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REVIEW

Recent advances of nanocellulose in drug delivery systems

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Abstract

Background Nanocellulose, which possesses great physical, chemical, and biological properties, is a natural polymer derived from widely available native cellulose. It has outstanding properties such as high mechanical strength, stiffness, low weight, biocompatibility, and renewability, which are beneficial for the design of advanced drug delivery systems, as either an excipient or a carrier.

Area covered This review introduces three types of nanocellulose: cellulose nanocrystals, cellulose nanofibers, and bacterial cellulose. Their physical and chemical properties along with their methods of preparation are also compared. Recent studies of nanocellulose for various drug delivery applications are summarized and discussed. Selected nanocellulose studies with significant findings for oral, ocular, intratumoral, topical, and transdermal delivery are also emphasized.

Expert opinion Nanocellulose has potential for drug delivery applications due to its high surface area-to-volume ratio and high polymerization, which provide nanocellulose with a high loading and binding capacity for active pharmaceutical ingredients, enabling the control of the drug release.

Keywords Nanocellulose · Cellulose nanocrystals · Cellulose nanofibers · Bacterial cellulose · Drug delivery system

Introduction

Drug delivery systems are defined as advanced technologies for the targeted/specific delivery and/or controlled release of therapeutic agents. For over a decade, the field of drug delivery systems has been growing, with new inventions every second. However, a major concern lies in the selection of appropriate, natural, nontoxic, and inexpensive materials/polymers, while maintaining bioactivity and minimizing undesirable side effects. Natural polymers, such as cellulose, starch, and glycogen, have been widely employed to circumvent this concern (Wang et al. 2013).

Nanocellulose is a renewable, biodegradable, and nanoscaled natural material extracted from a broad diversity of organisms (plants, animals, and bacteria), and it has appealing properties for applications in the field of drug delivery systems (Babu et al. 2013). Nanocellulose is useful in drug delivery systems due to its high surface area-to-volume ratio and high polymerization, which enable it to have a high loading and binding capacity for therapeutic agents to control the drug release mechanism. Its outstanding properties, such as high mechanical strength, stiffness, low weight, biocompatibility, and renewability, are beneficial for the design of advanced drug delivery systems, using it as either an excipient or a carrier. Nanocellulose can be categorized into three groups: (1) cellulose nanocrystals (CNC), (2) cellulose nanofibers (CNF), and (3) bacterial cellulose (BC). All types of nanocellulose have immense potential for drug delivery systems (Plackett et al. 2014).

Over the past few years, there have been many studies on the development of nanocellulose-based products with a broad variety of nanocellulose modifications, including single systems and hybrid or nanocomposite systems. This

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review will focus on the preparation of different types of nanocellulose and their applications for oral, ocular, intratumoral, topical, and transdermal routes. Some routes of administration such as parenteral, vaginal/anal, and nasal delivery will not be covered. This review deals mainly with recent trends in the field of nanocellulose materials for drug delivery systems to observe the direction of nanocellulose development and its potential use for various diseases.

Types of nanocellulose

Cellulose nanocrystals (CNC)

Nanocrystalline cellulose, cellulose nano whiskers (CNW), and rod-like cellulose microcrystals are other names for CNC. There are several sources of native cellulose (found in plants and animals) from which CNC are derived. Cellulose can be extracted from wood, hemp, cotton, flax, wheat straw, mulberry bark, ramie, avicel, potato tuber, sugar beet, tunicin, and algae (Klemm et al. 2011; Dufresne 2017). The production of CNC is a top-down process, in which the large unit (cm) is broken down to a small unit (nm). The process involves separating the amorphous part of native cellulose and preserving the crystalline part. Figure 1a shows the chemical structure of CNC. The crystalline regions of CNC are formed through intramolecular and intermolecular hydrogen bonds of cellulose macromolecules (Fig. 1b). CNC have a high-crystalline ratio of 54–88%. They have spindle, elongated rod-like, or needle-like shapes with a rigid cellulosic crystalline structure. Their size varies depending on the type of native cellulose; in the case of plant cellulose, they have diameters of 5–30 nm; and lengths of 100–500 nm. Meanwhile, the CNC extracted from tunicate and algal cellulose have lengths from 100 nm to several micrometers (Moon et al. 2011; Lin et al. 2012). CNC are attractive options due to their unique properties, such as having a high aspect ratio, large surface area, high modulus of elasticity, high mechanical strength, uniform nanorod shape, lower breaking expansion, liquid crystalline character, biocompatibility, and hydrophilicity (Peng et al. 2011; Zhou et al. 2011; Habibi 2014).

Preparation of CNC

The preparation of CNC involves several processes, including enzymatic/acid hydrolysis, and mechanical treatment or oxidation, which are designed to separate the amorphous chains from cellulose fibers and collect the crystalline component. The preparation steps are summarized in Fig. 2. Before the preparation of CNC, cellulose needs to be isolated from the source. Accordingly, the process involves several steps: (1) drying/grinding/dewaxing, (2) purification, (3) delignification (mechanical, chemical, biological, or combined), (4) bleaching, and (5) filtration/washing/drying (Trache et al. 2017). Du et al. isolated cellulose from fresh Douglas-fir wood chips, starting with milled wood and following several steps. The wood chips were hammer-milled to wood flour with a particle size of 235 µm and then subjected to a second milling with a gear-drive planetary ball mill to form ball-milled wood. Then, the ball-milled wood was hydrolyzed with Cellic HTec2 enzyme to obtain the

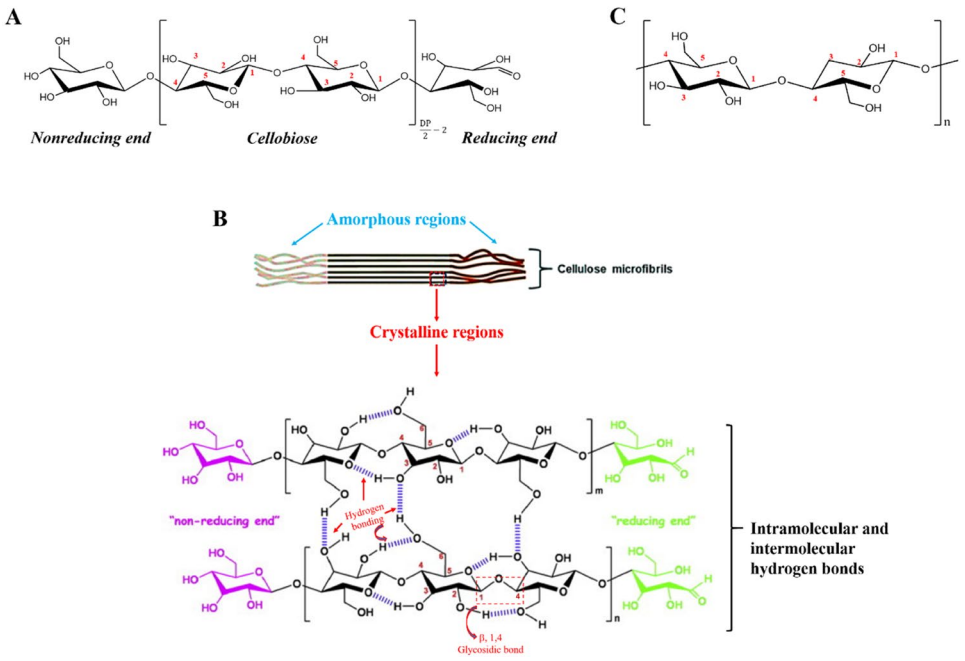


Fig. 1 **a** Chemical structures of CNC and CNF. **b** Intramolecular and intermolecular hydrogen bonds in crystalline cellulose [reproduced with modification from (Lin and Dufresne 2014)]. **c** Chemical structure of BC

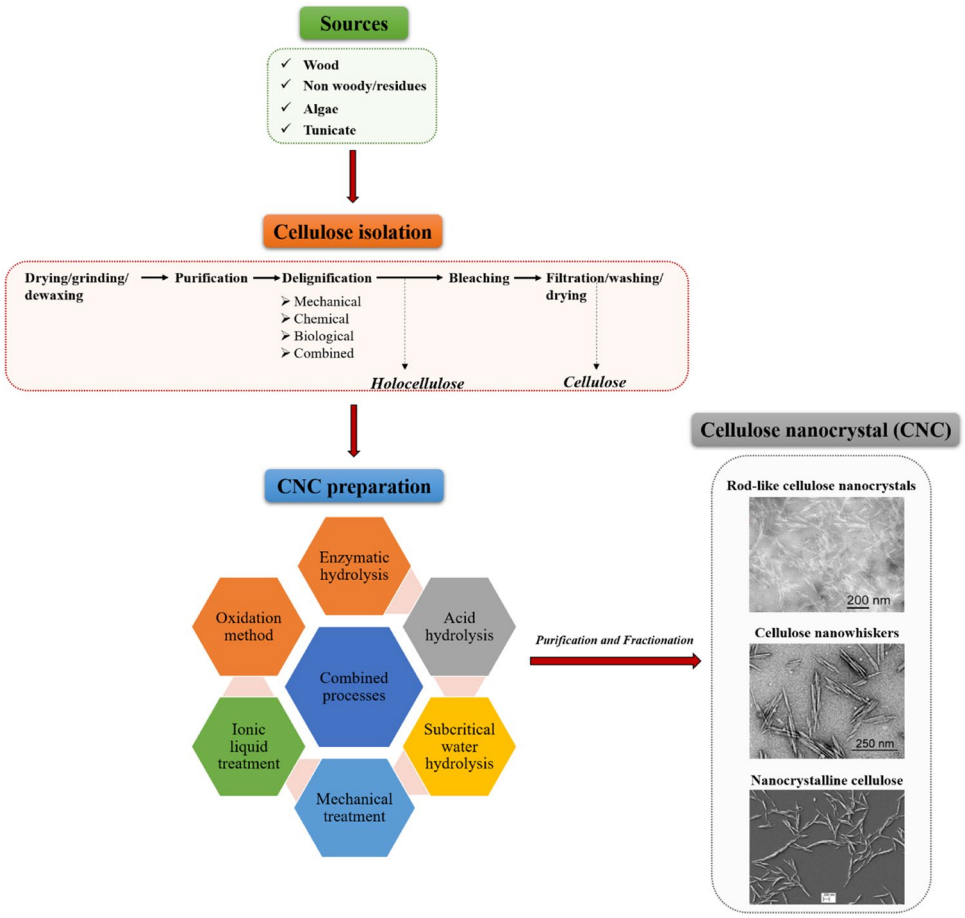


Fig. 2 Schematic representation of CNC preparation. Transmission electron microscopy (TEM) images of rod-like cellulose nanocrystals [reprinted with permission from (Li et al. 2018)]. Scanning electron microscopy (SEM) images of cellulose nanowhiskers [reprinted with permission from (Heath and Thielemans 2010)]. SEM images of nanocrystalline cellulose [reprinted with permission from (Anžlovar et al. 2018)]

solid sample (hydrolysis residue). The hydrolysis residue was mixed with cooking liquor in a neutral sulfite cooking process to yield neutral sulfite cooking residues and lignosulfonate. The next step involved treatment with sodium chlorite and acetic acid at 70 °C to form holocellulose by delignification. Cellulose was obtained after bleaching, in which the holocellulose was added to sodium hydroxide at 90 °C, filtered, washed, and dried. Repeating the delignification and bleaching process several times was recommended to improve the cellulose purity (Du et al. 2017).

To prepare CNC from cellulose, there are several methods that can be used. Enzymatic hydrolysis, in which celluloses (e.g., endoglucanases, exoglucanases, cellobiohydrolases) are used, is a common method (Zhou and Ingram 2000; Filson et al. 2009; Chen et al. 2018). Although harsh, acid hydrolysis can also be used to obtain CNC with concentrated acids, such as sulfuric, hydrochloric, nitric, phosphoric, hydrobromic, phosphotungstic, p-toluenesulfonic, maleic, formic, and oxalic acids (Araki et al. 1998; Wang et al. 2007; Camarero Espinosa et al. 2013; Huang et al. 2013; Yu et al. 2013; Chen et al. 2015, 2016; Li et al. 2015; Tang et al. 2015; Du et al. 2016; Cheng et al. 2017a, b; Niu et al. 2017; Sucaldito and Camacho 2017; Torlopov et al. 2017). Another method uses subcritical water hydrolysis (120 °C and 20.3 mPa for 60 min) in a stainless steel reactor (Novo et al. 2015, 2016). Ionic liquid treatment uses 1-butyl-3-methylimidazolium hydrogen sulfate ($bmimHSO_4$) to dissolve cellulose and form CNC (Mao et al. 2013; Abushammala et al. 2015; Mao et al. 2015; Tan et al. 2015; Miao et al. 2016; Iskak et al. 2017). An oxidation method is also used, in which sodium periodate-sodium chlorite, ammonium persulfate, or 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) are used as strong oxidants (Ifuku et al. 2009; Okita et al. 2010; Yang et al. 2013; Peyre et al. 2015; Mascheroni et al. 2016). Finally, mechanical treatments, such as homogenization, micro fluidization, ultrasonication, microwaving, conventional heating, and wet disk milling, are among common methods used to obtain CNC (Moon et al. 2011; Li et al. 2012; Amin et al. 2015). Some studies using a combined process, such as: mechanical treatment-assisted acid hydrolysis, enzymatic hydrolysis or TEMPO oxidation; acid hydrolysis-assisted enzymatic hydrolysis; and ultrasonication and microwave-assisted physicochemical treatments, were also reported (Trache et al. 2017).

Cellulose nanofibers (CNF)

Nano fibrillated cellulose, micro fibrillated cellulose, and cellulose nanofibrils are other names used for CNF. The source of CNF is similar to that of CNC; thus, the precursor cellulose can be extracted from wood, sugar beet, potato tuber, hemp, flax, cotton, rice straw, hyacinth weeds, algae, tunicate, banana peel, and bacteria cellulose. The molecular structure of CNF is also similar to that of CNC (Fig. 1a). The major difference between CNC and CNF lies in their morphology and crystallinity. CNF have smooth and long chains; due to the entanglement of the cellulose chains of CNF, their lengths are quite difficult to determine. However, they are generally regarded as being more than 1 µm long, as determined using a microscope technique. The diameters of CNF are approximately 3–100 nm depending on the defibrillation process and pretreatment. While CNC are only crystalline, the CNF structure is composed of both amorphous and crystalline regions. Due to their amorphous nature, CNF are more flexible than CNC. CNF possess excellent properties such as hydrophilicity, biocompatibility, and a large surface area (Klemm et al. 2011; Dufresne 2013; Xue et al. 2017).

Preparation of CNF

The preparation of CNF from raw materials requires a strong mechanical process with or without pretreatment and/or post-treatment (Fig. 3). However, mostly depending on the properties of the raw materials and the degree of processing, a chemical pretreatment is needed before the mechanical treatment (Chauhan and Chakrabarti 2012). There are several pretreatments that are commonly used, such as solvent-assisted pretreatment (Carrillo et al. 2014; Lee et al. 2018), organic acid hydrolysis (Bian et al. 2017a, b), enzymatic fractionation (Siqueira et al. 2010; Chen et al. 2017), TEMPO oxidation (Saito et al. 2006; Tarrés et al. 2016), periodate-chlorite oxidation (Liimatainen et al. 2012), oxidative sulfonation (Liimatainen et al. 2013; Sirviö et al. 2014), cationization (Abbott et al. 2006; Song et al. 2008), carboxymethylation (Eyholzer et al. 2011; Siró et al. 2011), ionic liquids (Ninomiya et al. 2018), and deep eutectic solvents (Li et al. 2017; Liu et al. 2017a, b, c). The selection of appropriate cellulose fibers pretreatment may affect the inner surface properties, change the crystallinity, and even disrupt the hydrogen bonds of the cellulose biomacromolecules (Antczak 2012). Mechanical treatments to prepare CNF include high-pressure homogenization (Dufresne et al. 2000; Nakagaito and Yano 2004; Wang and Sain 2007; Wang et al. 2007; Hassan et al. 2011), ultrafine friction grinding (Spence et al. 2011; Wang et al. 2012; Nechyporchuk et al. 2015), ball milling (Zhang et al. 2015), twin-screw extrusion (Hietala et al. 2014; Ho et al. 2015), cryocrushing (Dufresne et al. 1997; Bhatnagar and Sain 2005; Alemdar and Sain 2008), blending (Uetani and Yano 2011; Jiang and Hsieh 2013; Nakagaito et al. 2015), steam explosion (Deepa et al. 2011; Liu et al. 2017a, b, c; Yang et al. 2018), and aqueous counter collision (Kose et al. 2011; Kondo et al. 2014; Zhai et al. 2018) methods.

Bacterial cellulose (BC)

Microbial cellulose, bacterial nanocellulose, and bio-cellulose are other designations for BC. Unlike CNC and CNF,

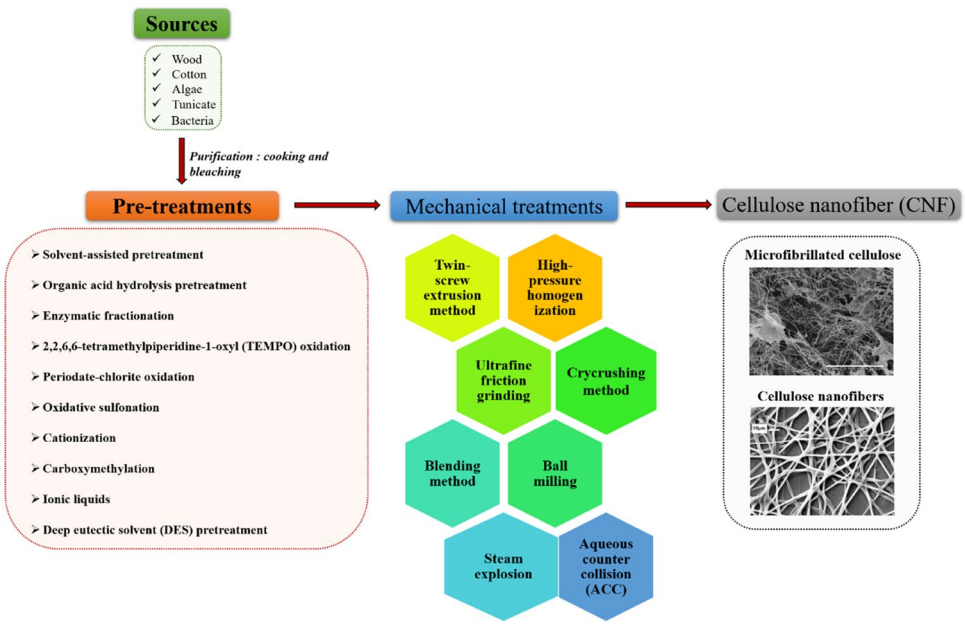


Fig. 3 Schematic representation of CNF preparation. SEM images of microfibrillated cellulose (reprinted with permission from [Henriksson et al. 2007)]. SEM images of cellulose nanofibers [reprinted with permission from (Kim et al. 2006)]

BC is produced by bacteria from low molecular weight sugar to build up the nanofiber (top-up process). Therefore, the cellulose produced is pure without impurities and contaminants, such as lignin, pectin, and hemicellulose, which are commonly found in CNC and CNF products. Various bacteria can be used to produce BC, from gram-positive bacteria, such as *Sarcina ventriculi*, to gram-negative bacteria, such as *Acetobacter xylinum*, *Acetobacter* sp. V6, *Acetobacter* sp. A9, *A. xylinum* ssp., *Gluconacetobacter hansenii*, *A. xylinum* E25, *Gluconacetobacter xylinus* K3, *G. xylinus* IFO 13773, *A. xylinum* NUST4.1, *Gluconacetobacter* sp. St-60-12 and *Lactobacillus mali* JCM1116 (co-culture), and *G. xylinus* sp. RKY (Lin et al. 2013). Bacteria that produce BC are incubated in aqueous nutrient media, and the BC is formed as an exopolysaccharide on the upper layer (interface with air). The resultant BC mainly consists of water (> 99%) and a nanofiber network with a fiber diameter of 20–100 nm (Klemm et al. 2011). Figure 1c shows the chemical structure of BC. The properties of this cellulose can be controlled, for example, by manipulating the substrate and culture conditions, and by selecting the appropriate bacterial strain (Islam et al. 2014). The properties of BC include high porosity, moldability, foldability, hemocompatibility, average molecular weight (Mw), mechanical stability, and crystallinity (Gorgieva and Trček 2019). The types and characteristics of nanocellulose are summarized in Table 1.

Preparation of BC

The preparation of BC is summarized in Fig. 4. Before the production of BC, several factors need to be considered, such as the selection of strains with high capacity for BC production and optimization of growth conditions (e.g., growth factors, temperature, pH, and suitable medium). The production of BC can be performed under static conditions in vessels with large surface areas, supplied with oxygen, and with or without agitation. BC can also be produced by using different types and scales of bioreactors with aeration (Gorgieva and Trček 2019). The most common methods for BC production can be subdivided into several production types: static, shaking culture, airlift bioreactor, rotating disc bioreactor, and trickle bed reactor. Each method has a different process and generates BC with different characteristics. Static production is mostly used for lab-scale BC biosynthesis for up to 2 weeks, producing hydrogel sheets (Rani et al. 2011). Shaking culture is suitable for large-scale manufacturing. It involves increasing the supply of oxygen to the bacteria. The process may result in the genetic instability of the bacteria and reduced BC yields. The produced BC has various shapes (mostly spherical) of different particle sizes (Watanabe et al. 1998; Wang et al. 2019). Production in an airlift bioreactor involves efficient supply of oxygen with low power consumption. The produced BC is in the form of pellets (Chao et al. 1997; Wang et al. 2019). A rotating disc bioreactor produces homogenous BC in yields that are comparable to those with static production (Serafica et al. 2002). Finally, production in a trickle bed reactor provides high oxygen concentrations and low shear forces that result in irregular sheets of BC (Lu and Jiang 2014).

Use of nanocellulose in drug delivery systems

Nanocellulose and its derivatives are commonly used in drug delivery systems as drug excipients (e.g., thickeners, emulsifiers, binding agents, film formers, stabilizers, surfactants, suspending agents, and lubricants) and as drug delivery matrices (carrier system), in which a drug (including insoluble drugs) can be loaded (Fakes et al. 2009; Onofrei and Filimon 2016). Sustained drug release is one of the main benefits of nanocellulose-based drug delivery systems. Nanocellulose can modify the drug release via several mechanisms, including water retention, film formation, adhesion enhancement, and rheology control (Kamel et al. 2008). A summary of recent advances in nanocellulose for drug delivery systems is shown in Fig. 5.

Oral delivery

Oral delivery has several advantages, namely, convenience, low cost, ease of use, safety, and noninvasiveness. This makes oral delivery a desirable route of administration, particularly for chronic diseases, which require frequent drug administration. However, there are several challenges that limit the effective delivery of drug dosage forms, such as enzymatic degradation, hydrolysis, and low permeability of the intestinal epithelium in the gastrointestinal (GI) tract (Liu et al. 2017a, b, c). Therefore, there is an urgent need for new strategies to overcome such limitations of oral delivery and to improve the bioavailability of orally delivered drugs. In this regard, nanocellulose, with its unique properties, can be utilized in innovative drug delivery systems as either an excipient or a carrier.

Nanocellulose possesses great compaction properties and can be mixed with other pharmaceutical excipients in a hybrid system, making it an ideal material or carrier for an oral drug delivery system (Jackson et al. 2011). Thomas et al. successfully synthesized alginate-CNC hybrid (ALG-CNC) nanoparticles (NPs) for the controlled oral delivery of rifampicin (RIF). Their study aimed to design an oral formulation using a nanoparticulate system that was able to protect the drug from gastric conditions and control drug release. For this purpose, several NP formulations and process variables, such as the ALG-CNC ratio, RIF-ALG ratio, and surfactant concentrations were tested. The results revealed that

Table 1 Types and characteristics of nanocellulose

Type	Size		Shape	Nanocellulose structure	Production process	Impurity	Properties
	Length	Diameter					
CNC	100–500 nm (plant cellulose) 100 nm to several micrometers (tunicate and algae cellulose)	5–30 nm	Spindle shape, elongated rod-like, or needle-like shape	Crystalline	Top-down	May contain hemicellulose, lignin, and pectin	The high aspect ratio, the large surface area, high modulus of elasticity, high mechanical strength, its uniform nanorod shape, lower breaking expansion, liquid crystalline character, biocompatibility, and hydrophilicity
CNF	More than 1 μm	3–100 nm	Smooth and long chains	Amorphous and crystalline	Top-down	May contain hemicellulose, lignin, and pectin	Flexible, excellent hydrophilicity, biocompatibility, and a high surface area

Table 1 (continued)

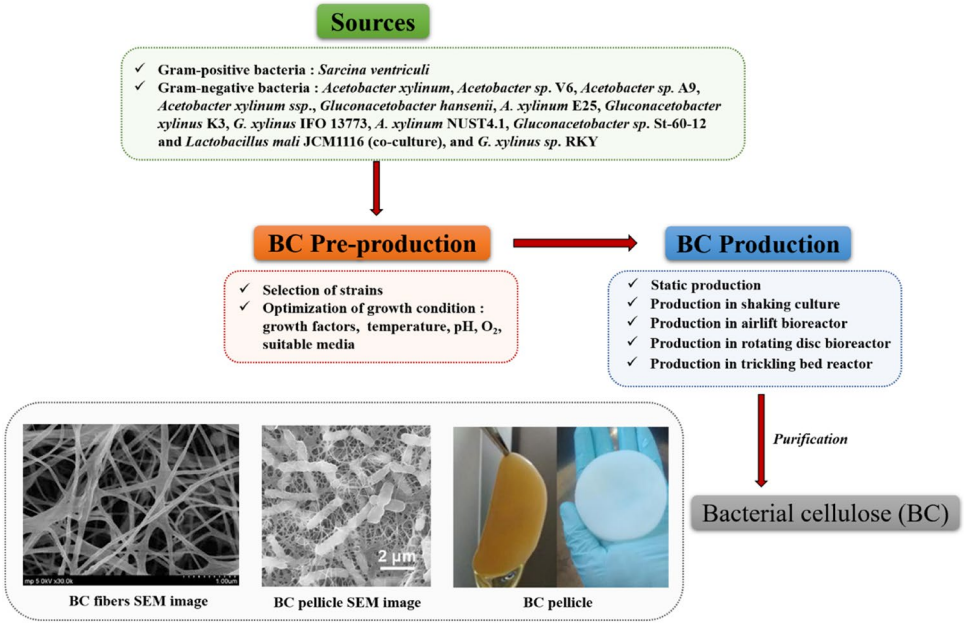
Type	Size		Shape	Nanocellulose structure	Production process	Impurity	Properties
	Length	Diameter					
BC	More than 1 µm	20–100 nm	A nanofiber network	Crystalline	Bottom-up	No hemicellulose, lignin, and pectin	Good porosity, moldability, foldability, hemocompatibility, a high average molecular weight (Mw), good mechanical stability, and high crystallinity

the best formulation was F3 with 1% surfactant, a 1:6 ratio of ALG:CNC, and a 1:4 ratio of RIF:ALG. These ALG-CNC NPs had a small average NP size (70 nm), yielding a high drug entrapment efficiency (69.73%). They showed poor swelling properties at pH 1.2, thus preventing a burst of drug release. In contrast, the ALG-CNC NPs swelled rapidly at pH 6.8 and 7.4 and released the drug within a 12-h time window. The CNC used in these studies can enhance the properties and overcome the limitations of ALG, such as poor porosity and low mechanical strength. The addition of CNC as a hybrid system in the NP formulation enhances the mechanical stability of ALG without disturbing the inherent network structure of ALG. Therefore, the ALG-CNC-NPs can avoid drug release in the harsh acidic environment of the stomach. In addition, the negative charge and large surface area of CNC enable binding to the drug molecule, improving the loading efficiency. In this study, CNC also improved the stability of the NPs and prolonged the drug release (Thomas et al. 2018).

There are several other advanced drug delivery systems based on nanocellulose that were successfully fabricated for oral drug delivery and are shown in Table 2. These new innovations utilized nanocellulose (as CNC, CNF, CNW, oxidized CNC, and BC) in several different forms, including self-stabilized Pickering emulsion (Yi et al. 2017), NP/CNC nanocomposites (Abo-Elseoud et al. 2018), micro hydrogel composite (Mauricio et al. 2015), solid cellulose nanofiber-based foam (Svagan et al. 2016), cellulose nano paper and nanofoam (Löbmann et al. 2017), self-assembled nanocellulose composite fibers (Gao et al. 2014), aerogels (Zhao et al. 2015), nanocomposite hydrogels (Rao et al. 2017), and BC-drug composites (Badshah et al. 2017). The addition of nanocellulose to these formulations offers several benefits in oral drug delivery, such as an increase in the dissolution rate and oral bioavailability of the drug; high drug entrapment efficacy, enabling sustained and controlled drug release; the potential for gastroretentive drug delivery due to the induction of positive buoyancy; prolonged drug release in fasted state-simulated stomach fluid; good mechanical and viscoelastic properties; good pH sensitivity; and applicability to single polymer-based oral drug delivery. Thus, nanocellulose has great potential for oral drug delivery systems.

Ocular delivery

The efficient delivery of drugs to the eye is challenging due to its distinctive structure (e.g., the epithelium, substantia propria, and endothelium of the human cornea), which contains several protective mechanisms to inhibit the penetration of foreign objects/drug molecules, such as tear turnover, protein binding, nasolacrimal drainage, enzymatic degradation, systemic absorption, and complex penetration barriers (e.g., blood-aqueous barrier, corneal barrier, and



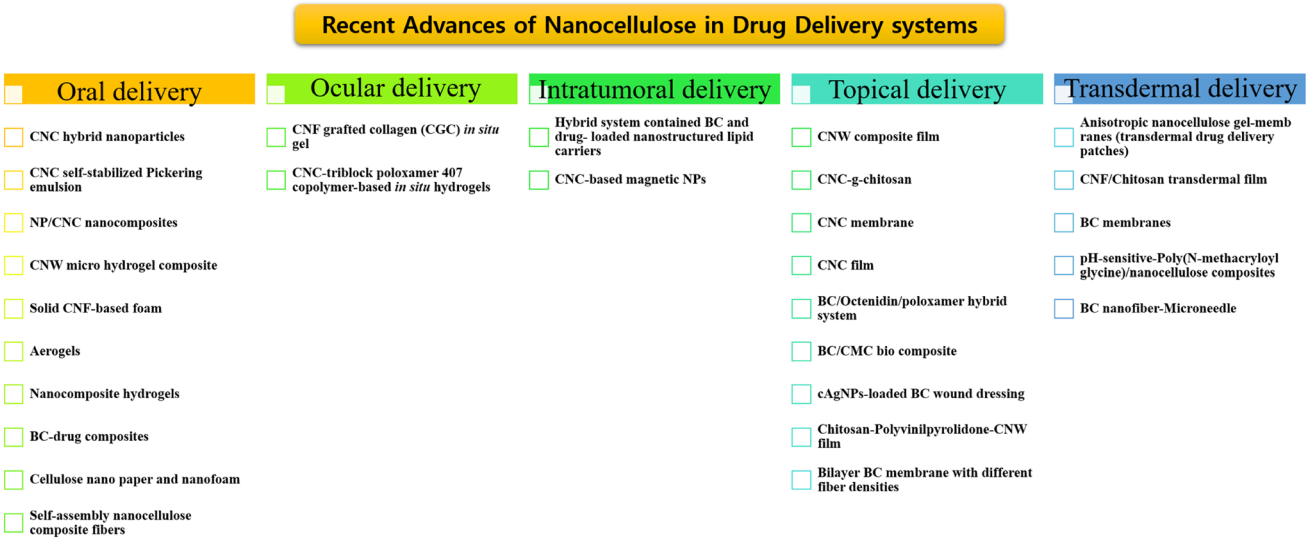


Fig. 4 Schematic representation of BC preparation. BC pellicle photograph [reprinted with permission from (Costa et al. 2017)]. SEM images of BC pellicle (reprinted with permission from [Wan et al. 2019)]. SEM images of BC fibers (reprinted with permission from [Wei et al. 2011)]

Fig. 5 Summary of recent advances of nanocellulose in drug delivery systems

blood-retinal barrier) (Bisht et al. 2018). Therefore, bioavailability of the drug after topical ocular administration is very low (< 5%), particularly for eye drops that will be washed away after application to the eye (Zhu et al. 2018). In this case, the increased frequency of drug administration that is needed lead to the emergence of side effects. To overcome these problems, an ophthalmic drug delivery system (ODDS) approach, having the ability to extend ocular residence time, is greatly needed.

Polymers, such as cellulose, alginate, pectin, and xanthan gum are widely used in topical ophthalmic dosage forms (Patchan et al. 2013). It was reported that cellulose-based macromolecule gel formulations have good viscosity; thus, they can enhance corneal residence time (Mohan et al. 2009). However, the conventional gel dosage form has some drawbacks, such as blurred vision, scabby eyelids, and the stimulation of tears. Therefore, an ODDS in the form of an in situ-formed hydrogel (e.g., temperature-sensitive, pH-sensitive, and ionic strength-sensitive) is a promising approach. An in situ-formed hydrogel is topically administered as eye drops and subsequently gels after contact with the eye (Agrawal et al. 2012).

In 2019, Orasugh et al. investigated the effect of CNF grafted collagen (CGC) on the performance of poloxamer

Table 2 Nanocellulose-based drug delivery systems and toxicological evaluations for oral delivery

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
Hybrid nanoparticles	CNC	Alginate	Rifampicin	Antibiotic against *Mycobacterium tuberculosis*	Sustained drug release	MTT assay toward L929 cells	Low or no toxicity	Thomas et al. (2018)
Self-stabilized Pickering emulsion	CNC		Silybin	Anti-tumor	Increased the dissolution rate and oral bioavailability of silybin	–	–	Yi et al. (2017)
NP/CNC nanocomposite	CNC, oxidized CNC	Chitosan (CH)	Repaglinide	Anti-hyperglycemic	High drug entrapment efficacy Sustained and controlled drug release	–	–	Abo-Elseoud et al. (2018)
Micro hydrogel composite (μHC)	CNW	Starch	Vit-B_{12}		Sustained release of Vit-B_{12}	–	–	Mauricio et al. (2015)
Solid cellulose nanofiber-based foam	CNF	Lauric acid sodium salt	Riboflavin		Gastro retentive effect Positive buoyancy Prolonged release of riboflavin	–	–	Svagan et al. (2016)
Cellulose nano paper and nanofoam	CNF		Indomethacin	Nonsteroidal anti-inflammatory drug (NSAID)	High porosity Sustained drug release	–	–	Löbmann et al. (2017)
Self-assembly nanocellulose composite fibers	CNF		Indomethacin	Nonsteroidal anti-inflammatory drug (NSAID)	High loading capacity and encapsulation efficiency Prolonged drug release			Gao et al. (2014)
Aerogels	CNF	Polyethyleneimine	Sodium salicylate	Wound healing agent, antidiabetic, anticancer	High drug loading -Sustained drug release s			Zhao et al. (2015)
Nanocomposite hydrogels	CNC	Poly (acrylamido-glycolic acid)	Diclofenac sodium	Nonsteroidal anti-inflammatory drug	Good mechanical and viscoelastic properties Good pH sensitive nature Controlled drug release	MTT assay toward NIH-3T3 fibroblast cells	No toxicity	Rao et al. (2017)

Table 2 (continued)

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
BC-drug composites	BC		Famotidine Tizanidine	Histamine-2 blocker Short-acting muscle relaxer	Uniform drug distribution Burst drug release Good friability test	–	–	Badshah et al. (2017)

407-based in situ gels in modulating ketorolac tromethamine (KT) release kinetics. The approach aimed for efficient ophthalmic drug delivery with an extended precorneal residence time and sustained bioavailability of KT. For this purpose, a series of nanocomposite formulations with 16.8% (w/v) poloxamer 407 were developed, including those without CGC (called P1) and others containing 1.0%, 1.25%, 1.5%, and 1.75% (w/v) CGC (called P2, P3, P4, and P5, respectively). The results revealed that CGC decreased the poloxamer 407 critical gelation concentration, increased gel strength, and prolonged the release of KT over a period of 15 h. Furthermore, the cumulative percentages of the KT release from P1, P2, P3, P4, and P5 were 98.54%, 85.33%, 67.96%, 69.69%, and 72.03%, respectively, 360 min post-test, thus affirming the effect of CGC in modulating the drug release kinetics (Orasugh et al. 2019a, b). The authors also reported a similar concept with CNC-triblock poloxamer 407 copolymer-based in situ hydrogels (Orasugh et al. 2019a, b). The addition of CNC in different concentrations (0.8%/M2, 1.0%/M3, and 1.2%/M4) to 16.6% (w/v) poloxamer 407 in cold water (4 °C) also produced a significant effect on gelation behavior, increased gel strength, and prolonged pilocarpine HCl release. The increase in mechanical strength of the hydrogel at high cellulose concentrations may be due to the increased fiber density or the intermolecular and intramolecular hydrogen bonds between polymer molecules (poloxamer 407 and collagen) and the free hydroxyl groups of cellulose molecules (CNC or CNF) (Patchan et al. 2013; Orasugh et al. 2019a, b). These results showed that CNC and CNF have great potential for ODDS approaches. Table 3 summarizes recent reports on nanocellulose-based ocular drug delivery systems.

Intratumoral delivery

Localized cancer treatment using nanocellulose as a matrix that sustains NPs and controls the release of doxorubicin (Dox) has been reported by Cacicedo et al. This hybrid system contained BC and neutral or cationic Dox-loaded nanostructured lipid carriers (NLCs-NH), which were administered intratumorally into an orthotopic breast cancer mouse model. The purpose of the study was to allow high drug concentrations at the tumor site and to eradicate the side effects of intratumorally administered Dox. In this regard, two formulations of NLCs containing cationic Dox (NLCs-H) and neutral Dox (NLCs-N) were prepared. The results showed that NLCs-H have lower encapsulation efficiency (48%) and faster drug release than NLCs-N (97%, sustained release). The two NLCs with different kinetic release profiles were then encapsulated into a BC matrix (BC-NLCs-NH). Free Dox-loaded BC (BC-Dox) was also prepared to compare the antitumor efficacy. A cancer model induced by implantation of BC-NLCs-NH films into MDA-MB-231 cells revealed a

Table 3 Nanocellulose-based drug delivery systems and toxicological evaluations for ocular delivery

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
Poloxamer407/CNF-g-nano collagen	CNF	Poloxamer 407, collagen	Ketorolac tromethamine	Non-steroidal anti-inflammatory drug (NSAID)	Increased hydrogel mechanical strength Prolonged drug release Thermo responsive property	Lactate dehydrogenase and hemolysis assay	No toxicity	Orasugh et al. (2019a, b)
In situ nanocomposite thermo responsive gels	CNC	Poloxamer 407	Pilocarpine HCl	Reduce pressure inside the eye	Increased gel mechanical strength Sustained release of pilocarpine HCl	Lactate dehydrogenase and hemolysis assay	No toxicity	Orasugh et al. (2019a, b)

significant decrease in the tumor-to-control (T/C) ratio of the tumor volume ex vivo (53%), when compared to that with BC-Dox (66%). The percentage of the ex vivo tumor weight was also lower for the BC-NLCs-NH films (62%) than for the BC-Dox (81%). The authors also observed no side effects, such as edema, inflammation, and necrosis, in the BC-NLCs-NH film-treated group (Cacicedo et al. 2018). This approach of combining a BC matrix with chemotherapeutic drug-loaded lipid nanocarriers is very promising as a neo adjuvant therapy for the local treatment of tumors. This hybrid system utilizing BC facilitates the delivery, sustained release, and accumulation of chemotherapeutic NPs at the tumor site, promotes an antitumor effect, and reduces/eliminates unwanted side effects. These results showed that BC has great potential as an intratumoral drug delivery system due to the similarity of the nanostructure and collagen morphology which makes BC suitable for cell immobilization, natural extracellular matrix scaffolds, and cell support (De Olyveira et al. 2016). Table 4 summarizes recent reports on nanocellulose-based intratumoral drug delivery systems.

Topical delivery

The main purpose of administering medication topically is to deliver the drug directly onto areas of the skin that are wounded, inflamed, irritated, itchy, or infected. Topical delivery has several advantages, such as enabling the delivery of a selected drug to a specific site, avoiding fluctuations in drug levels, improving patient compliance, and permitting self-medication (Nalamothu 2015). Most of the conventional topical drug dosage forms are used for local skin infections. Similarly, most of the nanocellulose-based topical drug delivery systems were prepared as dressings to treat cutaneous or infected wounds. The development of novel topical drug delivery systems is necessary to overcome the limitations of conventional topical dosage forms, such as poor retention and low bioavailability. The nanocellulose used in topical drug delivery systems, is the CNC, CNW, or BC-type form. These systems are engineered using several designs, such as grafted-, membrane-, hybrid system-, film-, biocomposite-, and bilayer-based topical drug delivery systems (Akhlaghi et al. 2014; Barbosa et al. 2016; Lazarini et al. 2016; Alkhatib et al. 2017; de Lima Fontes et al. 2018; Tong et al. 2018; Gupta et al. 2020). The use of nanocellulose in these systems, as either an excipient or a carrier, enables prolonged drug release, increases treatment efficacies, and improves mechanical properties of the final product.

In 2017, Hasan et al. successfully prepared a composite film using chitosan (CS) and polyvinylpyrrolidone (PVP), which incorporated CNW, for wound healing applications. The study aimed to improve the drug release profile of the wound dressing. Polymers, such as CS and PVP, have been used as wound dressing materials for many years, but these

Table 4 Nanocellulose-based drug delivery systems and toxicological evaluations for intratumoral delivery

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
BC hydrogel loaded lipid NPs	BC	Grodamol™ MM, Grodamol™ GTCC-LQ, Pluronic® F68	Doxorubicin	Anticancer	High drug loading Sustained drug release Good anti-tumor efficacy No side effects	MTT assay	No toxicity	Cacicedo et al. (2018)
Magnetic NPs	CNC	Tris(2-aminoethyl) amine, Fe_3O_4 NPs	Methotrexate	Anticancer	High drug loading Good binding ability Direct target to cancer cells Controlled and sustained drug release pH responsive-based drug release	–	–	Rahimi et al. (2017)

polymers have limitations in controlling drug release. CNW were used as nanofillers to improve the swelling behavior of mixed hydrophilic polymers for controlled drug release, while enhancing the thermal and mechanical properties of the films. The swellability of the films showed a decreasing trend when less PVP and more CNW were added. CP5W5Cur (CS 2%, PVP 5%, CNW 5%, and Curcumin 2%) showed a low cumulative percentage of curcumin release (46.12%) after 56 h, whereas CP10W0Cur (CS 2%, PVP10%, CNW 0%, and curcumin 2%) and CP5W0Cur (CS 2%, PVP 5%, CNW 0%, and curcumin 2%) showed cumulative percentages of curcumin release of 100% and 83%, respectively. This pattern was highly related to swellability. The CS-PVP-CNW films were biocompatible and showed potent antibacterial activity against *Escherichia coli* and *Enterococcus hirae*. This study showed the potential application of CNW in drug delivery as a film-based dressing for wound healing with a desirable sustained drug release pattern (Hasan et al. 2017). Table 5 summarizes recent reports on nanocellulose-based topical drug delivery systems.

Transdermal delivery

Transdermal drug delivery is designed to overcome the limitations of oral and parenteral drug delivery by avoiding GI and hepatic presystemic metabolism, regulating serum drug levels for improved efficacy-to-tolerability ratios, and prolonging drug release (Alexander et al. 2012). Nanocellulose has potential for transdermal drug delivery systems due to its unique properties. There are several studies related to nanocellulose-based transdermal drug delivery systems that have been reported recently. In 2019, Plappert et al. designed a transdermal drug delivery patch by tailoring the cellulose structure and interface into an anisotropic nanocellulose gel-membrane. The purpose of their study was to enable the transdermal delivery of piroxicam as well as to overcome the limitations of piroxicam and avoid GI disorders that may occur upon oral delivery. The results revealed that the assembly of CNF into anisotropic-layer membranes has several advantages, such as high internal surface area and tunable content of surface charges for drug loading. Piroxicam is known to have poor solubility, which has hindered its application. The surface charge density and carboxylate content of the CNF membrane can increase the adsorptive loading/affinity of piroxicam onto/for CNF membranes. In addition, the in vitro drug release under simulated human skin conditions was prolonged. The results confirmed the potential application of nanofiber membranes as patches for transdermal drug delivery (Plappert et al. 2019). Another study by Sarkar et al. also showed the potential of nanocellulose for transdermal drug delivery. A CNF/CS film loaded with the nonsteroidal anti-inflammatory drug (NSAID) KT was used for effective dose control of transdermal delivery and to reduce unwanted side effects in the GI tract. By increasing the concentration of CNF in the transdermal film formulation, the crystallinity and mechanical strength increased and the rate of KT release from the film decreased. CNC4 (CS 1 g, CNF 1 wt%, and KT 10%) displayed well-balanced profiles in drug loading and sustained drug release, showing potential as a carrier for transdermal

Table 5 Nanocellulose-based drug delivery systems and toxicological evaluations for topical delivery

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
CNC-g-chitosan	Native CNC, oxidized CNC, chitosan oligosaccharide-g-CNC	Chitosan oligosaccharide	Procaine HCl, imipramine HCl	Local anesthetic and periodontal cavities	Prolonged drug release	–	–	Akhlaghi et al. (2014)
CNC membrane	CNC	–	Chlorhexidine	Antibacterial	Sustained drug release Good antibacterial activity	–	–	Barbosa et al. (2016)
CNC film	CNC	Polyvinyl alcohol	Curcumin	Antibacterial	Controlled and sustained drug release Accelerated wound healing			Tong et al. (2018)
BC/Octenidine/poloxamer hybrid system	BC	Poloxamers 338 and 407	Octenidine	Antiseptic	Sustained drug release Improved gel mechanical strength Good antimicrobial activity	Shell-less hen's egg model	No toxicity	Alkhatib et al. (2017)
BC/CMC bio composite	BC	CMC	Methotrexate (MTX)	Anti-psoriasis	Controlled drug release	–	–	de Lima Fontes et al. (2018)
cAgNPs-loaded BC wound dressing	BC	HPβ-cyclodextrin	Curcumin	Wound healing agent with antimicrobial, antioxidant, and anti-inflammatory effects	Successful cAgNPs-loaded BC hydrogels Good antibacterial and antioxidant activities	MTT assay	No toxicity	Gupta et al. (2020)
Chitosan-Polyvinilpyrolidone-CNW film	CNW	-Chitosan -Polyvinilpyrolidone	Curcumin	Wound healing agent with antimicrobial, antioxidant, and anti-inflammatory effects	Increased thermal and mechanical properties of films Improved swelling behavior of film Sustained drug release High biocompatibility Good antibacterial effect	MTT assay	No toxicity	Hasan et al. (2017)

Table 5 (continued)

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
Bilayer BC membrane with different fiber densities	BC		Ceftriaxone	Antibiotic	Double layer and three-dimensional fiber network properties High densities fiber entangling High loading capacity Sustained drug release	–	–	Lazarini et al. (2016)

delivery systems. These studies should be complemented with additional experiments to improve the systems, but the findings showed the potential of drug delivery through the skin (Sarkar et al. 2017). Another CNF-based transdermal drug delivery system in the form of a microneedle (MN) has also been reported. Medhi et al. investigated the ability of fish scale biopolymer-nanocellulose (FSBP-NC) MNs to load and release lidocaine transdermally. The study aimed to deliver the drug with controlled skin permeation and to minimize the need for invasive local anesthesia. The MNs used in this study had consistent needle lengths that were inserted into the skin at a depth that is less than that known to cause pain. The MN arrays were produced by the combination of fish scale biopolymer and bacterial CNF loaded with lidocaine. The results showed that the MNs successfully pierced the stratum corneum and dissolved in the skin to release lidocaine. The prepared MNs had favorable composite structures with sufficient sharp and rigid needle tips due to the combination of the flexibility of the gelatin and structural strength of the cellulose. In addition, the MNs loaded with 7.5% (w/w) lidocaine had good skin permeation with increased drug permeation rates of 2.5 to 7.5% (w/w) after 36 h (Medhi et al. 2017). These studies showed the favorability and potential application of CNF in transdermal drug delivery due to the unique properties of CNF.

Another nanocellulose type (i.e. BC) also showed potential as a carrier for transdermal drug delivery systems (Saïdi et al. 2017; Abba et al. 2019). BC membranes showed a slow drug release profile with a steady flux compared to that of other polymers. The high water uptake, pore size density, and flexibility of BC make it a candidate for transdermal drug delivery (Trovatti et al. 2011, 2012). Table 6 summarizes recent reports on nanocellulose-based transdermal drug delivery systems.

Conclusion

The aim of this review was to describe the potential use of nanocellulose in drug delivery, including oral, ocular, intratumoral, topical, and transdermal routes of administration. Undoubtedly, nanocellulose has potential for application in drug delivery systems. However, many of the discussed examples, which were derived from recent studies, did not include toxicity assessments. The toxicity of nanocellulose-based delivery systems should not be ignored, and in fact, more attention should be paid to this potential caveat before addressing potential efficacies. The large surface area of nanocellulose, which is one of its unique characteristics, may contribute to its toxicity due to high reactivity. It has been reported that nanocellulose (e.g., CNF) administration to the lung can enter the blood stream and other organs and the inhaled CNF may reach

Table 6 Nanocellulose-based drug delivery systems and toxicological evaluations for transdermal delivery

Drug delivery system	Material component		Model drug	Drug uses	Drug delivery system results	Toxicological experiment	Toxicology result	Ref.
	Nano cellulose	*Co*-material						
Anisotropic nanocellulose gel-membranes (transdermal drug delivery patches)	CNF	–	Piroxicam	Non-steroidal anti-inflammatory drug (NSAID)	High surface area, small average pore, and tunable surface charge properties Good skin adsorption Sustained drug release	–	–	Plappert et al. (2019)
CNF/Chitosan transdermal film	CNF	Chitosan	Ketorolec trometh-amine	Non-steroidal analgesic	Sustained rug release Increased the mechanical strength of transdermal film Swelling behavior-based drug release mechanism	–	–	Sarkar et al. (2017)
BC membranes	BC	–	Crocin	Antioxidant	Stable and prolonged drug permeation Good uptake of the crocin into BC membranes	–	–	Abba et al. (2019)
pH-sensitive-Poly(*N*-methacryloyl glycine)/ nanocellulose composites	BC	Poly(*N*-methacryloyl glycine)			Good thermal, mechanical, and viscoelastic properties Non-cytotoxic and pH sensitive High water uptake capacity	MTT	No toxicity	Saïdi et al. (2017)
BC nanofiber-Microneedle	BNF	Silicone elastomer	Lidocaine	Anesthesia	Increased drug permeation rate Negligible swellability properties Good tissue insertion	–	–	Medhi et al. (2017)

the brain via the olfactory nerve. There is also a possibility that nanocellulose will accumulate in the body and cause toxicity. Therefore, drug delivery system-based nanocellulose must be assessed for toxicology, potential health effects, and safety risks before further recommendations can be made regarding their potential uses and applications in the field of drug delivery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human and animal rights This article does not contain any studies with human and animal subjects performed by any of the authors.

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