Carbohydrate Polymers 216 (2019) 247–259

Contents lists available at ScienceDirect

Carbohydrate Polymers

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

A review on cellulose nanocrystals as promising biocompounds for the synthesis of nanocomposite hydrogels

Jamileh Shojaeiarani[a,*], Dilpreet Bajwa[a], Alimohammad Shirzadifar[b]

[a] Department of Mechanical Engineering, North Dakota State University, Fargo, ND, 58102, United States
[b] Department of Agricultural and Biosystems Engineering, North Dakota State University, Fargo, ND, United States

ARTICLE INFO

Keywords:
Cellulose nanocrystals hydrogel
Nanomaterials
Biomedical application
Biosensor
Wastewater treatment

ABSTRACT

Hydrogels are hydrophilic cross-linked polymer networks formed via the simple reaction of one or more monomers with the ability to retain a significant extent of water. Owing to an increased demand for environmentally friendly, biodegradable, and biocompatible products, cellulose nanocrystals (CNCs) with high hydrophilicity have emerged as a promising sustainable material for the formation of hydrogels. The cytocompatibility, swellability, and non-toxicity make CNC hydrogels of great interest in biomedical, biosensing, and wastewater treatment applications. There has been a considerable progress in the research of CNC hydrogels, as the number of scientific publications has exponentially increased (> 600%) in the last five years. In this paper, recent progress in CNC hydrogels with particular emphasis on design, materials, and fabrication techniques to control hydrogel architecture, and advanced applications are discussed.

1. Introduction

Rising concerns regarding the negative impact of petroleum-based polymers on the environment, and the potential applications of biopolymers calls for a transition from petroleum-based polymers to sustainable and renewable ones. Such a transition imposes a substantial challenge for scientists and industries requiring innovative alternatives and the applicable methods improving the potential application of materials. With the emergence and progress of nanotechnology, hydrogels, a special form of bulk materials, have received much attention owing to their unique and excellent moisture retention characteristics. Hydrogels are 3D network colloidal gels formed through cross-linking of hydrophilic polymer chains (Nair et al., 2019) with the ability of absorbing and retaining large volumes of water in an aqueous environment, without itself dissolving in water (Mondal & Haque, 2019).

The hydrophilic nature of hydrogel component governs the water sorption, and the swelling response of the hydrogels in the swollen stage is attributed to the large free space between cross-linked networks (Olad, Zebhi, Salari, Mirmohseni, & Tabar, 2018). Hydrogels were introduced by Wichterle for the first time in 1960 through a cross-linked hydroxyethyl methacrylate (HDMA) (Otto & Drahoslav, 1960). Thereafter, hydrogels have received a significant amount of attention in different areas such as agriculture (Pakdel & Peighambardoust, 2018), waste management (Singh & Singhal, 2018), and stimuli-responsive sensors and actuators (Li, Liao et al., 2018; Nam et al., 2018).

Synthetic hydrogels used to be of great importance due to high processability, high water uptake, long service life, and the wide range of raw chemical resources (Zia et al., 2017). However, the use of these types of hydrogels imposed a significant economic and environmental burden on the society and remained a leading cause of global dependence on petroleum-based polymers.

Synthetic hydrogels such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polyvinyl pyrrolidone (PVP) are formed via chemical polymerization from man-made monomers. Synthetic hydrogels are difficult to biodegrade, and causes environmental damages such as oxygen demand (González, Agostini, & Milrad, 2008), septic systems and landfills (Julinová, Vaňharová, & Jurča, 2018). In addition, the application of petroleum-based polymers is tied to the negative impact to economy since the price of the petroleum in the international market is fluctuating over years, and this inspires researchers and industries into the field of biopolymer research.

Particularly, public awareness, social trends and technological

Abbreviations: CNCs, cellulose nanocrystals; AA, acrylic acid; HEMA, hyderoxy ethyl methacrylate; MBA, *N,N'*-methylenebisacrylamide; PAA, poly(acrylic acid); KPS, potassium persulfate; GQDs, graphene quantum dots; PEG, polyethylene glycol; PAM, polyacrylamide; HA, hyaluronic acid; QXH, quaternized xylan; CAA, cellulose acetoacetate; PVA, polyvinyl alcohol; GO, graphene oxide; PMC, polyacrylamide-sodium carboxymethylcellulose; SA, sodium alginate; SG, silica glass; HPCS, hydroxypropyl chitosan; GDL, glucono-*δ*-lactone; PNIPAAm, poly(*N*-isopropyl acrylamide); MB, methylene blue; CS, chitosan

* Corresponding author.
E-mail addresses: jamileh.shojaeiarani@ndsu.edu (J. Shojaeiarani), dilpreet.bajwa@ndsu.edu (D. Bajwa), alimohammad.shirzadi@ndsu.edu (A. Shirzadifar).

https://doi.org/10.1016/j.carbpol.2019.04.033
Received 17 January 2019; Received in revised form 10 March 2019; Accepted 7 April 2019
Available online 08 April 2019
0144-8617/

Table 1
Properties of some commonly used materials for biocomposite hydrogels fabrication.

Bio-based material	Key properties	Limitations	Application	References
Alginate	Biocompatible, biodegradable, pH sensitive	Fragile and low stretchability, weak absorbing capacity	Adsorbent for heavy metals, drug delivery, wound dressing	(Aderibigbe & Buyana, 2018; Yi et al., 2018)
Chitosan	Antimicrobial activity, antistatic activity, nontoxic, deodorizing property, chemical reactivity, cost-effectiveness	Low mechanical strength, poor water resistance	Wound dressing, drug delivery, cartilage repair	(Khorasani, Joorabloo, Moghaddam, Shamsi, & MansooriMoghadam, 2018)
Collagen	Cellular affinity, tissue compatibility	High rate of stress relaxation, weak and viscoelastic gel	Drug delivery, cell culture, tissue engineering	(Lou, Stowers, Nam, Xia, & Chaudhuri, 2018; Yu, Lee, Seo, Knowles, & Kim, 2015)
Lignin	Antioxidant, antifungal, heavy metals extraction	Low capacity and weak selectivity in wastewater treatment	Slow release of hydrophilic drugs, wastewater treatment	(Thakur & Thakur, 2015; Wang, Du et al., 2018)
Silk fibrion	Biocompatibility, bioresorbability, low immunogenicity, mechanical resilience, ease of processing and functionalization	Weak gelation performance and low mechanical strength	Drug delivery, tissue engineering, cell culture	(Kim, Kim, Choi, Park, & Ki, 2018)
Cellulose	Tasteless, hydrophilic, biodegradable, insoluble in water and most organic solvents, adsorbent	High permeability and low gas barrier, weak mechanical properties	Wound dressing, drug delivery, waste water management	(De France, Hoare et al., 2017)
Gelatin	Biocompatibility, and biodegradable and non-toxic nature	Weak mechanical properties	Drug delivery, tissue engineering, corneal engineering	(Goodarzi, Jadidi, Pourmotabed, Sharifi, & Aghamollaei, 2019)
Fibrin	Natural, insoluble protein biocompatibility, biodegradability	Weak mechanical properties	Tissue engineering, drug and cell delivery	(Gopalakrishnan, Shankarappa, & Rajanikant, 2019)

advancement in bio-based materials has gradually increased the application of natural hydrogels in commercial fields. Bio-based hydrogels exhibit a diverse application in biomedical area such as cell therapeutics, wound dressing (Ge et al., 2018), and tissue engineering (Yang, Lu et al., 2018) due to their inherent non-toxicity, biocompatibility, and highly hydrated three-dimensional porous structure. So far, a wide range of materials (both natural and synthetic) has been examined for the fabrication of hydrogels. Table 1 provides a comparative account of the properties of some of the commonly used polymers for preparing biocomposite hydrogels.

Cellulose, the most abundant renewable organic material in the world, has been extensively explored for producing new materials, especially in the form of micro or nano-scale with different shape and crystallinity. Cellulose nanocrystals (CNCs), the crystalline regions of cellulose, are extracted from cellulose using top-down approach (Capron, Rojas, & Bordes, 2017) through different methods such as acid hydrolysis, combined mechanical shearing, and enzymatic hydrolysis; in which, the amorphous or disordered regions of cellulose hydrolyzed, and the crystalline regions with higher resistance to acid attack remain intact and result in cellulose nanocrystals (CNCs) (Mohamed et al., 2017). Source of cellulose and acid hydrolysis conditions influence the properties of CNCs (Hasani, Cranston, Westman, & Gray, 2008).

CNCs with high hydrophilicity are regarded as a promising hydrogel component owing to their appealing intrinsic properties such as global abundance, biocompatible nature, promising mechanical properties (strength over 10 GPa, elastic modules of 150 GPa) (Iwamoto, Kai, Isogai, & Iwata, 2009), and low density (1.61 g.cm − 3) (Habibi, Foulon, Aguié-Béghin, Molinari, & Douillard, 2007).

2. Preparation of CNCs based hydrogels

Cellulose has numerous hydroxyl groups which can form hydrogen bonding linked network to drive gel formation. Cellulose-based hydrogels can be formed via either physical or chemical stabilization (Fig. 1a) of aqueous solution with specific concentration (Wang, Zhang, Teng, & Liu, 2017). The CNC concentration can be engineered via surface modifications, incorporating cross-liking agent, and water-soluble polymers. However, the formation of an inhomogeneous polymer network (loops, dangling ends, and heterogeneity in cross-link density) in CNC- based hydrogels is considered as a defect limiting the mechanical properties of CNC hydrogels (Fig. 1b).

Although high surface area and compatible mechanical properties make CNCs a promising candidate as rheological modifiers and cross-linking agents in hydrogels (Gu et al., 2018), the application of CNCs as the main backbone of hydrogel is limited due to weak mechanical property and rapid degradation of the hydrogels (Gu et al., 2018). In general, hydrogels can be prepared through entanglement and the formation of a continuous matrix to entrap water or any organic liquid (Clarke, Parmenter, & Scherman, 2018). However, the low entanglement properties in CNCs result in the formation of a structure with low viscosity and low resistance against the flow.

Lack of effective energy dissipation mechanism, low density of polymer chains, and small friction between the polymer chains are the main reasons for low mechanical stability and durability in hydrogels at swollen state (Cao, Li, Chen, Zhang, & Zhou, 2018). The mechanical strength of CNC hydrogels is mainly enhanced through the formation of an organic/inorganic network structure which can distribute the stress over a broad area and effectively increase the load bearing capacity of hydrogel (Zhao et al., 2019).

Several strategies such as surface modification (McKee et al., 2014), and incorporating cross linking agent (Kargarzadeh et al., 2018), inorganic nanomaterials (Beaumont, Potthast, & Rosenau, 2018), and salt (Sahlin et al., 2018) have been reported for improving the mechanical properties of CNC-based hydrogels. The direct incorporation of salt into CNC solution is based on the tendency of salt to decrease the hydration level by recollecting the water molecules around themselves and

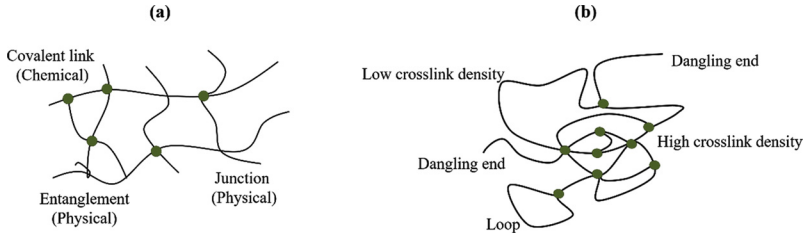

Fig. 1. a) Schematic illustration of chemical and physical bonding in a hydrogel. Reproduced from (Ullah, Othman, Javed, Ahmad, & Akil, 2015) with permission. b) Structural defects in hydrogel. Reproduced from (Ullah et al., 2015) with permission.

increasing the gelling phenomenon at relatively low temperature (~37 °C) (Sannino, Demitri, & Madaghiele, 2009). Abbasi et al. showed that, by adding sodium chloride (NaCl) into CNC solution, the self-similar clusters formation was improved via screening surface charges of CNCs. However, the formed gel was weak, breaking upon swelling and leaving suspended isolated clusters behind (Moud, Arjmand, Yan, Nezhad, & Hejazi, 2018).

The application of CNCs in a leading role might result in the formation of a brittle hydrogel, prone to fracture when handled at swollen state, probably due to the rigid and non-homogeneously cross-linked structure (Fig. 1b) which lead to insufficient interactions between the monomers (Cao, 2018; Du et al., 2019).

Therefore, the incorporation of CNCs into different natural (e.g. alginate, gelatin) or synthetic (e.g. poly (vinyl alcohol) (PVA), polyacrylamides (PAM), poly (ethylene glycol) (PEG)) polymer networks are of huge interest owing to their promising mechanical properties (Chau et al., 2016), cytocompatibility, non-toxic and biocompatibility (Tummala et al., 2016). In parallel, several review articles (De France, Hoare, & Cranston, 2017; Liu, He, Zhang, & Lee, 2018) and many research papers on hydrogels containing nanocelluloseic materials such as CNC and cellulose nanofiber (CNF) have been already published, and the scientific literature continues to grow exponentially.

Considering the difference in the properties of CNCs and CNFs, the current review mainly highlights the developments in the advanced applications of CNC hydrogels with the main focus on the most recent advances in this regard. In this review paper the basic working principle of hydrogels for each specific application as well as the latest innovations in the use of CNC in hydrogels are provided

3. CNC hydrogel classification

In general, different classifications have been introduced for hydrogels containing CNC depends upon their form, method of preparation, type of crosslinking, and applications. Fig. 2 exhibits the classification of hydrogels regarding their form and crosslinking interaction between components.

3.1. Traditional bulk hydrogel

Traditional bulk hydrogels in the form of beads, thick films, and membranes are mainly prepared via free radical polymerization technique. Free-radical polymerization is the most common technique for CNC hydrogel preparation through reacting hydrophilic monomers with multifunctional cross-linkers. This method is classified as a chemical preparation technique (explained later in chemically cross linked-hydrogels). In which, the process variations can be adjusted to systematically alter the micro and nanostructure of the scaffolds with favorable characteristics. It was also reported that the outstanding properties of CNC hydrogels emerge through using free-radical polymerization (Zhao, Fang, Rong, & Liu, 2017).

3.2. Bulk polymerization

Bulk polymerization is the simplest preparation technique for traditional bulk hydrogels which involves homogenous solution of hydrogel components (monomers and initiators) in undiluted solution. Bulk polymerization is considered as an environmentally friendly process due to the absence of any purification technique. In this technique, the high polymerization rate due to high concentration of monomers results in heat generation as a consequent of a viscosity increase in the solution. In general, the polymerization process is typically initiated by introducing radiation, ultraviolet, or chemical catalysts (Kiatkamjornwong, 2007). The hydrogels prepared through bulk polymerization could be engineered in a variety of different forms such as membranes, films, beads, and emulsions with an amorphous morphology, and rigid structure.

The non-connected porous structure in CNC hydrogels governs the water uptake rate (Wan Ishak, Ahmad, Ramli, & Mohd Amin, 2018) and the negatively charged surface of CNCs, extracted using sulfuric acid, plays a significant role in the water sorption character in CNC hydrogels (Lewandowska-Łańcucka, Karewicz, Wolski, & Zapotoczny, 2019). In the case of CNC hydrogels, bulk polymerization leads to a high molecular weight polymeric structure, which is rigid in its dried state and soft and flexible in its swollen form (Wu, 2016). Numerous methods

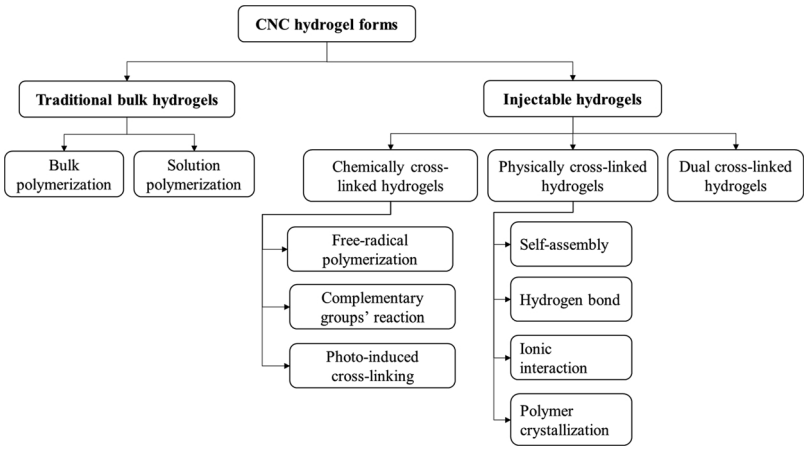

Fig. 2. Classification of hydrogels based on their form and corresponding interactions.

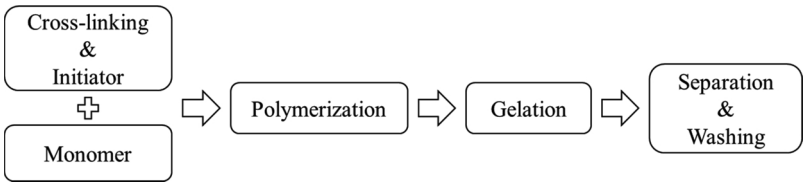

Fig. 3. Hydrogel synthesis by solution polymerization.

including increasing the crosslink density (Tummala, Bachi, & Mihranyan, 2019) or the total solids content of the hydrogel network (Shi et al., 2013) have been established for tuning the mechanical characteristics of bulk hydrogels. However, these methods did not improve the mechanical strength of the hydrogels, as smaller or fewer pores exhibit higher mechanical strength, and aforementioned methods negatively affected pore size in hydrogels. Low degree of swelling and slow swelling rate are other weaknesses in traditionally cross-linked hydrogels, which limits their application (Wirthl et al., 2017).

3.3. Solution polymerization

In solution polymerization, the gel formation relies mainly on the application of multifunctional crosslinking agent in the presence of initiators such as thermal, redox or UV initiator (Fig. 3). Separation and washing with a large excess of selected solvent such as water is an important step in hydrogel synthesis through solution polymerization to remove undesired monomers, initiators and crosslinkers.

Solution polymerization is a favorable hydrogel preparation technique as the presence of a large amount of the solvent can control the reaction; however, inappropriate volume of the solvent can result in the formation of hydrogel with syneresis behavior rather than swelling or precipitate particles (Sahabi & Kind, 2011). Rapid hydrogel synthesis and an increase in the homogeneity of the hydrogel microstructure are observed in solution polymerization. Shao et al., presented a study on furyl-modified CNC and maleimide coated polyethylene glycol (PEG) for preparation of hydrogels. They found that furyl/maleimide interaction can improve the reinforcing effect of CNCs and enhance the mechanical properties, self-recovery and anti-fatigue properties of CNC hydrogel through solution polymerization (Shao, Wang, Chang, Xu, & Yang, 2017).

3.4. Injectable hydrogels

Injectable hydrogels have appeared as promising absorbent materials owing to their properties such as highly porous structure, similarity to the natural extracellular matrix (ECM), capability of enclosing cells within the matrix, and ability to access deep seated areas (Singh, Bhardwaj, & Mandal, 2018). Injectable hydrogels have received significant attention in biomedical engineering with the main focus on tissue engineering due to their relatively low invasive impact, excellent ability in reaching the defects at any depth of tissue, and ease of administration (Liu, Sui Shi et al., 2018). Injectable hydrogels are generally low viscosity polymer solutions with the ability of gelation after injection (Yu, Liu, Tan, Scherman, & Abell, 2018). Injectable hydrogels exhibit a free-flowing behavior before injection, but spontaneously change into a semi-solid hydrogel just after injection due to the formation of either chemically or physically crosslinking reactions. Injectable hydrogels can experience reversible phase transitions triggered by temperature, pH, solvent composition, ionic strength, electric field, light or the presence of specific molecules (Fig. 4). The solution viscosity and the rate of gelation are important parameters in injectable hydrogels and are governed by polymer type, molecular weight, and concentration, as well as the type of cross-linking agent (Deng, Dong, Song, & Chen, 2019).

Thermo-responsive hydrogels experience sol-to-gel or volume phase change below and above the critical solution temperature (Shoujing & Zishun, 2018). Hydrogels showing different critical solution temperatures exhibit different responses upon heating. Typically, hydrogels with a lower critical solution temperature (LCST) turn out to be unsolvable upon heating. While, hydrogels exhibiting an upper critical solution temperature (UCST), become soluble at high temperatures (Sanna et al., 2013). As the allowable temperature range for living cells is 37–44 °C, the potential application of CNC hydrogels has been studied in this temperature range. Cellulose has shown thermosensitivity and a temperature induced sol-gel conversion property through surface modifications such as addition of alkyl groups (Lee, Cho, & Park, 2005).

The gelation in the hydrogels, which typically happens via physically or chemically crosslinking reactions, is affected by hydrogel components. The application of CNCs in a Triblock poloxamer copolymer (PM) has been studied by Orasugh et al. They reported that the incorporation of CNCs improved the *in situ* gelation behavior of PM by reducing the critical concentration of thermo-responsive gelation of gel. The higher strength and lower gelation temperature in PM-CNCs gels were attributed to the formation of intermolecular hydrogen bonding of the free hydroxyl groups of CNC molecules with PM molecules (Orasugh et al., 2019).

The pH-responsive hydrogels are usually synthesized from polymers containing weak acidic (−COOH) or weak basic ($-NH_2$) functional groups. The ionizable functional groups either receive or discharge protons and result in the swelling and collapsing processes. A pH sensitive hydrogel composed of poly(acrylic acid) (PAA) and CNCs exhibited a pH-sensitivity in the pH range of 3 to 11. In which, the hydrogels reinforced by 5 wt% CNCs exhibited the optimum swelling response at pH of 7 (Lim, Rosli, Ahmad, Mat Lazim, & Mohd Amin, 2017).

The development of hydrogels sensitive to multiple external stimuli such as pH and temperature are extensively explored. The simultaneous response to pH and temperature is favorable especially for hydrogels with biomedical applications. The pH and temperature sensitive hydrogels are composed of two classes of functional groups including ionizable functional groups, and temperature-responsive swelling and de-swelling hydrophobic functional groups (Yang, Fu, Yu, Zhou, & Cheng, 2018).

3.5. Physically cross-linked hydrogels

The physically cross-linked hydrogels are formed via secondary forces including hydrogen bonding (Khabibullin et al., 2017), van der Waal's interactions, and physical interactions between hydrogel components such as electrostatic (Roshanghias & Madadlou, 2018), hydrophobic (Nigmatullin et al., 2018), and supermolecular chemistry. All different types of stimuli that can induce physical interactions between the polymer chains such as pH, temperature, and ionic strength of the hydrogel components can control the phase transition in physically cross-linked hydrogels. CNC hydrogels fabricated via physical cross-linking process have several advantages over chemically cross-linked ones including lack of toxic crosslinking agents, easy degradation, reverse properties, shear thinning, and self-healing (Wang, Yu et al., 2018). Despite the above advantages, these types of hydrogels have marginal control over the clearance rate of the hydrogel in *vivo,* confining their use to short-acting drug release systems. In addition, they tend to show relatively low mechanical strength (Cheng et al., 2018).

Hydrogen bonding happens between two polar functions (i.e.

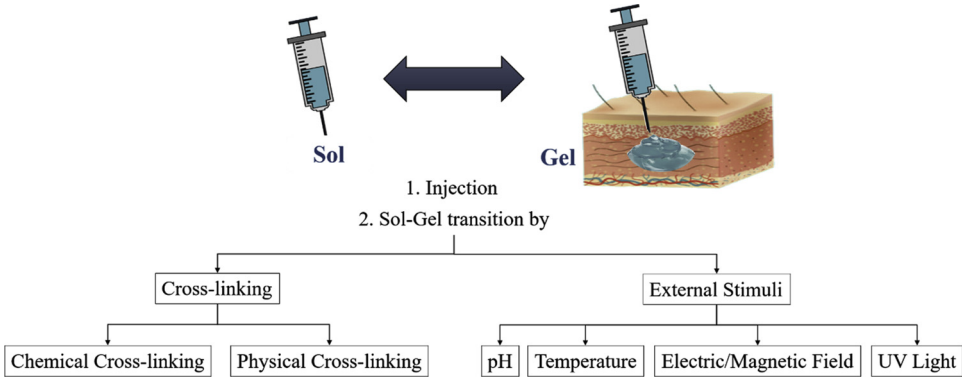

Fig. 4. The schematic illustration of the formation procedure of injectable hydrogels.

hydrogen atom and highly electronegative atom such as nitrogen (N), oxygen (O), and fluorine (F)). Strong intra and intermolecular hydrogen bonding interactions can be observed in the CNC gel structures. Hydrogen bonding is relatively weak in comparison with covalent and ionic bonding. The morphology and structure of CNCs are governed by the source of raw materials and extraction/processing methods, the presence of hydroxyl groups on the surface of CNCs favors the formation of hydrogen bonds and promotes self-assembly of multiple chains, which further induces aggregation through van der Waals interactions (Parker et al., 2018). Khabibullin et al, prepared a multifunctional hydrogel using CNCs and graphene quantum dots (GQDs) through physical cross-linking. The attractive force originated from hydrogen bonding between CNCs and QQDs overcame the repulsive interactions between negatively charged CNCs and QQDs and led to the formation of a tough hydrogel (Khabibullin et al., 2017).

The self-assembly of small molecules would result in the formation of a complex supramolecular structure with completely different viscoelastic properties such as sol–gel transition. Self-assembly is a spontaneous phenomenon in CNCs, forming chiral nematic liquid crystals above a critical concentration (> 4.55 wt%), which depends on the aspect ratio, and morphology of the CNCs (Hu & Abidi, 2016). Such a chiral nematic phase of CNCs is stable even after dehydration; however, the CNCs' randomly entangled gel would form at significantly higher concentrations depending on the aspect ratio, surface charge, and the ionic strength of the aqueous media (Nigmatullin et al., 2018). CNCs prepared through acid hydrolysis can self-assemble into cholesteric phases owing to an unequal charge distribution on their twisted crystal structure (Hu & Abidi, 2016).

Ionic interaction is charge-driven assembly in the formation of hydrogels in which, oppositely charged ionic components and the nature of the ionic interactions establish the physical crosslinks, providing tough and highly tunable networks. This type of boding can offer a high degree of dependence on a variety of stimuli such as pH (Byrne & Salian, 2008), ion exchange, and ion interactions (Koetting, Peters, Steichen, & Peppas, 2015).

A thermo-reversible hydrogel network was demonstrated using CNCs physically bounded to methylcellulose (MC). Depending upon the CNC concentration and temperature, CNC-MC hydrogels exhibited different viscoelastic behaviors. Low CNC loadings (< 0.25 wt%) resulted in more viscous behavior whereas higher CNCs concentrations (> 0.5 wt%) led to more elastic behavior. Additionally, an increase in temperature from 20 to 60 °C led to a more elastic gel (McKee et al., 2014).

3.6. Chemically cross-linked hydrogels

Typically, chemically cross-linked hydrogels are made by mixing the main hydrogel component with complementary reactive functional groups, which can result in the formation of irreversible covalent bonding between polymeric chains (Su & Okay, 2018). The application of a chemical cross-linker is the most common step in the formation of chemically cross-linked hydrogels. Cross-linkers are mainly molecules with no less than two reactive functional groups, inspiring the construction of bonds between polymeric chains. Contradictory results are reported regarding the effects of cross-linkers on water absorption capacity in hydrogels; incorporation of a cross-linker may reduce the adsorption capacity such as when the cross-linker binds to the functional groups on the polymer chain, which renders them unavailable and prevents adsorption (Ito et al., 2003). On the other hand, cross-linkers can improve the adsorption capacity owing to the presence of the reactive functional groups in the structure of the cross-linking agent. Chemically cross-linked hydrogels exhibit more uniform properties and less swelling sensitivity to different stimuli such as pH as compared to physically cross-linked hydrogels. However, the application of chemically cross-linked hydrogels in biomedical engineering is more restricted due to the residues of initiators and cross-linkers, which may give undesirable reactions with the bioactive components in the hydrogel matrix and decrease the biocompatibility of the final product even after thorough purification (Niu, Wang, Dai, Shao, & Huang, 2018; Shao et al., 2018). Silva et al., studied the viscoelastic and microstructural properties of a chemically cross-linked hyaluronic acid (HA) hydrogel reinforced with CNCs and platelet lysate (Fig. 5). The synthesized hydrogels exhibited higher mechanical performance with the addition of CNCs. Furthermore, CNC content exhibited a positive effect on the gelation time of the hydrogels (Silva et al., 2018).

An injectable hydrogel from poly(oligoethylene glycol methacrylate) and magnetically aligned CNCs was prepared via chemical cross-linking. An external magnetic field was employed to align the CNCs, and the improvement in the swelling ratio and compressive moduli was attributed to the enhancement of the CNCs planar alignment in the direction perpendicular to the external magnetic field (De France, Yager et al., 2017).

Free radical polymerization is a common method of preparing CNC hydrogels in the presence of an initiator capable of preparing free radicals. The presence of CNCs in the hydrogels would improve the potential of forming initiation sites via creating free radicals on the surface of CNCs. Hence, this would intensify the formation of the polymer-CNC network through the surface-initiated polymerization process. Kumar et al. used a free radical polymerization process for the preparation of CNC reinforced polyacrylamide/SA /SG hybrid hydrogels for regeneration of damaged tissues. In this case, the hybrid hydrogel was prepared *in situ* PASG (PAAm/SA/SG) and PASG/CNC with potassium persulfate (KPS, K2S2O8) and MBAA as an initiator and cross-linking agent. Their results exhibited improvement in mechanical properties, in vitro degradation stability, and thermal stability of the hydrogels with incorporating CNCs in the range of 2.5–10 wt% (Kumar, Rao, & Han, 2017).

Photo-induced cross-linking created by exposing the polymer to the

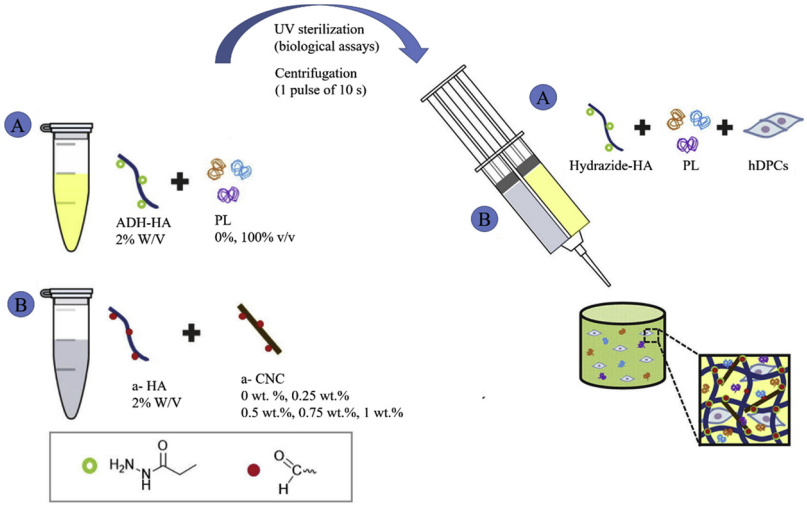

Fig. 5. Schematic illustration of *in situ* crosslinking system. (A) hydrazide-functionalized hyaluronic acid (ADH-HA) solution with or without PL and (B) aldehydefunctionalized hyaluronic acid (a-HA), with or without aldehyde-modified CNCs (a-CNCs).
Reproduced with the permission from (Silva et al., 2018).

irradiation of UV or visible light in the presence of an appropriate photo-initiator has been used for preparing hydrogels in therapeutic agent delivery and tissue engineering. This method is an efficient method of CNC hydrogels preparation; however, photo-induced cross-linking hydrogels have limited application due to the difficulty of eliminating the unreacted photo-initiator in addition to trace initiator byproducts (De France, Chan, Cranston, & Hoare, 2016).

3.7. Dual cross-linked hydrogels

Dual cross-linked hydrogels have both physical and chemical cross-linking bonds (Huang, Wang, Rehfeldt, & Zhang, 2018). Typically, covalent bonds have higher binding energy than physically cross-linked bonds, such as hydrogen bonds, hydrophobic interactions, and super molecular interactions. Dual cross-linked hydrogels have received huge attention owing to their superior mechanical and self-healing properties. In a network containing both covalent and non-covalent bonding, the weaker non-covalent bonds play the sacrificial role when the structure is subjected to loading (Liu, He et al., 2018). The physical bonds break and reform, providing an effective energy dissipation mechanism and synergic mechanical reinforcement at a rate which is independent of stress but is relevant to temperature (Liu, Guo et al., 2018). In dual cross-linked hydrogels, the amount of cross-linking agent can alter the overall properties of hydrogels, as the addition of more reversible cross-linking improves the viscoelastic dissipation through exposing dissipative mechanisms at molecular levels (Teng et al., 2018). In a recently published work, the application of a dual cross-linked network in polyacrylamide grafted CNCs and poly(acrylic acid) hydrogels exhibited a combination of high strength, owing to the formation of permanent covalent crosslinking, along with reversible properties due to the presence of ionic interactions and hydrogen bonds between the cross-linking agent and the polymer chains (Li, Zhang, Wu, Guo, & Luo, 2018). An injectable CNC-reinforced polysaccharide was prepared via the addition of amino-modified cellulose nanocrystals (CNC-NH_2) into cellulose acetoacetate (CAA) and hydroxypropyl chitosan (HPCS). The interaction between amino functional groups of CNC-NH2 and the acetoacetyl functional groups of CAA resulted in the formation of chemical cross-linking, while the hydrogen bonds formed between the CNCs surfaces and CAA. The hydrogel with honeycomb macroporous structure and pore size of 50–100 μm was capable of cell proliferation and nutrient transportation (Liu, Li, Wang, Sui, & Wang, 2018).

4. CNC hydrogels applications

4.1. Biomedical application

The soft and rubbery structure of the hydrogel in its swollen state mimics the behavior of extracellular matrix (ECM) in biological tissues. Their highly porous structure enables the hydrogels to absorb the small molecules inside physical structure and retain them until triggered by a desirable medium for the release of these molecules (Martino et al., 2011). Hydrogels provide a hydrated and porous environment for cells, which improves their suitability for different applications in biomedical field such as drug delivery, tissue engineering, and wound dressing (Table 2).

4.1.1. Drug delivery

The most common applications of CNC hydrogels in the biomedical field includes drug delivery carriers (Liu, He et al., 2018; Ooi, Ahmad, & Amin, 2016). Over the last decades, scientists are exploring nanotechnology-based drug carriers such as smart gels. In which the drug can be encapsulated and delivered to the target sites in the body. The special physical characteristics of hydrogels have attracted considerable attention in the field of drug delivery. The porosity of hydrogels can simply be altered through adjusting the concentration of cross-linking agent and the affinity of the hydrogels for the aqueous media in which they are swollen. The highly porous structure allows loading and unloading of drugs at a constant rate depending on the diffusion coefficient of drug molecules or macromolecules through the hydrogel network (Li & Mooney, 2016).

The stimuli responsive hydrogels acting as drug delivery carriers should possess the ability of regulating drug release, minimizing drug leakage, and switching on and off for certain functions under the local stimuli of the target zone. Hereby, the incorporation of biocompatible materials such as CNCs into different drug carriers has been studied to reduce the voids in the hydrogel structure and protect the drug from leakage (Thomas, Latha, & Thomas, 2018). Since drug-loading behavior of pristine CNCs is low, different surface modification techniques including physical absorption and chemical grafting have been reported to improve the properties of CNCs as a drug carrier. Controlling the drug release rate as well as introducing controllable response against different stimuli are two key parameters in defining different routes for CNC hydrogels with the focus on drug delivery application (Cao, 2018). The controlled drug release process in hydrogels includes three different mechanisms, such as degradation, swelling, and deformation.

Table 2
Properties for CNC hydrogels including surface functionalization methods, hydrogel preparation techniques.

Material	CNCs (wt %)	CNCs surface modification	Hydrogel form/ preparation technique	Application	Characteristics	Ref
Alginate	–	Magnetizing CNCs	Beads freeze drying	Drug delivery	Increment in the swelling degree and decline in the rate of drug release	(Supramaniam, Adnan, Kaus, & Bushra, 2018)
PEG	1.5	Furyl-Modification	Solution polymerization	Biomedical	Excellent recovery performance and self-healing property	(Shao et al., 2017)
ADH-HA	0.25– 0.75	Aldehyde-modification	Covalent cross-linking	Tissue engineering	Increase in storage modulus, higher resistance to degradation	(Domingues et al., 2015)
Gelatin	–	Aldehyde-modification	Chemically cross-linked	Tissue engineering	Controllable permeability, ability to control the anisotropic properties of hydrogels	(Prince et al., 2018)
Alginate	10–50	TEMPO-treated	freeze-drying	Wound healing, tissue engineering	Improvement in bioadhesion and growth of fibroblasts cells	(Siqueira et al., 2019)
CS	20, 33, 50	periodate-oxidation	cross-linking	Drug delivery	The cumulative drug release at pH 1.5 rather than that at pH 7.4, controllable swelling ratio	(Xu et al., 2019)
Alginate, Honey	–	–	Ionic gelation/ Centrifugation and vacuum dry	Oral drug delivery	pH dependent swelling rate effective protection for drug against gastric conditions	(Thomas et al., 2018)
Graphene oxide, PMC	2.5–10	–	Free radical solutions polymerization	Tissue engineering	Improvement in compressive strength and stiffness	(Kumar et al., 2018)
PNIPAAm	0.1–5	–	Covalent and non-covalent cross-linking, free radical polymerization	Biosensor, drug loading and releasing	Reinforcing effect, good drug-loading at room temperature, burst drug release followed by a slow release at 37 °C	(Zubik et al., 2017)
PAAm, SA, SG	2.5–10	–	Free radical polymerization/ cross-linking	Bone tissue engineering	Decreased porosity as CNC increase, improvement in the mechanical performance	(Kumar et al., 2017)
Gelatin, HA		–	cross-linking/ freeze-drying	Wound dressing	NIH-3T3 cell attachment, growth	(Yin et al., 2019)
CNF	0.5, 1, 1.5	–	3D printing	Wound dressing	Easy printability due to reduced complex viscosity	(Heggset et al., 2019)

These mechanisms are related to how the hydrogels are exposed to specific conditions (Fig. 6).

Degradation can occur in either polymer backbone or at the cross-links, typically mediated by hydrolysis or enzyme activity (O'Shea, Aimetti, Kim, Yesilyurt, & Langer, 2015). For this reason, the exposure to acidic condition is common method to regulate drug release. In swelling mechanism, as a hydrogel swells in response to various external stimuli and the mesh size increases and drug molecules migrate through the network. Mechanical deformation in hydrogel networks which occurs through changing the network structure of hydrogel is another approach to release the drug molecules. Deformation might be happen through different approaches such as mechanical deformation, or using ultrasound and magnetic field-induced deformations (Li & Mooney, 2016).

Åhlén et al. prepared polyvinyl alcohol (PVA)-based hydrogels reinforced with CNCs to develop contact lens platforms for controlled ophthalmic drug delivery. The enzymatic degradation of nanoparticles in the presence of lysozyme controlled the drug release. It is reported that interlocking between the nanoparticles and CNCs resulted in *in-situ* gelation, which prevented drug leaching (Åhlén, Tummala, & Mihranyan, 2018). A pH sensitive hydrogel was prepared using poly (acrylic acid) (PAA) reinforced by CNCs through chemical cross-linking using *N, N*-methylenebisacrylamide. The hydrogels reinforced by 5% CNCs achieved the optimum swelling, and higher drug release rate at pH 7 (Lim et al., 2017). Some researchers reported an improvement in the stability of different natural hydrogels through the incorporation of modified CNCs, which restricts leaching from hydrogels and improves the efficiency of drug delivery. Nigmatullin et al. reported that octyl modified CNCs possessed high affinity to starch, enabling the formation of strong gels at relatively low concentrations in comparison with unmodified CNCs (Nigmatullin et al., 2018).

4.1.2. Tissue engineering

Tissue engineering is an attempt in producing a renewable source for the restoration or modification of tissues through the proposition of engineering, biological sciences and medicine. Hydrogels have great potential for tissue engineering applications as a substrate on which cell populations can attach and migrate due to their chemical resemblance to the extracellular matrix, flexibility, and porous structure that facilitate transport and diffusion of essential nutrients, metabolites, oxygen, and waste across the scaffold. Tissue engineering is a fast growing area of biomedical science, and many interesting results have been reported on the application of different hydrogels like fibrin (Dhahri, Romagnuolo, & Laflamme, 2018), gelatin (AnilKumar et al., 2018; Luo, Li, Qin, & Wa, 2018), and collagen (Yang, Lu et al., 2018) in this field. In tissue engineering, hydrogel is generally a structure consisting of interconnecting pores that allow the 3D flow of culture medium providing cells oxygen and nutrients critical for their survival. In addition, hydrogels should act like scaffold to mechanically support the tissue so that it can regenerate and repair the damaged tissues and organs (Sayyar et al., 2015).

Recently, the incorporation of CNCs into different hydrogels as macroporous scaffolds in tissue engineering has been evaluated and the results show the improvement in the stability against hydrolytic and enzymatic degradation (Silva et al., 2018). Prince et al. introduced a microextrusion-based 3D printing method to create a printable ink composed of a covalently cross-linked anisotropic hydrogel sheets with CNCs in the direction of extrusion. Aldehyde was employed to oxidize the surface of CNCs. Cytocompatibility and different concentrations of CNCs/gelatin resulted in the formation of hydrogels with variable biophysical and mechanical properties. In which, the higher porosity in the hydrogel resulted in the lower mechanical properties (Prince et al., 2018).

Polyacrylamide-sodium carboxymethylcellulose (PMC) was reinforced with graphene oxide (GO) and CNCs via in situ free-radical polymerization. The incorporation of GO and CNCs resulted in the

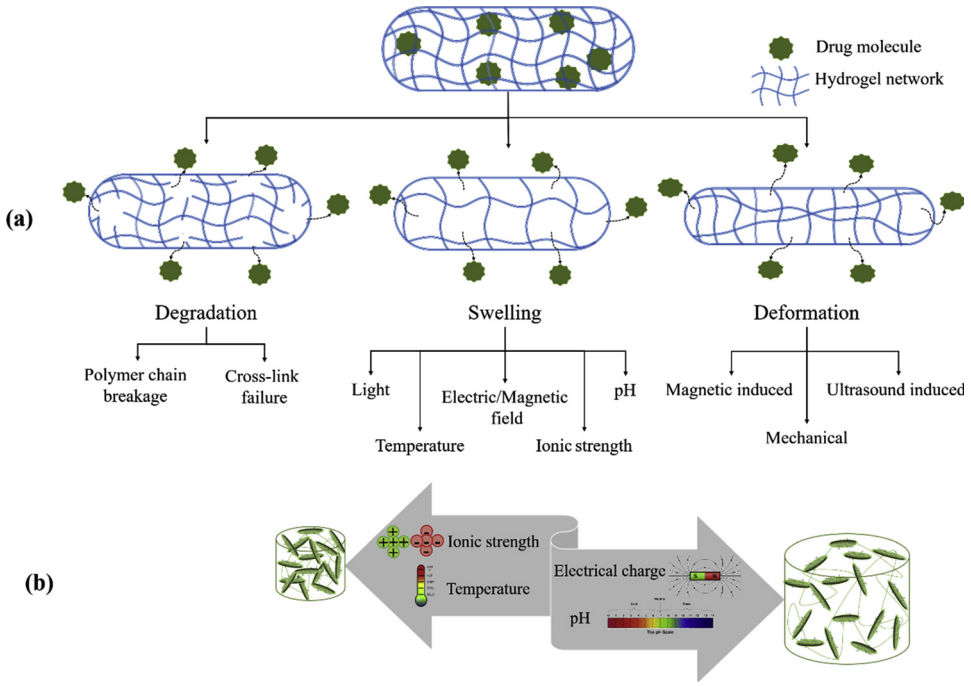

Fig. 6. (a) Drug release mechanisms followed by drug particles in hydrogel medium. (b) Stimuli-responsive property of CNC hydrogels results in the alteration in hydrogel structure and appearance.

formation of a hydrogel with shape-recovery behavior, and self-healing capability with potential applications in tissue engineering (Kumar, Rao, & Han, 2018). It was reported that a hydrogel composed of bacterial CNCs along with collagen and alginate coated with chitosan have great potential as scaffolds. The composite hydrogel was formed via internal gelation using $CaCO_3$-d-glucono-δ-lactone (GDL) as cross liker. The release of CO_2 from $CaCO_3$ during crosslinking process enhanced the hydrogel porosity. The addition of collagen and bacterial CNCs into the alginate matrix improved cell attachment to the hydrogel, which further favored cell proliferation and growth (Yan et al., 2018).

4.1.3. Wound dressing

The human skin is the largest organ in the body in direct contact with environment. Skin injuries which occur in daily life require an effective treatment to prevent serious illnesses or even mortality (Du et al., 2019). Wound dressing is a simple and practical way to keep the wounds clean and protect them from bacterial infection. Wound dressings also need to be oxygen permeable to let the wound exudates dry (Hamedi, Moradi, Hudson, & Tonelli, 2018). Among different wound dressing materials, hydrogels have received special attention owing to their unique characteristics such as super high absorbability, good oxygen permeability, easy replacement, and controlled drug release. In particular, CNC hydrogel are promising material for wound-healing applications owing to their aptitude to absorb exudates during dressing process and facilitating the movement of high molecular weight template for blood clotting and tissue repair activity (Dong & Li, 2018) (Fig. 7).

Wound dressings are efficient physical barriers protecting internal organs against outside microbial invasion and providing a moist environment to provoke wound healing process (Ge et al., 2018). Because of the appropriate biological properties of bacterial CNCs, it has received more attention in the case of wound healing applications than regular CNCs. In addition, thermo-responsive injectable hydrogels reinforced by CNCs have the ability to effectively direct medicine to deep or narrow-opening wounds and the ability of sustained release of antibiotics, which are desirable in wound dressing applications. The application of poly(N-isopropyl acrylamide) (PNIPAAm) and CNC injectable hybrid hydrogels for wound dressing was evaluated by Zubik et al. Their results confirmed a good drug-loading ability at room temperature and a burst drug discharge followed by a slow and constant release at 37 °C, which is close to the human body temperature (Zubik, Singhsa, Wang, Manuspiya, & Narain, 2017).

In some studies the incorporation of CNCs into hydrogels with wound dressing applications resulted in a dual advantage of improved mechanical strength and imparting higher hydrophilicity character into the hydrogel (Dong & Li, 2018). The recent surfacing of CNCs brings a motivating approach to improve the application of nanoparticles in conjunction with CNCs to form an effective wound dressing. A nano

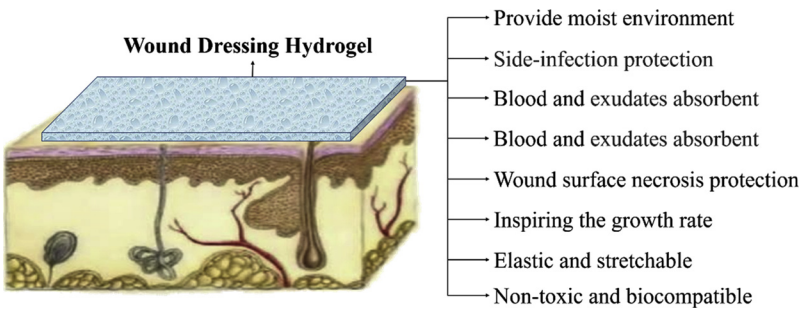

Fig. 7. Schematic illustration representing of application of hydrogel materials in wound dressing field.

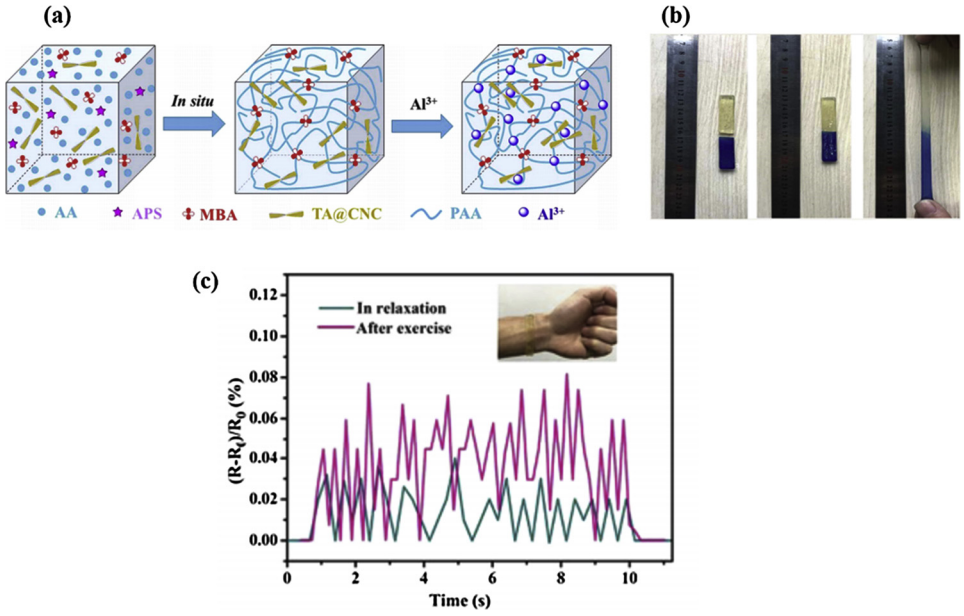

Fig. 8. a) Schematic illustration of ionic gel synthetic process including the *in situ* polymerization and immersion in Al^{3+} solution to produce ionic coordination. b) Self-healing properties of the hydrogels at 25 °C. c) Real-time resistance signal variation of the gel strain sensor adhered onto the radial artery of the wrist to monitor the pulse under relaxation and exercise conditions.
Reproduced from (Shao et al., 2018) by permission.

biocomposite hydrogel consisting of bamboo CNCs and silver nanoparticles (AgNPs) were prepared via in situ method; *S.cumini* leaf extract was employed as a biological reducing agent to reduce $AgNO_3$. CNCs were extracted from bamboo by a combination of chemical (bleaching, alkali and acid treatment) and mechanical (ultrasonication) methodology. The effectiveness of the synthesized hydrogel was evaluated for curing wounds in streptozotocin-induced diabetic. Accelerated diabetic wound healing process was reported owing to low inflammation risk as well as early collagen deposition (Singla et al., 2017).

Yin et al, reported the synthesis of hydrogels by crosslinking CNCs with gelatin and, hyaluronic acid for potential application in wound dressing field. The resulting hydrogels exhibited the formation of amide bond and hydrogen bonding between hydrogel components. The cytocompatibility of GA-HA-CNC hydrogels was through NIH-3T3 cell culture. Dense living cells emerged in the GA-HA-CNC hydrogels confirmed the promising survival environment for NIH-3T3 cells growth and proliferation (Yin, Lin, & Zhan, 2019).

The incorporation of divalent calcium (Ca^{2+}) or copper ions (Cu^{2+}) as crosslinking agents in wood-derived CNCs was studied by Basu et al. The prepared hydrogels exhibited barrier and antibacterial properties against the bacterial strains *Staphylococcus epidermidis* and *Pseudomonas aeruginosa*. The observation was attributed to bacteria-impermeable nature of wood-derived ion-crosslinked hydrogels (Basu, Heitz, Strømme, Welch, & Ferraz, 2018).

4.1.4. Bio-sensing application

The unique characteristics of hydrogels such as high water absorption ability, resistance to disbanding, and the formation of hydrophilic aqueous microenvironments demonstrate their high performance as biosensors in sensing and converting biological responses to optical, chemical, electrical, or physical signals (Tavakoli & Tang, 2017). The ideal materials for bio-sensing applications should be capable of tailoring the materials adsorption to capture the proper analyte. The incorporation of biocompatible materials in hydrogel resulted in the emergence of sustainable biosensors. Among different biocompatible materials, CNCs have found use in the preparation of sensitive materials for bio-sensing or bio-imaging application owing to their promising viscoelasticity and biocompatibility, resemblance to biological tissue, and capability of self-healing character (Liu et al., 2015). The incorporation of CNCs as reinforcement agent into bio-based hydrogels could give rise to hydrogels with enhanced mechanical properties and dimensional stability as well as electromechanical properties. Stimuli–responsive CNC reinforced hydrogels can monitor changes in the pH, ionic strength, temperature and electric field charge via altering their structure and appearance (e.g. volume and shape). Moreover, the application of CNCs can prevent the transducer surface from degradation since the strong hydrophilicity character of CNCs can control the non-selective adsorption of biological materials (Zheng, Wang, Qiu, Li, & Yan, 2019). The large number of hydroxyl groups on the surface of the CNCs permits a high degree of surface bound fluorophores, assisting in the detection of pH change in the media (Grishkewich, Mohammed, Tang, & Tam, 2017).

Different swelling and deswelling behavior (Basu, Samanta, & Ganguly, 2018), and gel-sol transitions due to the lack of sufficient binding force between hydrogel components (Liu, Li et al., 2018) are the common responses which can be observed against different pH media in pH- sensitive hydrogels. Hydrogels shrink at acidic pH, while, they expand at alkaline pH. In CNC hydrogels, the detection of pH change in the media can be assisted via different surface modification treatments (Grishkewich et al., 2017). Incorporation of amine groups on the surface of CNCs at a high pH can result in gelation, however, at low pH gelation is inhibited as a result of protonating and electrostatic repulsion (Way, Hsu, Shanmuganathan, Weder, & Rowan, 2012). Lim et al. used graft copolymerization to obtain pH-sensitive hydrogel made of CNCs and PAA. Deprotonation of carboxylic acid groups of PAA formed the negatively charged carboxylate ions and resulted in electrostatic repulsion and inhibited hydrogel swelling (Lim, Ahmad, Lazim, & Amin, 2014). Zhangkang et al. synthesized a double-network hydrogel from poly(N-isopropylacrylamide) (PNIPPAm), PAA, PVA, and CNCs via photo-crosslinking method. A classical pH-sensitive profile at different pH from 1 to 7 was observed which was attributed to high weight ratio of PAA (Li, Bai et al., 2018).

A self-healing and self-adhesive ionic gel with strain sensitive feature has been identified as a wearable strain sensor (Fig. 8). The interfacial dynamic coordination bonds among tannic acid (TA)-coated CNCs, poly- (acrylic acid) chains, and metal ions in a covalent polymer network formed the ionic gel. The presence of catechol groups from the incorporated TA played multiple roles in both sticking the gel to different substrates such as human skin tissue and forming mechanically strong and dynamic networks, which can distinguish both large motions and subtle motions (Shao et al., 2018).

Jayaramudu et al. studied polyvinyl alcohol (PVA) - CNC hydrogels containing different CNC contents (1, 2, and 3 wt%) as an electroactive

Table 3
CNC hydrogels used for adsorption of various heavy metals and dyes in water purification.

Hydrogel components	CNC modification	Hydrogel form/ technique	Dye	Heavy metals	Ref
PVA-CNC-poly HEMA	–	Bead/ photo cross linking/freezing/ thawing	Xylenol orange, Methylene blue	–	(Bai et al., 2018)
CNC-HEMA-AA-MBA	–	Radical polymerization	Crystal violet	–	(Hosseinzadeh, Hosseinzadeh, & Pashaei, 2019)
CNC-SA-PAM	–	Ionic crosslinking	Methyl blue	–	(Yue et al., 2019)
CNC-GQDs	Aldehyde Groups	Chemical cross-linking	–	Hg^{2+}, Cu^{2+}, Ni^{2+}, and Ag^{+} ions	(Alizadehgiashi et al., 2018)
CNCs-AA-MBA	Polymer grafting	Thermal treatment/freeze drying	Methyl blue	–	(Liu, Yang et al., 2018)

hydrogel. The hydrogels were prepared using the freeze–thaw process, and the hydrogels containing higher CNC content exhibited higher displacement in the presence of electric field (Jayaramudu et al., 2018).

4.2. Industrial application

4.2.1. Wastewater treatment application

In the past few decades, research in the field of wastewater treatment has shifted to the adsorption methods via using multicomponent hydrogels with high adsorption capacity of water purification, including cationic and anionic dyes, and heavy metal ions (Table 3). Hydrogel beads (Mohammed, Grishkewich, Waeijen, Berry, & Tam, 2016), hydrogel films (Shi, Tao, & Cui, 2018), and hydrogel nanocomposites (Yue et al., 2019) are three common types of hydrogels, which have been used in wastewater treatment field.

High mechanical strength, high surface area and hydrophilic nature are essential characteristics for functional hydrogels to trap selective contaminates from wastewater. The adsorption mechanism in hydrogels, which can be either physical (reversible process) or chemical (irreversible process) (Yu, Deschamps, Hamon, Prabhakaran, & Pré, 2017), is heavily dependent on ion exchange, and electrostatic interaction (Van Tran, Park, & Lee, 2018). In addition, hydrogels geared towards the application of wastewater treatment, the pore structure especially those pores which are located away from the surface, governs the adsorption quality of the hydrogel (Le & Nunes, 2016). The pore size of a hydrogel or scaffold, which directly regulates the transport characteristics, is an important parameter in cell-attachment, migration, and proliferation. Pore size in hydrogels is in the range of few to tens of nanometers and measured as the average distance between crosslinks along the polymer chains forming the hydrogel network (Fernandez-Colino et al., 2018). It was reported that by increasing the degree of cross-linking in the hydrogels, the adsorption efficiency would be decreased due to pore size reduction in the hydrogels (Abdelwahab, Hassan, Mostafa, & El Sadek, 2016).

CNCs have very high adsorption capacity to positive ions owing to the negatively charged carboxylic group on their surface (Lee, 2018). CNCs with surface modification treatments or grafting of selected monomers were also employed to enhance the heavy metal adsorption capacity from aqueous solution (Ahmad, Ahmed, Swami, & Ikram, 2015). The application of CNCs solely or in hydrogel matrix like chitosan has led to a higher surface area for adsorption capacity as well as enhanced mechanical properties (Bao, Wu, Wang, & Su, 2014). Heavy metal adsorption mainly depends on concentration, pH, and temperature of the solution. In general, adsorption is a time-dependent reaction according to the adsorbate and adsorbent nature (Jiang, Dinh, & Hsieh, 2017).

The combination of graphene oxide (GO), CNCs, and vitamin C self-assembled into porous hybrid sponges with a honeycomb structure. Methylene blue, Cu^{2+} and Cd^{2+} were used as model organic dye contaminant and heavy metal ions to evaluate the adsorption quality of the hydrogel. The adsorption kinetics of the manufactured sponge for methylene blue (MB) were 48 times faster than granular activated carbon (GAC), which is an industry standard in water contaminant removal (Yousefi et al., 2018). The facile separation in batch adsorption or in a continuous flow packed bed system has been reported for CNC hydrogel beads (Mohammed et al., 2016). Furthermore, the incorporation of metal oxides into CNCs hydrogels facilitates the heavy metal adsorption from the solution. Ren et al. reported a hydrogel with high compression strength, elasticity, and elongation, where CNCs and Quaternized xylan (QXH) formed ionic crosslinking. The Fe_3O_4 nanoctahedra was prepared in situ within the CNCs-QXH hydrogel matrix. A high absorption capacity was reported for single metal ions including Zn^{2+}, Pb^{2+}, Cd^{2+}, and Cu^{2+}, indicating the key role of electronegativity in the adsorption capacity of hydrogels for metal ions (Ren et al., 2018). Zhan et al. also fabricated a chemically cross-linked nanocolloidal hydrogel from CNCs and graphene quantum dot to trap metal ions including Ag^{+}, Ni^{2+}, Cu^{2+}, and Hg^{2+} from aqueous solutions. A significant increase in adsorption quality was observed at higher content of GQD, owing to the higher number of active sites on the surface of GQD (Alizadehgiashi et al., 2018).

Bai et al. prepared PVA/CNC/polyHEMA and PVA/CNC/polyHEMBA through photo-crosslinking followed by freezing/thawing (F-T) cycle. They reported poor dye adsorption in PVA and PVA-CNC hydrogel owing to thin porous walls; however, the incorporation of polyHEMA and polyMBA resulted in thicker walls and improved the dye removal capacity in the hydrogels via interpenetrating polymer network (IPN) between hydrogel components (Bai, Li, Zhang, Wang, & Dong, 2018). The formation of IPN is known as a multi-functional cross-linking method, improving the adsorption quality in hydrogels. In addition, anionic cellulose hydrogel was studied for removal of cationic dyes from contaminated water (Soleimani, Tehrani, & Adeli, 2018). The adsorption of anionic dyes on this hydrogel was attributed to the ion-exchange between the anion groups of CNCs and the cation groups on the dye Table 3. Shows CNC hydrogels used for water treatment.

5. Summary and future perspectives

Hydrogels are 3D network colloidal gels formed through cross-linking of hydrophilic polymer chains with the ability to absorb and retain large volumes of water in an aqueous environment, but not dissolving it. Because of the increasing worldwide demand for environmentally friendly and biocompatible materials, the potential applications of CNCs in hydrogel manufacturing have received great attention over the past years. CNC hydrogels are extremely advantageous in comparison with synthetic polymers, owing to CNCs' biodegradability, biocompatibility, and competitive mechanical properties. This review exhibits the most recent literature in the field of CNC hydrogels, which refers to the classification of CNC hydrogels considering the different physical and chemical preparation routes with a focus on stimuli-responsive hydrogels for biomedical, environmental, and industrial applications. Since the overall properties of CNC hydrogels are extremely dependent on preparation techniques, the mechanical and physical manufacturing routes are discussed in this review. The observed advancement in the field of CNC hydrogels confirms the

potential application of this fascinating material structure in different fields; however, the application of CNC hydrogels is still in its infancy.

The huge interest in the application of CNC as an alternative for synthetic hydrogels leads to the fabrication of CNC hydrogels with desirable properties appropriate for different applications including biomedical, bio-sensing, and water purification. Although the commercial production of CNCs in large scale is facile, its commercial application in the form of hydrogel still suffers from some drawbacks such as CNC hydrogels degradation, excessive swelling ratio, and mechanical instability. However, in the case of biomedical engineering, swelling and deswelling kinetics, and controllable degradation is principal for cell growth and tissue regeneration. The application of different reactive functionalization techniques can improve the hydrogel stability for a short period, however, the hydrophilic nature of CNCs favors the degradation over long time periods. In addition to surface modification techniques as an essential step for a strong network in hydrogels, the synthesis routes also need to be investigated for providing control of swelling, deswelling, and degradation in CNC hydrogels.

The high dependency of CNCs behavior on their origin and the processing technique is another concern which needs to be considered regarding CNC hydrogels preparation routes. There are a restricted number of works examined the effect of CNCs' origin and isolation routes on the properties of CNCs (Jonoobi et al., 2015; Mohammed et al., 2016; Yu, Zhang, Lu, & Yao, 2016). Therefore, a profound understanding of the effect of CNCs properties as a function of their origin and processing techniques on the properties of CNC hydrogels is essential.

In general, the promising mechanical characteristics of CNCs has built up new horizons on advanced applications of CNC hydrogels in different areas such as biomedical, environmental, and bio-sensing, which are still in their infancy stages. However, the increasing efforts devoted to controlling the application of CNC hydrogels would further exploit the new methods for fabrication of CNC hydrogels fulfilling expectations.

Acknowledgment

No funding was procured for this study.

References

Abdelwahab, H. E., Hassan, S. Y., Mostafa, M. A., & El Sadek, M. M. (2016). Synthesis and characterization of glutamic-chitosan hydrogel for copper and nickel removal from wastewater. *Molecules, 21*(6), 684.

Aderibigbe, B. A., & Buyana, B. (2018). Alginate in wound dressings. *Pharmaceutics, 10*(2), 42.

Åhlén, M., Tummala, G. K., & Mihranyan, A. (2018). Nanoparticle-loaded hydrogels as a pathway for enzyme-triggered drug release in ophthalmic applications. *International Journal of Pharmaceutics, 536*(1), 73–81.

Ahmad, M., Ahmed, S., Swami, B. L., & Ikram, S. (2015). Adsorption of heavy metal ions: Role of chitosan and cellulose for water treatment. *Langmuir, 79*, 109–155.

Alizadehgiashi, M., Khuu, N., Khabibullin, A., Henry, A., Tebbe, M., Suzuki, T., et al. (2018). Nanocolloidal hydrogel for heavy metal scavenging. *ACS Nano, 12*(8), 8160–8168.

AnilKumar, S., Allen, S. C., Tasnim, N., Akter, T., Park, S., Kumar, A., et al. (2018). The applicability of furfuryl-gelatin as a novel bioink for tissue engineering applications. *Journal of Biomedical Materials Research Part B, Applied Biomaterials, 107*(2), 314–323.

Bai, H., Li, Z., Zhang, S., Wang, W., & Dong, W. (2018). Interpenetrating polymer networks in polyvinyl alcohol/cellulose nanocrystals hydrogels to develop absorbent materials. *Carbohydrate Polymers, 200*, 468–476.

Bao, S., Wu, D., Wang, Q., & Su, T. (2014). Functional elastic hydrogel as recyclable membrane for the adsorption and degradation of methylene blue. *PloS One, 9*(2), e88802.

Basu, A., Heitz, K., Strømme, M., Welch, K., & Ferraz, N. (2018). Ion-crosslinked wood-derived nanocellulose hydrogels with tunable antibacterial properties: Candidate materials for advanced wound care applications. *Carbohydrate Polymers, 181*, 345–350.

Basu, S., Samanta, H. S., & Ganguly, J. (2018). Green synthesis and swelling behavior of Ag-nanocomposite semi-IPN hydrogels and their drug delivery using Dolichos biflorus Linn. *Soft Materials, 16*(1), 7–19.

Beaumont, M., Potthast, A., & Rosenau, T. (2018). Cellulose nanofibrils: From hydrogels to aerogels. *Cellulose Science and Technology: Chemistry, Analysis, and Applications,* 277–339.

Byrne, M. E., & Salian, V. (2008). Molecular imprinting within hydrogels II: Progress and analysis of the field. *International Journal of Pharmaceutics, 364*(2), 188–212.

Cao, Y. (2018). Applications of cellulose nanomaterials in pharmaceutical science and pharmacology. *Express Polymer Letters, 12*(9).

Cao, J., Li, J., Chen, Y., Zhang, L., & Zhou, J. (2018). Dual physical crosslinking strategy to construct moldable hydrogels with ultrahigh strength and toughness. *Advanced Functional Materials, 28*(23), 1800739.

Capron, I., Rojas, O. J., & Bordes, R. (2017). Behavior of nanocelluloses at interfaces. *Current Opinion in Colloid & Interface Science, 29*, 83–95.

Chau, M., De France, K. J., Kopera, B., Machado, V. R., Rosenfeldt, S., Reyes, L., et al. (2016). Composite hydrogels with tunable anisotropic morphologies and mechanical properties. *Chemistry of Materials, 28*(10), 3406–3415.

Cheng, Y., He, C., Ren, K., Rong, Y., Xiao, C., Ding, J., et al. (2018). Injectable enzymatically cross-linked hydrogels with light-controlled degradation profile. *Macromolecular Rapid Communications*1800272.

Clarke, D. E., Parmenter, C. D., & Scherman, O. A. (2018). Tunable pentapeptide self--assembled β-Sheet hydrogels. *Angewandte Chemie, 57*(26), 7709–7713.

De France, K. J., Chan, K. J., Cranston, E. D., & Hoare, T. (2016). Enhanced mechanical properties in cellulose nanocrystal–poly (oligoethylene glycol methacrylate) injectable nanocomposite hydrogels through control of physical and chemical cross-linking. *Biomacromolecules, 17*(2), 649–660.

De France, K. J., Hoare, T., & Cranston, E. D. (2017). Review of hydrogels and aerogels containing nanocellulose. *Chemistry of Materials, 29*(11), 4609–4631.

De France, K. J., Yager, K. G., Chan, K. J., Corbett, B., Cranston, E. D., & Hoare, T. (2017). Injectable anisotropic nanocomposite hydrogels direct in situ growth and alignment of myotubes. *Nano Letters, 17*(10), 6487–6495.

Deng, H., Dong, A., Song, J., & Chen, X. (2019). Injectable thermosensitive hydrogel systems based on functional PEG/PCL block polymer for local drug delivery. *Journal of Controlled Release, 297*, 60–70.

Dhahri, W., Romagnuolo, R., & Laflamme, M. A. (2018). Training heart tissue to mature. *Nature Biomedical Engineering, 2*(6), 351.

Domingues, R. M., Silva, M., Gershovich, P., Betta, S., Babo, P., Caridade, S. G., et al. (2015). Development of injectable hyaluronic acid/cellulose nanocrystals bionanocomposite hydrogels for tissue engineering applications. *Bioconjugate Chemistry, 26*(8), 1571–1581.

Dong, F., & Li, S. (2018). Wound dressings based on chitosan-dialdehyde cellulose nanocrystals-silver nanoparticles: Mechanical strength, antibacterial activity and cytotoxicity. *Polymers, 10*(6), 673.

Du, H., Liu, W., Zhang, M., Si, C., Zhang, X., & Li, B. (2019). Cellulose nanocrystals and cellulose nanofibrils based hydrogels for biomedical applications. *Carbohydrate Polymers, 209*, 130–144.

Fernandez-Colino, A., Wolf, F., Keijdener, H., Rütten, S., Schmitz-Rode, T., Jockenhoevel, S., et al. (2018). Macroporous click-elastin-like hydrogels for tissue engineering applications. *Materials Science and Engineering C, 88*, 140–147.

Ge, L., Xu, Y., Li, X., Yuan, L., Tan, H., Li, D., et al. (2018). Fabrication of antibacterial collagen-based composite wound dressing. *ACS Sustainable Chemistry & Engineering, 6*(7), 9153–9166.

González, P. S., Agostini, E., & Milrad, S. R. (2008). Comparison of the removal of 2, 4-dichlorophenol and phenol from polluted water, by peroxidases from tomato hairy roots, and protective effect of polyethylene glycol. *Chemosphere, 70*(6), 982–989.

Goodarzi, H., Jadidi, K., Pourmotabed, S., Sharifi, E., & Aghamollaei, H. (2019). Preparation and in vitro characterization of cross-linked collagen–gelatin hydrogel using EDC/NHS for corneal tissue engineering applications. *International Journal of Biological Macromolecules, 126*, 620–632.

Gopalakrishnan, A., Shankarappa, S. A., & Rajanikant, G. (2019). Hydrogel scaffolds: Towards restitution of ischemic stroke-injured brain. *Translational Stroke Research, 10*(1), 1–18.

Grishkewich, N., Mohammed, N., Tang, J., & Tam, K. C. (2017). Recent advances in the application of cellulose nanocrystals. *Current Opinion in Colloid & Interface Science, 29*, 32–45.

Gu, F., Wang, W., Cai, Z., Xue, F., Jin, Y., & Zhu, J. (2018). Water retention value for characterizing fibrillation degree of cellulosic fibers at micro and nanometer scales. *Cellulose, 25*(5), 2861–2871.

Habibi, Y., Foulon, L., Aguié-Béghin, V., Molinari, M., & Douillard, R. (2007). Langmuir?Blodgett films of cellulose nanocrystals: Preparation and characterization. *Journal of Colloid and Interface Science, 316*(2), 388–397.

Hamedi, H., Moradi, S., Hudson, S. M., & Tonelli, A. E. (2018). Chitosan based hydrogels and their applications for drug delivery in wound dressings: A review. *Carbohydrate Polymers, 199*, 445–460.

Hasani, M., Cranston, E. D., Westman, G., & Gray, D. G. (2008). Cationic surface functionalization of cellulose nanocrystals. *Soft Matter, 4*(11), 2238–2244.

Heggset, E. B., Strand, B. L., Sundby, K. W., Simon, S., Chinga-Carrasco, G., & Syverud, K. (2019). Viscoelastic properties of nanocellulose based inks for 3D printing and mechanical properties of CNF/alginate biocomposite gels. *Cellulose, 26*(1), 581–595.

Hosseinzadeh, S., Hosseinzadeh, H., & Pashaei, S. (2019). Fabrication of nanocellulose loaded poly (AA-co-HEMA) hydrogels for ceftriaxone controlled delivery and crystal violet adsorption. *Polymer Composites, 40*(S1), E559–E569.

Hu, Y., & Abidi, N. (2016). Distinct chiral nematic self-assembling behavior caused by different size-unified cellulose nanocrystals via a multistage separation. *Langmuir, 32*(38), 9863–9872.

Huang, H., Wang, X., Rehfeldt, F., & Zhang, K. (2018). Dually heterogeneous hydrogels via dynamic and supramolecular cross-links tuning discontinuous spatial ruptures. *ACS Sustainable Chemistry & Engineering, 6*(3), 4294–4301.

Ito, K., Chuang, J., Alvarez-Lorenzo, C., Watanabe, T., Ando, N., & Grosberg, A. Y. (2003). Multiple point adsorption in a heteropolymer gel and the Tanaka approach to imprinting: Experiment and theory. *Progress in Polymer Science, 28*(10), 1489–1515.

Iwamoto, S., Kai, W., Isogai, A., & Iwata, T. (2009). Elastic modulus of single cellulose microfibrils from tunicate measured by atomic force microscopy. *Biomacromolecules, 10*(9), 2571–2576.
Jayaramudu, T., Ko, H.-U., Kim, H., Kim, J., Muthoka, R., & Kim, J. (2018). Electroactive hydrogels made with polyvinyl alcohol/cellulose nanocrystals. *Materials, 11*(9), 1615.
Jiang, F., Dinh, D. M., & Hsieh, Y.-L. (2017). Adsorption and desorption of cationic malachite green dye on cellulose nanofibril aerogels. *Carbohydrate Polymers, 173*, 286–294.
Jonoobi, M., Oladi, R., Davoudpour, Y., Oksman, K., Dufresne, A., Hamzeh, Y., et al. (2015). Different preparation methods and properties of nanostructured cellulose from various natural resources and residues: A review. *Cellulose, 22*(2), 935–969.
Julinová, M., Vaňharová, L., & Jurča, M. (2018). Water-soluble polymeric xenobiotics–polyvinyl alcohol and polyvinylpyrrolidon–and potential solutions to environmental issues: A brief review. *Journal of Environmental Management, 228*, 213–222.
Kargarzadeh, H., Huang, J., Lin, N., Ahmad, I., Mariano, M., Dufresne, A., et al. (2018). Recent developments in nanocellulose-based biodegradable polymers, thermoplastic polymers, and porous nanocomposites. *Progress in Polymer Science, 87*, 197–227.
Khabibullin, A., Alizadehgiashi, M., Khuu, N., Prince, E., Tebbe, M., & Kumacheva, E. (2017). Injectable shear-thinning fluorescent hydrogel formed by cellulose nanocrystals and graphene quantum dots. *Langmuir, 33*(43), 12344–12350.
Khorasani, M. T., Joorabloo, A., Moghaddam, A., Shamsi, H., & MansooriMoghadam, Z. (2018). Incorporation of ZnO nanoparticles into heparinised polyvinyl alcohol/chitosan hydrogels for wound dressing application. *International Journal of Biological Macromolecules, 114*, 1203–1215.
Kiatkamjornwong, S. (2007). Superabsorbent polymers and superabsorbent polymer composites. *Science Asia, 33*(s1), 39.
Kim, H., Kim, J., Choi, J., Park, Y., & Ki, C. (2018). Characterization of silk hydrogel formed with hydrolyzed silk fibroin-methacrylate via photopolymerization. *Polymer, 153*, 232–240.
Koetting, M. C., Peters, J. T., Steichen, S. D., & Peppas, N. A. (2015). Stimulus-responsive hydrogels: Theory, modern advances, and applications. *Materials Science and Engineering R Reports, 93*, 1–49.
Kumar, A., Rao, K. M., & Han, S. S. (2017). Synthesis of mechanically stiff and bioactive hybrid hydrogels for bone tissue engineering applications. *Chemical Engineering Journal, 317*, 119–131.
Kumar, A., Rao, K. M., & Han, S. S. (2018). Mechanically viscoelastic nanoreinforced hybrid hydrogels composed of polyacrylamide, sodium carboxymethylcellulose, graphene oxide, and cellulose nanocrystals. *Carbohydrate Polymers, 193*, 228–238.
Le, N. L., & Nunes, S. P. (2016). Materials and membrane technologies for water and energy sustainability. *Sustainable Materials and Technologies, 7*, 1–28.
Lee, K.-Y. (2018). *Nanocellulose and sustainability: Production, properties, applications, and case studies.* CRC Press.
Lee, S. C., Cho, Y. W., & Park, K. (2005). Control of thermogelation properties of hydrophobically-modified methylcellulose. *Journal of Bioactive and Compatible Polymers, 20*(1), 5–13.
Lewandowska-Łańcucka, J., Karewicz, A., Wolski, K., & Zapotoczny, S. (2019). Surface functionalization of nanocellulose-based hydrogels. *Cellulose-Based Superabsorbent Hydrogels,* 705–733.
Li, J., & Mooney, D. J. (2016). Designing hydrogels for controlled drug delivery. *Nature Reviews Materials, 1*(12), 16071.
Li, Z., Bai, H., Zhang, S., Wang, W., Ma, P., & Dong, W. (2018). DN strategy constructed photo-crosslinked PVA/CNC/P (NIPPAm-co-AA) hydrogels with temperature-sensitive and pH-sensitive properties. *New Journal of Chemistry, 42*(16), 13453–13460.
Li, M., Liao, H., Deng, Q., Wu, Y., Xiao, F., Wei, X., et al. (2018). Preparation of an intelligent hydrogel sensor based on g-C3N4 nanosheets for selective detection of Ag +. *Journal of Macromolecular Science Part A- Pure and Applied Chemistry, 55*(5), 408–413.
Li, B., Zhang, Y., Wu, C., Guo, B., & Luo, Z. (2018). Fabrication of mechanically tough and self-recoverable nanocomposite hydrogels from polyacrylamide grafted cellulose nanocrystal and poly (acrylic acid). *Carbohydrate Polymers, 198*, 1–8.
Lim, L. S., Ahmad, I., Lazim, M. A. S. M., & Amin, M. C. I. M. (2014). Chemical cross-linking of acrylic acid to form biocompatible pH sensitive hydrogel reinforced with cellulose nanocrystals (CNC). *AIP Conference Proceedings, Vol. 1614*, 366–370.
Lim, L. S., Rosli, N. A., Ahmad, I., Mat Lazim, A., & Mohd Amin, M. C. I. (2017). Synthesis and swelling behavior of pH-sensitive semi-IPN superabsorbent hydrogels based on poly (acrylic acid) reinforced with cellulose nanocrystals. *Nanomaterials, 7*(11), 399.
Liu, Q., Zhang, M., Huang, L., Li, Y., Chen, J., Li, C., et al. (2015). High-quality graphene ribbons prepared from graphene oxide hydrogels and their application for strain sensors. *ACS Nano, 9*(12), 12320–12326.
Liu, H., Li, C., Wang, B., Sui, X., Wang, L., et al. (2018). Self-healing and injectable polysaccharide hydrogels with tunable mechanical properties. *Cellulose, 25*(1), 559–571.
Liu, M., Guo, J., Hui, C.-Y., Creton, C., Narita, T., & Zehnder, A. (2018). Time-temperature equivalence in a PVA dual cross-link self-healing hydrogel. *Journal of Rheology, 62*(4), 991–1000.
Liu, X., Yang, R., Xu, M., Ma, C., Li, W., Yin, Y., et al. (2018). Hydrothermal synthesis of cellulose nanocrystal-grafted-acrylic acid aerogels with superabsorbent properties. *Polymers, 10*(10), 1168.
Liu, Y., He, W., Zhang, Z., & Lee, B. P. (2018). Recent developments in tough hydrogels for biomedical applications. *Gels, 4*(2), 46.
Liu, Y., Sui, Y., Liu, C., Liu, C., Wu, M., Li, B., et al. (2018). A physically crosslinked polydopamine/nanocellulose hydrogel as potential versatile vehicles for drug delivery and wound healing. *Carbohydrate Polymers, 188*, 27–36.
Lou, J., Stowers, R., Nam, S., Xia, Y., & Chaudhuri, O. (2018). Stress relaxing hyaluronic acid-collagen hydrogels promote cell spreading, fiber remodeling, and focal adhesion formation in 3D cell culture. *Biomaterials, 154*, 213–222.
Luo, Y., Li, Y., Qin, X., & Wa, Q. (2018). 3D printing of concentrated alginate/gelatin scaffolds with homogeneous nano apatite coating for bone tissue engineering. *Materials & Design, 146*, 12–19.
Martino, M. M., Tortelli, F., Mochizuki, M., Traub, S., Ben-David, D., Kuhn, G. A., et al. (2011). Engineering the growth factor microenvironment with fibronectin domains to promote wound and bone tissue healing. *Science Translational Medicine, 3*(100) 100ra189–100ra189.
McKee, J. R., Hietala, S., Seitsonen, J., Laine, J., Kontturi, E., & Ikkala, O. (2014). Thermoresponsive nanocellulose hydrogels with tunable mechanical properties. *ACS Macro Letters, 3*(3), 266–270.
Mohamed, M. A., Salleh, W., Jaafar, J., Ismail, A., Mutalib, M. A., Mohamad, A. B., et al. (2017). Physicochemical characterization of cellulose nanocrystal and nanoporous self-assembled CNC membrane derived from Ceiba pentandra. *Carbohydrate Polymers, 157*, 1892–1902.
Mohammed, N., Grishkewich, N., Waeijen, H. A., Berry, R. M., & Tam, K. C. (2016). Continuous flow adsorption of methylene blue by cellulose nanocrystal-alginate hydrogel beads in fixed bed columns. *Carbohydrate Polymers, 136*, 1194–1202.
Mondal, M. I. H., & Haque, M. O. (2019). Cellulosic hydrogels: A greener solution of sustainability. *Cellulose-Based Superabsorbent Hydrogels,* 3–35.
Moud, A. A., Arjmand, M., Yan, N., Nezhad, A. S., & Hejazi, S. H. (2018). Colloidal behavior of cellulose nanocrystals in presence of sodium chloride. *ChemistrySelect, 3*(17), 4969–4978.
Nair, S. K., Basu, S., Sen, B., Lin, M.-H., Kumar, A. N., Yuan, Y., et al. (2019). Colloidal gels with tunable mechanomorphology regulate endothelial morphogenesis. *Scientific Reports, 9*(1), 1072.
Nam, J., Jung, I.-B., Kim, B., Lee, S.-M., Kim, S.-E., Lee, K.-N., et al. (2018). A colorimetric hydrogel biosensor for rapid detection of nitrite ions. *Sensors and Actuators B, Chemical, 270*, 112–118.
Nigmatullin, R., Harniman, R. L., Gabrielli, V., Muñoz-Garcia, J. C., Khimyak, Y. Z., Angulo, J., et al. (2018). Mechanically robust gels formed from hydrophobized cellulose nanocrystals. *ACS Applied Materials & Interfaces, 10*(23), 19318–19322.
Niu, J., Wang, J., Dai, X., Shao, Z., & Huang, X. (2018). Dual physically crosslinked healable polyacrylamide/cellulose nanofibers nanocomposite hydrogels with excellent mechanical properties. *Carbohydrate Polymers, 193*, 73–81.
Olad, A., Zebhi, H., Salari, D., Mirmohseni, A., & Tabar, A. R. (2018). Water retention and slow release studies of a salep-based hydrogel nanocomposite reinforced with montmorillonite clay. *New Journal of Chemistry, 42*(4), 2758–2766.
O'Shea, T. M., Aimetti, A. A., Kim, E., Yesilyurt, V., & Langer, R. (2015). Synthesis and characterization of a library of in-situ curing, nonswelling ethoxylated polyol thiol-ene hydrogels for tailorable macromolecule delivery. *Advanced Materials, 27*(1), 65–72.
Ooi, S. Y., Ahmad, I., & Amin, M. C. (2016). Cellulose nanocrystals extracted from rice husks as a reinforcing material in gelatin hydrogels for use in controlled drug delivery systems. *Industrial Crops and Products, 93*, 227–234.
Orasugh, J. T., Sarkar, G., Saha, N. R., Das, B., Bhattacharyya, A., Das, S., et al. (2019). Effect of cellulose nanocrystals on the performance of drug loaded in situ gelling thermo-responsive ophthalmic formulations. *International Journal of Biological Macromolecules, 124*, 235–245.
Otto, W., & Drahoslav, L. (1960). Hydrophilic gels in biologic use. *Nature, 185*, 117–118.
Pakdel, P. M., & Peighambardoust, S. J. (2018). A review on acrylic based hydrogels and their applications in wastewater treatment. *Journal of Environmental Management, 217*, 123–143.
Parker, R. M., Guidetti, G., Williams, C. A., Zhao, T., Narkevicius, A., Vignolini, S., et al. (2018). The self-assembly of cellulose nanocrystals: Hierarchical design of visual appearance. *Advanced Materials, 30*(19), 1704477.
Prince, E., Alizadehgiashi, M., Campbell, M., Khuu, N., Albulescu, A., De France, K., et al. (2018). Patterning of structurally anisotropic composite hydrogel sheets. *Biomacromolecules, 19*(4), 1276–1284.
Ren, J., Dai, Q., Zhong, H., Liu, X., Meng, L., Wang, X., et al. (2018). Quaternized xylan/cellulose nanocrystal reinforced magnetic hydrogels with high strength. *Cellulose, 25*(8), 4537–4549.
Roshanghias, S., & Madadlou, A. (2018). Functional and gel properties of whey protein nanofibrils as influenced by partial substitution with cellulose nanocrystal and alginate. *International Dairy Journal, 81*, 53–61.
Sahabi, H., & Kind, M. (2011). Consolidation of inorganic precipitated silica gel. *Polymers, 3*(3), 1423–1432.
Sahlin, K., Forsgren, L., Moberg, T., Bernin, D., Rigdahl, M., & Westman, G. (2018). Surface treatment of cellulose nanocrystals (CNC): Effects on dispersion rheology. *Cellulose, 25*(1), 331–345.
Sanna, R., Fortunati, E., Alzari, V., Nuvoli, D., Terenzi, A., Casula, M. F., et al. (2013). Poly (N-vinylcaprolactam) nanocomposites containing nanocrystalline cellulose: A green approach to thermoresponsive hydrogels. *Cellulose, 20*(5), 2393–2402.
Sannino, A., Demitri, C., & Madaghiele, M. (2009). Biodegradable cellulose-based hydrogels: Design and applications. *Materials, 2*(2), 353–373.
Sayyar, S., Murray, E., Thompson, B., Chung, J., Officer, D. L., Gambhir, S., et al. (2015). Processable conducting graphene/chitosan hydrogels for tissue engineering. *Journal of Materials Chemistry B, 3*(3), 481–490.
Shao, C., Wang, M., Chang, H., Xu, F., & Yang, J. (2017). A self-healing cellulose nanocrystal-poly (ethylene glycol) nanocomposite hydrogel via Diels–Alder click reaction. *ACS Sustainable Chemistry & Engineering, 5*(7), 6167–6174.
Shao, C., Wang, M., Meng, L., Chang, H., Wang, B., Xu, F., et al. (2018). Mussel-inspired cellulose nanocomposite tough hydrogels with synergistic self-healing, adhesive, and strain-sensitive properties. *Chemistry of Materials, 30*(9), 3110–3121.
Shi, C., Tao, F., & Cui, Y. (2018). Evaluation of nitriloacetic acid modified cellulose film on adsorption of methylene blue. *International Journal of Biological Macromolecules,*

114, 400–407.
Shi, X., Hu, Y., Tu, K., Zhang, L., Wang, H., Xu, J., et al. (2013). Electromechanical polyaniline–cellulose hydrogels with high compressive strength. *Soft Matter, 9*(42), 10129–10134.
Shoujing, Z., & Zishun, L. (2018). Phase transition of temperature-sensitive hydrogel under mechanical constraint. *Journal of Applied Mechanics, 85*(2), 021002.
Silva, C. R., Babo, P. S., Gulino, M., Costa, L., Oliveira, J. M., Silva-Correia, J., et al. (2018). Injectable and tunable hyaluronic acid hydrogels releasing chemotactic and angiogenic growth factors for endodontic regeneration. *Acta Biomaterialia*.
Singh, T., & Singhal, R. (2018). *Efficient and economical application of a spent waste adsorbent Cu2+-loaded poly (AAc-AM-SH) superabsorbent hydrogels by reusing It for adsorption of phosphate ion. Water quality management*. Springer257–267.
Singh, Y. P., Bhardwaj, N., & Mandal, B. B. (2018). Injectable hydrogels: A new paradigm for osteochondral tissue engineering. *Journal of Materials Chemistry B, 6*(35), 5499–5529.
Singla, R., Soni, S., Patial, V., Kulurkar, P. M., Kumari, A., Mahesh, S., et al. (2017). In vivo diabetic wound healing potential of nanobiocomposites containing bamboo cellulose nanocrystals impregnated with silver nanoparticles. *International Journal of Biological Macromolecules, 105*, 45–55.
Siqueira, P., Siqueira, É, de Lima, A. E., Siqueira, G., Pinzón-Garcia, A. D., Lopes, A. P., et al. (2019). Three-dimensional stable alginate-nanocellulose gels for biomedical applications: Towards tunable mechanical properties and cell growing. *Nanomaterials, 9*(1), 78.
Soleimani, K., Tehrani, A. D., & Adeli, M. (2018). Bioconjugated graphene oxide hydrogel as an effective adsorbent for cationic dyes removal. *Ecotoxicology and Environmental Safety, 147*, 34–42.
Su, E., & Okay, O. (2018). Hybrid cross-linked poly (2-acrylamido-2-methyl-1-propanesulfonic acid) hydrogels with tunable viscoelastic, mechanical and self-healing properties. *Reactive & Functional Polymers, 123*, 70–79.
Supramaniam, J., Adnan, R., Kaus, N. H. M., & Bushra, R. (2018). Magnetic nanocellulose alginate hydrogel beads as potential drug delivery system. *International Journal of Biological Macromolecules*.
Tavakoli, J., & Tang, Y. (2017). Hydrogel based sensors for biomedical applications: An updated review. *Polymers, 9*(8), 364.
Teng, L., Chen, Y., Jin, M., Jia, Y., Wang, Y., & Ren, L. (2018). Weak hydrogen bonds lead to self-healable and bioadhesive hybrid polymeric hydrogels with mineralization-active functions. *Biomacromolecules, 19*(6), 1939–1949.
Thakur, V. K., & Thakur, M. K. (2015). Recent advances in green hydrogels from lignin: A review. *International Journal of Biological Macromolecules, 72*, 834–847.
Thomas, D., Latha, M., & Thomas, K. K. (2018). Synthesis and in vitro evaluation of alginate-cellulose nanocrystal hybrid nanoparticles for the controlled oral delivery of rifampicin. *Journal of Drug Delivery Science and Technology, 46*, 392–399.
Tummala, G. K., Bachi, I., & Mihranyan, A. (2019). Role of solvent on structure, viscoelasticity, and mechanical compressibility in nanocellulose-reinforced poly (vinyl alcohol) hydrogels. *Journal of Applied Polymer Science, 136*(6), 47044.
Tummala, G. K., Joffre, T., Lopes, V. R., Liszka, A., Buznyk, O., Ferraz, N., et al. (2016). Hyperelastic nanocellulose-reinforced hydrogel of high water content for ophthalmic applications. *ACS Biomaterials Science & Engineering, 2*(11), 2072–2079.
Ullah, F., Othman, M. B. H., Javed, F., Ahmad, Z., & Akil, H. M. (2015). Classification, processing and application of hydrogels: A review. *Materials Science and Engineering C, 57*, 414–433.
Van Tran, V., Park, D., & Lee, Y.-C. (2018). Hydrogel applications for adsorption of contaminants in water and wastewater treatment. *Environmental Science and Pollution Research - International,* 1–31.
Wan Ishak, W., Ahmad, I., Ramli, S., & Mohd Amin, M. (2018). Gamma irradiation-assisted synthesis of cellulose nanocrystal-reinforced gelatin hydrogels. *Nanomaterials, 8*(10), 749.
Wang, W., Zhang, X., Teng, A., & Liu, A. (2017). Mechanical reinforcement of gelatin hydrogel with nanofiber cellulose as a function of percolation concentration. *International Journal of Biological Macromolecules, 103*, 226–233.
Wang, Y., Du, B., Wang, J., Wang, Y., Gu, H., & Zhang, X. (2018). Synthesis and characterization of a high capacity ionic modified hydrogel adsorbent and its application in the removal of Cr (VI) from aqueous solution. *Journal of Environmental Chemical Engineering, 6*(6), 6881–6890.
Wang, D.-C., Yu, H.-Y., Fan, X., Gu, J., Ye, S., Yao, J., et al. (2018). High aspect ratio carboxylated cellulose nanofibers crosslinked to robust aerogels for super-absorption − flocculants: Paving way from nano − scale to macro − scale. *ACS Applied Materials & Interfaces, 10*(24), 20755–20766.
Way, A. E., Hsu, L., Shanmuganathan, K., Weder, C., & Rowan, S. J. (2012). pH-responsive cellulose nanocrystal gels and nanocomposites. *ACS Macro Letters, 1*(8), 1001–1006.
Wirthl, D., Pichler, R., Drack, M., Kettlguber, G., Moser, R., Gerstmayr, R., et al. (2017). Instant tough bonding of hydrogels for soft machines and electronics. *Science Advances, 3*(6), e1700053.
Wu, X. (2016). *Conductive cellulose nanocrystals for electrochemical applications*.
Xu, Q., Ji, Y., Sun, Q., Fu, Y., Xu, Y., & Jin, L. (2019). Fabrication of cellulose nanocrystal/chitosan hydrogel for controlled drug release. *Nanomaterials, 9*(2), 253.
Yan, H., Huang, D., Chen, X., Liu, H., Feng, Y., Zhao, Z., et al. (2018). A novel and homogeneous scaffold material: Preparation and evaluation of alginate/bacterial cellulose nanocrystals/collagen composite hydrogel for tissue engineering. *Polymer Bulletin, 75*(3), 985–1000.
Yang, X., Lu, Z., Wu, H., Li, W., Zheng, L., & Zhao, J. (2018). Collagen-alginate as bioink for three-dimensional (3D) cell printing based cartilage tissue engineering. *Materials Science and Engineering C, 83*, 195–201.
Yang, Z., Fu, K., Yu, J., Zhou, P., & Cheng, Z. (2018). Preparation and characterization of temperature-and pH-responsive diblock copolymers and their silica-coated nanoparticles. *Polymers for Advanced Technologies, 29*(8), 2273–2280.
Yi, X., Sun, F., Han, Z., Han, F., He, J., Ou, M., et al. (2018). Graphene oxide encapsulated polyvinyl alcohol/sodium alginate hydrogel microspheres for Cu (II) and U (VI) removal. *Ecotoxicology and Environmental Safety, 158*, 309–318.
Yin, F., Lin, L., & Zhan, S. (2019). Preparation and properties of cellulose nanocrystals, gelatin, hyaluronic acid composite hydrogel as wound dressing. *Journal of Biomaterials Science Polymer Edition,* 1–12.
Yousefi, N., Wong, K. K., Hosseinidoust, Z., Sørensen, H. O., Bruns, S., Zheng, Y., et al. (2018). Hierarchically porous, ultra-strong reduced graphene oxide-cellulose nanocrystal sponges for exceptional adsorption of water contaminants. *Nanoscale, 10*(15), 7171–7184.
Yu, H.-S., Lee, E.-J., Seo, S.-J., Knowles, J. C., & Kim, H.-W. (2015). Feasibility of silica-hybridized collagen hydrogels as three-dimensional cell matrices for hard tissue engineering. *Journal of Biomaterials Applications, 30*(3), 338–350.
Yu, H.-Y., Zhang, D.-Z., Lu, F.-F., & Yao, J. (2016). New approach for single-step extraction of carboxylated cellulose nanocrystals for their use as adsorbents and flocculants. *ACS Sustainable Chemistry & Engineering, 4*(5), 2632–2643.
Yu, Z., Deschamps, J., Hamon, L., Prabhakaran, P. K., & Pré, P. (2017). Hydrogen adsorption and kinetics in MIL-101 (Cr) and hybrid activated carbon-MIL-101 (Cr) materials. *International Journal of Hydrogen Energy, 42*(12), 8021–8031.
Yu, Z., Liu, J., Tan, C. S. Y., Scherman, O. A., & Abell, C. (2018). Supramolecular nested microbeads as building blocks for macroscopic self-healing scaffolds. *Angewandte Chemie International Edition, 57*(12), 3079–3083.
Yue, Y., Wang, X., Han, J., Yu, L., Chen, J., Wu, Q., et al. (2019). Effects of nanocellulose on sodium alginate/polyacrylamide hydrogel: Mechanical properties and adsorption-desorption capacities. *Carbohydrate Polymers, 206*, 289–301.
Zhao, S., Wang, Z., Kang, H., Zhang, W., Li, J., Zhang, S., et al. (2019). Construction of bioinspired organic-inorganic hybrid composite by cellulose-induced interfacial gelation assisted with Pickering emulsion template. *Chemical Engineering Journal, 359*, 275–284.
Zhao, Z., Fang, R., Rong, Q., & Liu, M. (2017). Bioinspired nanocomposite hydrogels with highly ordered structures. *Advanced Materials, 29*(45), 1703045.
Zheng, X., Wang, Y., Qiu, F., Li, Z., & Yan, Y. (2019). Dual-functional mesoporous films templated by cellulose nanocrystals for the selective adsorption of Lithium and rubidium. *Journal of Chemical and Engineering Data, 64*(3), 926–933.
Zia, K. M., Tabasum, S., Khan, M. F., Akram, N., Akhter, N., Noreen, A., et al. (2017). Recent trends on Gellan Gum blends with natural and synthetic polymers: A review. *International Journal of Biological Macromolecules, 109*, 1068–1087.
Zubik, K., Singhsa, P., Wang, Y., Manuspiya, H., & Narain, R. (2017). Thermo-responsive poly (N-isopropylacrylamide)-cellulose nanocrystals hybrid hydrogels for wound dressing. *Polymers, 9*(4), 119.