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Nanocellulose Applications for Drug Delivery: A Review

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Abstract

Nanocellulose, which can exist as either cellulose nanocrystals or cellulose nanofibrils, has been used as a biomaterial for drug delivery owing to its non-immunogenicity, biocompatibility, high specific area, good mechanical properties, and variability for chemical modification. Various water-soluble drugs can be bound to and released from nanocelluloses through electrostatic interactions. The high specific surface area of nanocellulose allows for high specific drug loading. Additionally, a broad spectrum of drugs can bind to nanocellulose after facile chemical modifications of its surface. Controlled release can be achieved for various pharmaceuticals when the nanocellulose surface is chemically modified or physically formulated in an adequate manner. This review summarizes the potential applications of nanocelluloses in drug delivery according to published studies on drug delivery systems.

Key Words: nanocellulose, drug delivery, controlled release, stimuli-responsive release

Introduction

Nanocellulose, a nanoscale cellulosic material, is a naturally occurring and abundant biomass. Nanocelluloses can be classified into three types depending on whether they are prepared through chemical or mechanical processes or obtained from bacteria: cellulose nanocrystals (CNCs), cellulose nanofibrils (CNFs), and bacterial cellulose (BC) (Abitbol et al. 2016). CNCs are mainly prepared from amorphous celluloses through acid hydrolysis, where those obtained from plant sources have a crystallinity of approximately 90% and dimensions of 4-20 nm in diameter × 100-500 nm in length. CNFs have a length in the order of 1 μm and contain both a crystalline and an amorphous cellulose domain. Mechanical or chemical methods or combinations of both have been used to prepare CNFs from lignocellulosic fibers. BC, a type of extracellular nanocellulose that is synthesized by microorganisms such as *Gluconacetobacter xylinus*, has a diameter of approximately 20-100 nm and a length of several micrometers. Unlike cellulosic materials obtained from plants, BC is free of lignin and hemicellulose.

Each type of nanocellulose has its own crystallinity, aspect ratio, surface chemistry, and exhibits properties different to the other types (Xu et al. 2013; Sacui et al. 2014). For example, CNC has a high Young's modulus and tensile strength owing to its high crystallinity. CNFs are entangled with one another, forming viscous aqueous suspensions

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even at concentrations below 1% (w/w). The BC nanofibers can also be entangled to form network structures. CNCs that are prepared through sulfuric acid hydrolysis have a surface that facilitates the attachment of sulfate half-ester groups, the electrostatic repulsion among which results in colloidally stable aqueous suspensions. Moreover, rod-like CNCs exhibit a concentration-dependent, liquid crystalline, self-assembly behavior.

Nanocelluloses have applications in various fields, including as cosmetic additives, rheology modifiers for foods, packaging materials, materials with antimicrobial activity, sensors, shape memory materials, biomaterials for tissue culture scaffolds, implants, wound dressing, and drug delivery carriers (Shanmuganathan et al. 2010; Qiu and Hu 2013; Lin and Dufresne 2014; Plackett et al. 2014; Jorfi and Foster 2015). Recently, nanocellulose has been used as a material for drug delivery systems because it is known to be non-immunogenic and biocompatible, has a high specific surface area and good mechanical properties, and can be easily chemically modified (Kolakovic et al. 2011). Various water-soluble drugs can bind to and release from nanocellulose through electrostatic interactions. The high specific surface area of nanocellulose allows for high specific drug loading, and chemical modification of the nanocellulose surface can broaden the spectrum of drugs capable of binding to it. For various pharmaceuticals, nanocellulose materials can facilitate different forms of controlled release (e.g., sustained release, zero order-like release, stimuli-responsive release, and targeted release) if chemically modified or physically formulated in an adequate manner. In this review, the potential applications of nanocellulose materials to drug delivery are summarized based on a literature review. Additionally, drug delivery carrier-related studies are briefly reviewed, and various ideas for the use of nanocellulose as a drug delivery material are suggested.

Literature Review of Nanocellulose in Drug Delivery Systems

Based on a literature review, the potential applications of nanocelluloses in drug delivery systems according to their different types are summarized below.

Cellulose nanocrystals

CNCs incorporated into calcium cross-linked alginate microspheres have been shown to increase the loading efficiency of theophylline (a drug used in the treatment of respiratory diseases) and to facilitate sustained drug release (Plackett et al. 2014). The CNC was speculated to suppress burst release in the early stage, while being able to sustain the drug release over a long time. A hydrogel composed of beta-cyclodextrin (β-CD), CNCs, and Pluronic polymer was developed using the nanocellulose component as a cross-linking junction (Lin and Dufresne 2013). The β-CDs were grafted onto the CNC surface and then connected to each other as host-guest inclusions. The hydrogel exhibited a prolonged release of the anticancer drug doxorubicin. The CNC was speculated to suppress the release of the anticancer agent when incorporated into the hydrogel mesh. In another study, the CNC surface was modified with an aromatic linker to allow efficient binding of amine-containing drugs and to facilitate their controlled release (Dash and Ragauskas 2012). CNCs have also been surface modified with cetyltrimethylammonium bromide through electrostatic attraction, whereupon a hydrophobic domain was formed on the nanocellulose surface that allowed the loading of hydrophobic anticancer drugs (paclitaxel, docetaxel, and etoposide). The drug release was delayed in the release medium (phosphate-buffered saline (PBS)) and the surface-modified CNC was absorbed by cells in vitro (Jackson et al. 2011; Plackett et al. 2014). One research team conjugated folic acid to CNCs to aim the anticancer agents toward cancer cells. Fluorescence imaging revealed that CNCs bound to the cells readily and internalized through endocytosis (Dong et al. 2014). Positively charged drugs, such as doxorubicin and tetracycline hydrochloride, were found to bind readily (through ionic bonding) to sulfated CNCs that had been produced by sulfuric acid hydrolysis. Most of these drugs were released from the CNCs within 4 h under physiological conditions (10 mM PBS, 37°C), possibly owing to ion exchanges (Jackson et al. 2011). As excipients, pure and cationic Conks have been investigated in terms of their capacity to bind water-soluble antibiotics (e.g., tetracycline and doxorubicin) and non-ionized hydrophobic anticancer agents (e.g., docetaxel, paclitaxel, and etoposide) (Jackson et al.

2011). Carboxylated CNCs, prepared through (2, 2, 6, 6-tetramethylpiperidin-1-yl) oxidanyl (TEMPO) modification, were coupled with a chitosan oligosaccharide through an amidation reaction. Procaine hydrochloride (a local anesthetic) was loaded onto the chitosan-conjugated CNCs to investigate the drug release profile. Because the conjugate exhibited an initial burst re¬lease of the drug in PBS, its application as a wound dressing was proposed (Akhlaghi et al. 2013). CNFs and CNCs coated with a bifunctional fusion protein film could adsorb hydrophobic solid-drug nanoparticles and enhance the drug's stability under physiological conditions (Varjonen et al. 2011). In another study, complexes composed of chitosan and CNCs were prepared by exploiting the electrostatic attraction between the amino group of chitosan and the sulfate group of CNC. The polyelectrolyte-macro ion complex could be applied as a carrier for intestinal drug delivery (Wang and Roman 2011). To date, CNC-related toxicity has not been reported. However, extensive studies are required to confirm the safety of CNCs for application in the human body.

Cellulose nanofibrils

Several model drugs, such as indomethacin, metoprolol tartrate, verapamil hydrochloride, nadolol, ibuprofen, and atenolol, have been loaded onto CNF microspheres through spray drying. In the release medium (distilled water and PBS), the microspheres rapidly released their payloads for the first 10-14 days after which the release slowed down substantially for up to 60 days. The microparticles released their payload in a sustained manner over 2 months. The solubility and binding affinity of the drugs to the CNFs were thought to be determinants for the release kinetics (Kolakovic et al. 2012a). Spray-dried CNFs have been investigated as a tablet excipient and exhibited faster disintegration compared with a tablet prepared using a commercial excipient (viz., Avicel) with a pH of 1-2. This suggested that spray-dried CNFs could be used as an excipient in the tablet formulation of aqueous nanocellulose suspensions (Gavillon and Budtova 2008; Liebner et al. 2010). In one study, drug-loaded nanoparticles were embedded in four different CNF aerogels for controlled drug release, where the CNF type was reported to affect the drug release profile (Valo et al. 2013). In another study, CNF film prepared through filtration processing released the model drugs in a sustained manner for more than 3 months. Diffusion-limited release was observed with indomethacin (a non-steroidal anti-inflammatory agent), whereas zero-order release was obtained with itraconazole (a triazole antifungal agent) and beclomethasone (a steroidal anti-inflammatory agent). The solubility of the drug in the dissolution medium and its binding affinity to the CNF chains had an effect on the release kinetics (Kolakovic et al. 2012b). Silver nanoclusters (AgNC) attached to CNF films have been prepared by immersing the CNF film (prepared using the casting method) into an AgNC solution. The CNF-AgNC films exhibited in vitro antibacterial activity and could be applied to wound dressings (Diez et al. 2011). A genetically engineered hydrophobin fusion protein was coupled with cellulose-binding domains (CBD) and then coated with itraconazole nanoparticles. These coated drug nanoparticles could bind to CNFs by exploiting the cellulose-binding capability of the CBD. In this manner, the formulation and shelf stability of the drug nanoparticles were enhanced (Valo et al. 2011). Multilayers composed of CNFs and N-isopropylacrylamide have been prepared to release their payloads in response to temperature changes (Utsel et al. 2010). The use of CNFs in drug formulations, with a focus on poorly soluble drugs, has also been reported (Löbmann and Svagan 2017). The poor aqueous solubility of drugs is one of the most challenging characteristics to overcome in drug delivery systems. CNFs are also attractive as excipients and stabilizers for crystalline drug nanoparticles, as matrix formers to obtain a long-lasting sustained drug release over several weeks, and as film formers with immediate-release properties for poorly soluble drugs (Löbmann and Svagan 2017; Gopi et al. 2018). CNF aerogels with favorable floatability and mucoadhesive properties have been reported as possible carriers for controlled oral drug delivery systems (Bhandari et al. 2017).

Bacterial cellulose

BC can absorb liquids and imbibe moisture efficiently. Moreover, because it can eliminate exudate from wounded skin and provide moisture adequately, it is used mainly in preparing wound-healing products (Alvarez et al. 2004; Czaja et al. 2007). Exudate removal and skin moisturization are important for normal wound healing (Sulaeva et al. 2015). A BC film with antibacterial activity was prepared

by immersing a lyophilized BC film in a benzalkonium chloride (BZK) solution and then lyophilizing the wet film. The BZK-loaded dry film exhibited a high water-absorbing capacity and sustained antibacterial activity (for 24 h), and could therefore be used as a wound dressing film (Wei et al. 2011). A BC membrane that was capable of releasing antibiotics (e.g., ampicillin and gentamicin) in a sustained manner without an initial burst release was prepared to investigate its potential application to wound dressing, and was found to exhibit a high water uptake capacity (~66% swelling ratio) and maintain its antibacterial activity for 3 days (Kaplan et al. 2014). In another study, silver nanoparticles (AgNP) were deposited onto BC fibers by first modifying the BC fibers with TEMPO and then exposing the carboxylated BC fibers to a silver nitrate solution. The AgNPs prepared with this method exhibited a narrow size distribution. The AgNPs deposited onto the BC fibers could be used as an antimicrobial material for wound dressing (Ifuku et al. 2009). Antimicrobial porous hybrids composed of AgNPs and BC have been prepared through a three-step BC modification process: the activation of BC through treatment with N,N′-carbonyldiimidazole, the immersion of the activated BC into a 1,4-diaminobutane solution, and the exposure of the BC to an aqueous solution of sodium acetate and silver nitrate. The AgNPs could bind chemically to the activated BC fibers owing to the amine groups introduced into the fibers. The AgNPs-BC porous hybrids could be applied to antimicrobial wound dressings (Berndt et al. 2013). BCs impregnated with silver sulfadiazine particles were shown to exhibit high in vitro antimicrobial activity and promote in vivo burn wound healing (Wen et al. 2015). A BC membrane was used as a carrier for the transdermal delivery of a drug because of its capability of releasing payloads, which in turn diffused into the skin or systemic circulation without deteriorating the skin barrier function and causing erythema (Almeida et al. 2014). Another BC membrane containing tetracycline was prepared for use in transdermal delivery (Stoica-Guzun et al. 2007). When the BC membrane surface was treated with electron beam irradiation, permeation of the drug through the membrane was suppressed. A BC membrane containing an isoquinoline group alkaloid (viz., berberine) has been investigated as a vehicle for transdermal delivery of the active ingredient, particularly with respect to its in vitro skin permeation. Additionally, in vitro release experiments have revealed that the release rate was higher in the order of neutral conditions > alkaline conditions > acidic conditions (Huang et al. 2013). This phenomenon was attributed to the pH dependence of the swelling of the fibers and the lower solubility of the drug under acidic conditions. Hybrid membranes have been prepared by growing BC in the presence of a hydroxyethylcellulose (HEC) matrix. The BC-HE biocomposite membrane exhibited higher tensile strength compared to pure BC membrane and can be used for controlled drug delivery (Zhou et al. 2009). Paracetamol tablets that had been coated with BC powder through spray drying have been observed to exhibit prolonged drug release (Amin et al. 2012). In another study, a hydrogel was prepared using BC and gelatin that exhibited a higher swelling ratio under acidic conditions than that under alkaline conditions, owing to the amphoteric property of gelatin. Its use has been proposed as a gastroretentive drug carrier because the stomach has characteristically an acidic environment (Păvăloiu et al. 2015). Another BC hydrogel was prepared as a carrier for the delivery of luciferase, which was released from the hydrogel without being denatured (Müller et al. 2013). A pH-responsive hydrogel has been prepared by grafting poly (acrylic acid-co-acrylamide) to BC. The swelling ratio under neutral conditions was higher than that observed under acidic conditions. Additionally, release of the drug was promoted at a neutral pH, but was suppressed at a lower pH. Hence, the hydrogel could be used to develop drug carriers capable of releasing a payload in the lower part of the gastrointestinal tract (Amin et al. 2014). Acid-labile drugs, peptides, and proteins should preferably be loaded onto pH-responsive hydrogels. The release profiles of a drug loaded onto aerogels made of nanocelluloses from different raw materials have been investigated (Valo et al. 2013). The aerogel prepared using BC, quince seed, and TEMPO-oxidized birch cellulose could release drugs in a sustained manner and whereas the aerogel prepared using, microcrystalline cellulose could not. The in vivo skin compatibility of BC membranes was investigated to assess whether the membrane causes irritation when applied to human skin. Not only was skin irritation not observed, but also good skin tolerance was observed 24 h after application of the BC membrane (Almeida et al. 2014).

Stimuli-responsive Delivery Carriers Investigated by the Author Group

Studies on stimuli-responsive drug carriers have been conducted by the Author group and are briefly presented in three categories: cubic phase, liposomal, and polymeric drug vehicles.

Cubic phase vehicles

The cubic phase is known to form spontaneously when amphiphilic molecules with a packing parameter value slightly greater than 1 become equilibrated with a sufficient amount of water (Nakano et al. 1999). Monoolein (1-oleoyl-rac-glycerol; MO) is a frequently used building block in the cubic phase. The crystallographic unit of the MO cubic phase is a nanocube with a size of 8.7-13 nm. The nanocube structure is characterized by inter-crossing water channels of approximately 5 nm in diameter, surrounded by MO bilayers approximately 3.5 nm in thickness (Shah et al. 2001).

The MO cubic phase, which is optically isotopic and characterized as a semi-solid gel, can be of two types: the gyroid and diamond phases, with water contents approximately 28%-32% and 32%-40%, respectively (Seddon et al. 2014). The MO cubic phase has various advantages as a drug carrier (Bender et al. 2008). First, MO is biodegradable, and acute toxicity in the cubic phase has not been reported. Moreover, because polar and nonpolar spaces coexist within the MO cubic phase, it can accommodate both water-soluble and oil-soluble drugs.

Moreover, the MO cubic phase can release its payload in response to stimuli, such as temperature changes (Kim 2015b; Zhang and Kim 2016a), pH changes (Kwon and Kim 2011a; Kwon and Kim 2011b; Zhang and Kim 2015b; Kim et al. 2018), photo irradiation (Dai and Kim 2013; Lee and Kim 2014; Kim 2015b; Zhang and Kim 2015a; Park et al. 2018; Park and Kim 2019), redox (Zhang and Kim 2016b; Kwon and Kim 2018), and glucose concentration changes (Kwon and Kim 2016a; Yoon and Kim 2016) as well as the presence of an electric field, when the corresponding stimuli-responsive materials (e.g., polymers) are included into the water channel. For example, the MO cubic phase exhibited a temperature-responsive release property when a polymer with a critical solution temperature (CST) was immobilized in the water channel. The thermosensitive polymer could dramatically alter its conformation when the temperature of the medium changed throughout the CST. Thus, it may play a thermally actuated valve role in the water channel.

Liposomes

The bilayer vesicle is an aqueous core enclosed by a bilayer membrane formed spontaneously by an entropy-driven process when an amphiphile (with a packing parameter value of ~1) is in equilibrium with water (Akbarzadeh et al. 2013). A bilayer vesicle prepared using a phospholipid as the basic building block is called a liposome. Similar to the MO cubic phase, a liposome is known to be a versatile drug carrier and has the advantages of being easy to prepare, non-toxic to the human body, biodegradable, and capable of loading both polar and nonpolar drugs (Budai and Szógyi 2001).

Additionally, the release of the liposome's payload can be controlled by manipulating the membrane composition or modifying the liposome surface. Stimuli-responsive materials, such as polymers, have been immobilized onto a liposomal surface to endow the liposome with responsiveness to stimuli, including temperature changes (Wang and Kim 2014; Guo and Kim 2015b; Kim and Kim 2018), pH changes (Cho et al. 2008; Jo et al. 2008; Hong et al. 2009; Hong and Kim 2010; Hong et al. 2010; Hong et al. 2011; Seo and Kim 2013; Guo and Kim 2017), light (Seo and Kim 2011; Seo and Kim 2012; Seo and Kim 2013; Seo et al. 2013; Guo and Kim 2015a; Kim 2015a), glucose (Hong et al 2009; Jo and Kim 2009; Jo et al. 2009), redox (Kwon and Kim 2017), electric fields (Kim and Kim 2018), and ions (Hong and Kim 2010).

For example, gold nanoparticles were added to a suspension of liposomes bearing a thermosensitive polymer to render the liposomes responsive to near infrared (NIR) irradiation. When the suspension was irradiated with NIR light, heat was generated from the gold nanoparticles owing to the surface plasmon resonance. The heat triggered the liposome's release by immobilizing the polymer chains on the liposomal membrane, which then underwent conformational changes and applied a mechanical force to the liposomal membrane (Guo and Kim 2015b).

Polymer-based vehicle

A thermo-triggered nanogel composed of cinnamoyl Pluronic F127 (CinPlu) and cinnamoyl polymeric beta-cyclodextrin (CinPβCD) was prepared by exploiting the self-assembling property of these components in an aqueous solution. CinPlu and CinPβCD are amphiphilic because the cinnamoyl group is hydrophobic. The degree of doxorubicin release from the nanogel was proportional to the temperature of the release medium. When the temperature was increased, the Pluronic chains dehydrated and became hydrophobic and were thus likely to interact more extensively with the βCD cavities. Hence, the doxorubicin included in the βCD cavities was expelled from the cavities, leading to a thermally triggered release (Wang et al. 2016).

A triple-responsive microgel was developed using the self-assembling property of a polyethyleneimine (PEI)-cinnamic acid (CA) conjugate formed through ionic bonding. Additionally, the conjugate was amphiphilic because the cinnamoyl group was hydrophobic and the polymer chain was hydrophilic. In aqueous solutions, the conjugate could self-assemble into a microgel, which disintegrated and released most of its payload in a burst manner, when the pH value of the medium was changed, or when the temperature was increased above the upper critical solution temperature of the PEI-CA conjugate, or under ultraviolet (UV) irradiation. The pH change of the medium may have led to the breakdown of the ionic bond between PEI and CA, whereas the temperature increase may have increased the solubility of CA and decreased the amphiphilicity of the PEI-CA conjugate. Additionally, UV irradiation could have caused the cis-to-trans isomerization of CA and could have decreased the amphiphilicity of the PEI-CA conjugate (Park and Kim 2017; Kim and Kim 2018; Park and Kim 2019). A reduction-responsive alginate microsphere with cystamine (a disulfide compound) incorporated was prepared by first emulsifying the alginate and cystamine solution mixture, and then cross-linking the alginate chains using calcium ions. Cystamine could also cross-link alginate through ionic bonding because the disulfide compound has an amino group at each terminal. The release of the payload was promoted under reducing conditions, possibly because of breakage of the disulfide bond and a decrease in the cross-linking density (Kwon and Kim 2016b).

Concluding Remarks

Nanocellulose is very promising as a biomaterial for drug delivery, owing to its good biocompatibility, high specific surface area, favorable mechanical properties, and facile chemical modification. Thus, it has been fabricated in the form of microparticles, films, and gels, and proposed as a potential drug carrier mainly for topical, transdermal, and oral administration. With various chemical modifications and physical formulations, pharmaceuticals can be released from nanocellulose-based carriers in sustained- and targeted-release manners. In this paper, various studies on stimuli-responsive cubic phase, liposomal, and polymeric drug vehicles have also been reviewed. In future works, these drug vehicles should be combined with nanocellulose for the development of novel drug carriers.

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