersing BNC into a simulated body fluid. The authors reported that the tensile strength of the nanocomposite hydrogel was 2.53 MPa. Duarte *et al.*¹³⁹ synthesized a nanocomposite hydrogel of BNC and hydroxyapatite by alternated immersion in a solution of CaCl_2 and Na_2HPO_4 . BNC was obtained using agroindustrial residues (cashew and sisal juice) as the carbon source. Preliminary *in vitro* results have shown that the obtained hydrogel is biocompatible. Park *et al.*¹⁴⁰ stabilized hydroxyapatite nanoparticles in a TEMPO-oxidized BNC colloidal suspension for the production of a double-network hydrogel of gelatin and BNC cross-linked with GA. The obtained hydrogels presented an elastic modulus between 11–48 MPa and the degree of swelling between 800 and 1500% depending on the ratio of gelatin to BNC.

Shi *et al.*¹⁴¹ reported the synthesis of an anisotropic electroconductive hydrogel (ECH) formed by the electrodeposition of a conductive polymer on BNC. BNC was immersed in an aqueous solution rich in aniline or pyrrole to immobilize the conductive polymer and then fixed it between the two surfaces (electrode and counter electrode). When an electrical potential difference between the two surfaces was applied, migration, electrochemical polymerization and deposition of the conductive polymer on the surface of BNC occurred. Due to the formation of a two-phase Janus system, the obtained hydrogel exhibited distinct chemical and physical properties at each phase (surface). Lv *et al.*¹⁴² incorporated nitrogen-doped carbon dots into the three-dimensional network of BNC *in situ* using culture media containing 1% carbon dots (Fig. 14). The

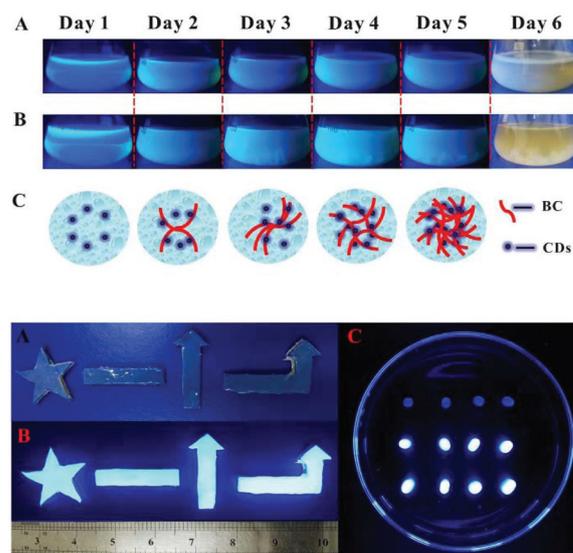


Fig. 14 (Above) The cultivation process of the BNC membrane containing N-CDs by *G. xylinus*: a photographic image of 5-days trace of BNC growth: (A, B) static, agitated conditions by UV light (350 nm), respectively; the 6th day growth of BC in the presence of N-CDs under a fluorescent lamp; (C) a schematic illustration of BNC/N-CDs formation. (Below) Photographs of BNC/N-CDs composite membranes. (A) Photos were taken under a fluorescent lamp; photos were taken in a dark room by using a 350 nm ultraviolet lamp as an excitation source: (B) the "Indicator" pattern; (C) the "spheroid" pattern.¹⁴² Copyright 2017, Elsevier.

hydrogel was used as a light sensor to detect Fe^{3+} in aqueous medium. In the presence of Fe^{3+} ions, the carbon dots formed stable complexes that altered the energy required for quantum dots' electron transfer. The hydrogel can be used as an environmental sensor for the detection of heavy metals.

Applications

As previously mentioned, nanocomposite hydrogels containing nanocellulose can be produced by different methods with the following improved properties: high mechanical strength, thermal stability, electrical conductivity, high dye absorption capacity, controlled release, biocompatibility and biodegradability. Thus, these hydrogels can be exploited in a range of applications, as will be discussed below.

Biomedicine

Hydrogels have been used extensively in many clinical applications, including skin, cartilage and bone regeneration, as wound dressings and for drug carrier systems. In particular, nanocomposite hydrogels containing nanocellulose can have great importance in the current medicine due to the mechanical properties, biocompatibility and biodegradability of nanocellulose. Particularly for wound healing materials, some other requirements are addressed by nanocellulose-containing nanocomposites which are also important for providing a suitable

environment to accelerate the healing process, such as high water holding capacity and moderate moisture permeability preventing fluid accumulation in exuding wounds¹⁴³ while keeping a moist environment around the wound, oxygen permeability to provide good cellular proliferation and to prevent growth of anaerobic bacteria,¹⁴⁴ and also a high degree of adherence to several kinds of tissues.¹⁴⁵

Ruiz-Palomero *et al.*¹⁴⁶ prepared a laccase fluorescent biosensor formed by the non-covalent interaction between CNFs and quantum dots of graphene. The hydrogel was used as a support for the immobilization and monitoring of laccase with good sensitivity and specificity. The authors concluded that the hydrogel can be used as a low cost and environmentally friendly biosensor to detect, stabilize, store and recycle enzymes.

Gonzalez *et al.*¹²⁰ showed that PVA hydrogels containing 3% CNCs have high tensile strength, elastic modulus and transparency, as well as good barrier properties against the penetration of different microorganisms. Gelatin microspheres containing fibroblast growth factor (bFGF) were fabricated and incorporated into a porous scaffold of collagen and CNCs.¹⁰⁴ The cytotoxicity assay indicated that the hydrogel was non-toxic to human fibroblast cells and showed good antibacterial activity. In addition, the tests indicated that the curative nanocomposite significantly increased the number of newly formed and mature blood vessels in the acute wounds of Sprague-Dawley rats. Wu *et al.*¹⁴⁷ prepared BNC hydrogels containing Ag nanoparticles by immersing BNC in a silver ammonium solution. *In vivo* results in rats indicated that the dressing decreased inflammation and promoted wound healing.

Recently, Mertaniemi *et al.*¹⁴⁸ reported the construction of mechanically robust threads from GA cross-linked CNF extruded hydrogels for the delivery of human adipose mesenchymal stem cells (hASC) in injured areas (Fig. 15). The mechanical strength of the threads was preserved in different tissues (muscle, fat and skin) even after exposing the threads to moist cell culture conditions for more than one week. In addition, the threads showed good adherence, rate of proliferation and permanence of hASC in an *ex vivo* suture assay. These results provide possibilities for a new generation of functionalized nanobiomaterials to accelerate the healing of wounds. However, the gap in understanding how these nanoparticles behave *in vivo* should be mitigated in order for those materials to be safely applied. In this sense, there is a need to develop a robust methodology to standardize information that can meet regulatory concerns.

Food

BNC gel is a multifunctional food ingredient to control the properties of food or beverage as a thickener and stabilizer.¹⁴⁹ It has been “generally recognized as safe” (GRAS) since 1992 by the USA Food and Drug Administration (FDA).¹⁴⁹ Since cellulose is indigestible by human enzymes, BNC is categorized into dietary fiber, which has a variety of health benefits, including the promotion of the feeling of satiety, as well as slowing the rate of uptake of small carbohydrates and reducing

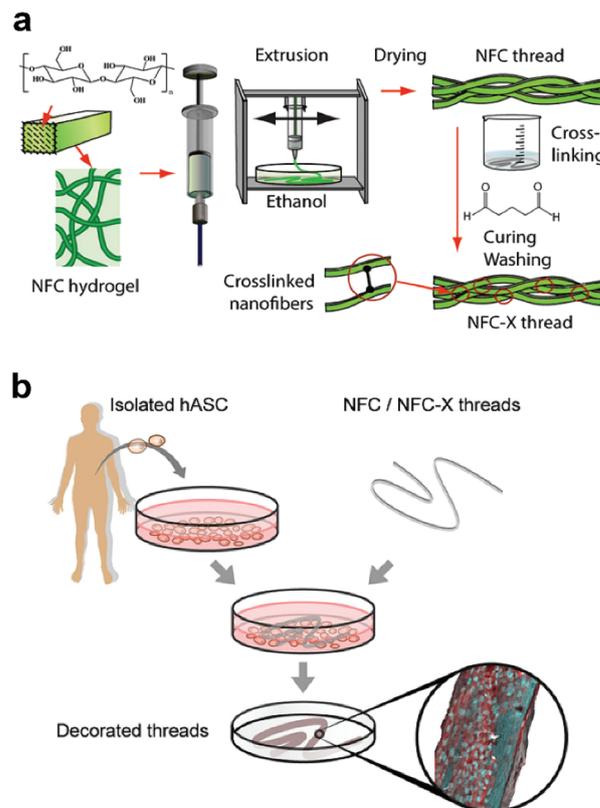


Fig. 15 Schematics for the preparation of NFC threads and their cross-linking with glutaraldehyde for NFC-X threads and (b) the process to decorate NFC and NFC-X threads with human adipose mesenchymal stem cells (hASC).¹⁴⁸ Copyright 2016, Elsevier.

the reabsorption of bile salts, thus helping to control plasma glucose and cholesterol levels and to reduce the risk of a series of chronic diseases such as diabetes and cardiovascular diseases.¹⁵⁰

Shi *et al.*¹⁴⁹ have mentioned some advantages of BNC when compared to other dietary fibers. One of them is the variety of shapes that may be produced, such as films, filaments, spheres *etc.* Another advantage is the possibility of obtaining products with different flavors and colors by using different culture media such as fruit syrups. One of the most common products from BNC (which is a natural hydrogel itself) is a dessert hydrogel called nata, originating from the Philippines. There are different kinds of nata, including nata de coco (the most common, with coconut flavor) and nata de pina (with pineapple flavor), the culture medium defining their flavor.¹⁴⁹

Hydrogels have been also exploited for a variety of other food applications. One of them involves the delivery of nutrients or bioactive compounds. Such systems may protect the bioactive compounds during processing and storage while controlling their release into the gastrointestinal tract, which is an adapted pharmacological approach.¹⁵¹ These systems are especially useful when the nutrients or bioactive compounds are sensitive to processing or storage conditions or to the gastric pH, and when they have undesirable flavors. ‘Smart’

food and food packaging systems have been developed from hydrogels due to the chemical properties of their functional groups. Such systems may be able to respond to specific external stimuli such as pH, temperature, and the concentration of a compound, which act as triggers for controlling their degree of swelling and consequent release rates of active compounds loaded in them.¹⁵²

Another application of hydrogels in food is texture modification, which is a very useful strategy for healthier replacement of some food components. Gelatin/pectin hydrogel microspheres have been studied to mimic the texture produced by swollen starch granules, which also presented rheological properties similar to those of starch pastes.¹⁵³ BNC gels also have been studied as a texture modifier¹⁴⁹ for the production of low-calorie food products. Since the product retains its original structure and has good mechanical properties, BNC has been regarded as an acceptable fat-replacement in this category of food.¹⁵⁴

Several food packaging applications have also been studied for hydrogels to extend the food stability and protect food during transportation and storage.¹⁵⁵ Hydrogel films have been particularly studied as packaging materials for respiring agricultural products such as fresh fruits and vegetables.¹⁵⁶ Because of the high-water affinity and water holding capacity of hydrogels, their water content promotes a high free volume, which increases their permeability. Their high water vapor permeability (WVP) makes the water produced by respiration to permeate through the film, preventing its condensation on the product surface, which might promote microbial growth and spoilage.¹⁵⁷ Moreover, their moderate permeability to gases allows a reduced respiration rate of the product (extending its shelf life), but not to the point of creating conditions for anaerobic spoilage. On the other hand, swelling resulting from the high water absorbing capacity of hydrogels may compromise the mechanical properties of the material, eventually leading to its disintegration and dissolution.¹⁵² To overcome this issue, films are generally subjected to physical, chemical, enzymatic or mixed treatments with hydrophobic additives and/or nanofillers.¹⁵⁶ Obviously, any additive to be included in films intended for food packaging must be safe, since migration onto the food might occur.

Nanocellulose can be used to modify the mechanical, barrier, swelling, hydrogel and slow release properties of bioactive compounds. For example, Tummala *et al.*¹⁵⁸ reported the synthesis of a hyperelastic hydrogel consisting of PVA and CNC oxidized *via* TEMPO containing 93% water and with 383% rupture deformation. Azzam *et al.*¹⁵⁹ developed layer-by-layer films obtained from CNFs and poly(allylamine) hydrochloride with swelling, porosity and optical properties sensitive to changes in the ionic strength of the medium. Huq *et al.*¹⁶⁰ observed an increase in tensile strength and water vapor permeability as well as a decrease in the degree of swelling of hydrogels films consisting of CNC-reinforced alginate. Sirviö *et al.*¹⁶¹ prepared CNF-reinforced alginate films with good tensile strength and low water vapor permeability when compared to the neat alginate film. Chaichi *et al.*¹⁶² reported the

production of CNC/pectin edible films with mechanical properties and water vapor permeability better than the pectin-only film. However, our knowledge of the type and effect of the interactions between nanoparticles and food is still insufficient.¹⁶³ Thus, part of the studies about the properties of nanocellulose should be directed to questions of this nature, seeking to avoid future problems with the regulation of these materials as food packaging. Despite this gap, in comparison with other nanocarbons, nanocellulose remains a good candidate for the development of resistant, biodegradable and renewable food packaging.

Agriculture

Irrigation problems increase the incidence of disease and can lead to death of seedlings. Thus, the development of systems with the capacity to keep and gradually release water can be used in agriculture to improve the management of resources and the quality of the food produced.¹⁶⁴ In particular, hydrogels can be used to increase the water retention capacity, change the plant quality and growth rate, and also as a controlled release vehicle for agrochemicals.¹⁶⁵ For example, Elbarbary *et al.*¹⁶⁶ showed that polyacrylamide/sodium alginate superabsorbent hydrogels, capable of absorbing about 200 times their mass, increased the corn grain yield by 50% in sandy soil. Santo *et al.*¹⁶⁷ analyzed the survival and growth of *Jatropha curcas* L. when using a commercial hydrogel (Terracottem®) and observed a positive effect on biomass and leaf area production. The authors indicate that hydrogel application can reduce the water volume by 50% without affecting the plant growth.

Recently, Bortolin *et al.*¹⁶⁸ developed superabsorbent nanocomposites using hydrolyzed polyacrylamide and methylcellulose reinforced with montmorillonite for the loading and slow release of agricultural nutrients. The hydrogel showed a capacity to retain about 2000 times its mass and simultaneous slow release of urea (macronutrient) and sodium octaborate (micronutrient).

Irrigation and the application of herbicides, insecticides, fungicides, fertilizers, pheromones and growth regulators only in the affected areas of the crop are of great importance for precision agriculture. Moreover, the loss of agrochemicals or other active ingredients by leaching affects their availability for plants, resulting in the need for applying new dosages.¹⁶⁵ Hence, when compared to the dose-release system, controlled release of pesticides minimizes the exposure during the handling of toxic substances and the operational costs due to the use of a single dosage over a long period of time. Nevertheless, the fast release of inputs (burst effect) may damage the plant or result in an undesirable release gradient for plant growth. Furthermore, some materials used for the production of hydrogels are non-degradable and soil toxic and can dramatically alter the soil pH.¹⁶⁹ In this context, nanocellulose can promote high water absorption capacity, biodegradability and slow release of inputs due to the “obstruction effect” and imprisonment of the input in the percolation network or “locking effect”.¹³⁷ At the same time, the high cost of nanocellulose is

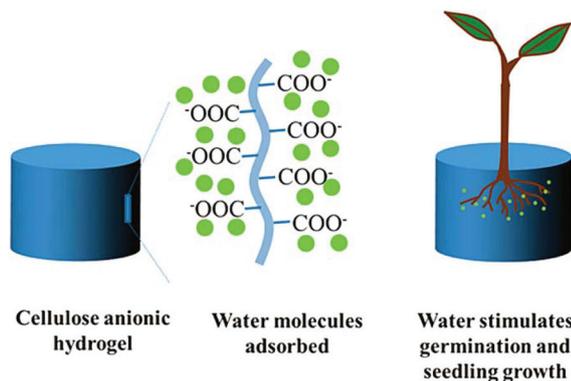


Fig. 16 Mechanism of seed germination and seedling growth.¹⁷⁰ Copyright 2017, American Chemical Society.

still an obstacle to applications in agriculture. Despite this, the recent literature shows encouraging results related to the production of fully biodegradable, biocompatible, and highly swellable hydrogels. For example, Zhang *et al.*¹⁷⁰ have shown that hydrogels obtained from the dissolution of CNFs and cross-linked with epichlorohydrin can regulate seed growth (Fig. 16).

Araki and Yamanaka⁹⁹ prepared carboxymethylcellulose and CNC hydrogels with an absorption capacity of about 150 times their dry weight. Zhou *et al.*¹⁷¹ showed that carboxymethylcellulose hydrogels grafted with poly(acrylate-*co*-acrylamide) containing CNFs oxidized *via* TEMPO have a swelling degree higher than the nanocellulose-free hydrogel. Zhou *et al.*¹⁷² reported the production of the partially hydrolyzed polyacrylamide/CNC nanocomposite capable of absorbing about 600 times their mass in water and adsorbing more than 90% methylene blue. In addition to the function of a soil conditioner, these hydrogels can be used to treat effluents containing toxic metals and other agricultural wastes. Thus, with the advance of the large-scale production of nanocellulose, its price is expected to decrease, and this material can incorporate low cost as one of its exceptional characteristics.

Environmental issues

Increasingly stringent environmental regulations have been a strong incentive to search for novel sustainable products. Despite the recent technological advances, petroleum is still the major source of fuels, solvents, and polymers.¹⁷³ Its replacement by renewable materials is an important step towards reducing greenhouse gas emissions.¹⁷⁴ Presently, several countries being the members of the Organization for Economic Co-operation and Development (OECD) have strengthened policies and investments in biotechnology, with a forecast of 2.7% of GDP derived from the bioproducts marketing until 2030.¹⁷⁵

However, it is worth noting that the term “renewable” is not synonymous with “sustainable”. First, it is necessary to evaluate environmental issues related to the life cycle to ensure that the new product does not have environmental and socioeconomic

impacts greater than the product it seeks to replace. The term “life cycle” refers to the consideration of the various processes that occur during the production, consumption and final disposal of a product in the evaluation of its sustainability.¹⁷⁹ Each of these processes requires the use of natural inputs and generates pollutants that can cause environmental hazards.

Therefore, the impact of the final product must have on its DNA the impacts from agricultural and agroforestry activities, its production, use and disposal, in other words, the impacts of food, fiber and wood production, product fabrication, use, and disposal. For example, the change from forest to agricultural areas, and the use of pesticides and fertilizers are linked to impacts such as climate change, loss of biodiversity, water scarcity and eutrophication.¹⁷⁶ The deconstruction of this biomass for isolating chemical substances such as cellulose, CNCs and CNFs requires the use of solvents and chemical reagents, water and energy. This production can have impacts such as climate change, water scarcity and toxicity.¹⁷⁷ The use of nanocellulose in the production of biocomposites and their disposal in the environment can, in addition to other impacts, have a toxic effect on worker health, consumer health and biodiversity.¹⁷⁸ When the effects of the final disposal of bioproducts are known at the stage of experimentation, it is possible to modify product characteristics and design appropriate systems for recycling or treatment of the waste.¹⁷⁹

The knowledge and minimization of the potential environmental impacts of nanocomposites reinforced with nanocellulose require continuous evaluations of the sustainability of these products, considering their life cycle. Without considering all the processes that integrate their life cycle, some decisions in a given process can only transfer impacts between processes, without necessarily reducing environmental problems.

Many industries and countries use life cycle assessment (LCA) integrated with the technological development process as a tool to assess the life-cycle impacts of a product.¹⁸⁰ LCA’s management approach seeks to integrate Product Technology Quality and Environmental Quality, adding value to the customer and society.¹⁸¹ Its application in the stages of design and experimentation of bioproducts facilitates the identification of inefficiencies in the process, assists in the choice of raw materials and inputs of less impact and supports the proposition and implementation of improvements in new processes.¹⁸² Interventions in new processes and products at this early stage of technological development are low cost and allow for changes that, if carried out on an industrial scale, would be costly.

In this perspective, the use of agroindustrial residues and co-products, with little or no added value, as raw materials or an input into the production of biopolymers has gained notoriety.^{183–185} Plant fibers from bark, such as coconut fiber, cotton linter and sugarcane bagasse are important sources of cellulose and nanocellulose, and other biochemicals.

The application of LCA as a support for the sustainable development of CNCs and CNFs is the main theme of several studies published in the last decade. For example, de Figueirêdo *et al.*¹⁸⁶ showed that the production of 1 g of CNCs from cotton fibers has a lower environmental impact

than the extraction of 1 g of CNCs from green coconut fibers, while do Nascimento *et al.*¹⁸⁷ promoted the process improvement, evaluating alternative routes and choosing the least impacting CNC extraction process from this fiber. Li *et al.*¹⁸⁸ reported that the combination of oxidation with the TEMPO radical and homogenization of kraft cellulose has a lower environmental impact for the production of CNFs than the following combinations: (1) oxidation *via* TEMPO/sonication, (2) carboxymethylation/sonication, and (3) carboxymethylation/homogenization. The results obtained by Arvidsson *et al.*¹⁸⁹ indicated that homogenization and combination of enzymatic treatment/microfluidization have a significantly lower environmental impact than the carboxymethylation/homogenization combination.¹⁸⁹ Piccinno *et al.*^{190,191} investigated the environmental aspects of CNF production by wet spinning using the enzymatically hydrolyzed carrot bagasse. The authors showed that enzymatic treatment contributed more to the environmental impact than wet spinning, and observed a reduction in these impacts (6×) when the process was modeled for an industrial scale of production.

Hydrogels containing CNCs meet many of the principles of green chemistry, such as being renewable, biodegradable, and biocompatible, and therefore are considered eco-friendly. However, LCA studies for hydrogels are still scarce. The only study found was by Bardone *et al.*¹⁹² that evaluated the life cycle impacts of starch hydrogels obtained for the production of aerogels, which was the focus of the evaluation. The hydrogel, produced using only water and energy as inputs in the processes of gelatinization and retrogradation, had impacts on the categories of depletion of the ozone layer, ecotoxicity, climate change and acidification.

The synthesis of cellulose hydrogels uses in addition to this biomaterial, water and energy, solvents, cross-linking agents and nanocellulose. Thus, its life cycle involves the processes of biomass production, separation of cellulose from other compounds present in biomass, such as lignin and hemicelluloses, solvent production, cross-linking and nanocellulose, hydrogel production, consumption and biodegradation. All these processes should be considered in hydrogel LCA studies, seeking to identify critical inputs and processes, opportunities for improvement, and intelligent end-of-life strategies for the product. For example, alternative sources of cellulose, organic solvents, cross-linking agents, CNCs and CNFs may be selected by choosing the option that leads to a lower impact on the hydrogel life cycle.

Furthermore, the use of LCA is recommended for evaluating double modifications that aim in decreasing the use of reagents and improving the yield of the final product. For this reason, the use of microwave radiation, gamma, UV, high hydrostatic pressures, ultrasound, *etc.* should be explored together to increase the viability of cellulose hydrogels.

One point that should be further investigated is the production and use of nanocellulose as a booster in hydrogels, in approaches that avoid steps of separation, purification and drying of the nanocellulose prior to its incorporation into the polymer matrix.

Although nanocellulose-containing hydrogels are good candidates for replacing hydrogels containing non-renewable polymers, questions about the cost of this nanofiller should also be considered. In the last decade, initiatives for the commercial exploitation of nanocellulose have arisen, such as CelluForce, American Process, Alberta Innovates – Technology Futures, US Forest Service's Forest Products Laboratory, Blue Goose Biorefineries, FPIinnovations, Melodea, Paperlogic, Borregaard, Innventia, Cellutech AG, Stora Enso, SAPPI, and Oji Holdings Corporation.¹³ However, the use of alternative sources of cellulose (agroindustrial waste) to produce large-scale nanocellulose is still timid. In this sense, the price of nanocellulose is expected to decrease with the use of cheaper (or zero cost) sources of pulp, increased demand and productivity.

The demand for reformulation or adaptation of existing products and processes for products that meet regulatory changes and that pursue more sustainable characteristics will grow in the coming years. Thus, environmental and economic assessments of hydrogels will be widely employed, ensuring the sustainable industrial revolution of carbohydrates such as wood, corn, sugar cane and other cellulose-based materials for innovative uses and high added value.

Conclusions

Nanocellulose is a promising material for the development of green nanocomposite hydrogels. These materials can be used in different industries that need materials with advanced properties. Recent developments include: (1) extraction and production of nanocomposite hydrogels with superior mechanical properties and transparency, (2) new applications and functions, and (3) set of swelling properties, water vapor permeability, and controlled release. However, many gaps need to be filled in to achieve the feasibility in these products and introduce them to the market, in particular (1) reduction of nanocellulose production costs; (2) use of life cycle assessment to solve environmental aspects of nanocomposites; (3) studies addressing more complex issues *in vivo* and (4) development of new methods, ideally with a single step, which reduce the time and energy consumption of the hydrogel preparation. In conclusion, hydrogel nanocomposites reinforced with nanocellulose are strong candidates for application in different sectors. The high added value of these hydrogels would lead to the production of cost-effective and environmentally friendly products due to the wide variety of possible applications. Despite the problems pointed out, we expect these challenges to be overcome in the coming years and “green” hydrogels containing nanocellulose promote significant advances and improvements in people's quality of life.

Conflicts of interest

There are no conflicts to declare.

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