Environmental Chemistry Letters (2021) 19:2043–2055
https://doi.org/10.1007/s10311-021-01182-2

REVIEW

Pharmaceutical and biomedical applications of cellulose nanofibers: a review

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Received: 6 December 2020 / Accepted: 5 January 2021 / Published online: 16 January 2021

Abstract

Most actual medicine materials are derived from fossil fuel resources, thus accentuating pollution and climate change, calling for alternative, sustainable materials. For example, cellulose nanofibers possess high specific surface area, high mechanical strength, reactive surface, biocompatibility, biodegradability, nontoxicity, and low cost. Here, I review pharmaceutical applications of cellulose nanofibers in controlled drug delivery, excipient, wound healing dressing material, anticancer, antimicrobial, and transdermal drug delivery. Methods to prepare cellulose nanofiber-based hydrogels, with a focus on three-dimensional printing, and applications in drug delivery and tissue engineering, are detailed. Cellulose nanofiber films show drug entrapment efficiency of more than 90%, thus facilitating the release of hydrophobic drugs, e.g. indomethacin in 15–30 days and itraconazole up to 3 months. Cellulose nanofibers as excipient are increasing the tensile strength of tablets, and enhancing the stability of emulsion by viscosity modification. Cellulose nanofibers wound dressing revealed high biocompatibility and rapid epithelialization of burn wounds in 11–21 days. Anticancer drug-loaded hydrogels exhibited the highest drug release at pH 7.4 by diffusion. Additionally, I present 14 miscellaneous biomedical applications of cellulose nanofibers for blood vessel, nucleus pulposus replacement, enzyme immobilization, cardiac, ophthalmic, and neural tissue engineering.

Keywords Cellulose nanofibers · Novel excipient · Hydrogel · Wound dressing · Tissue engineering

Abbreviation

TEMPO 2,2,6,6 tetramethylpiperidine1-oxyl

Introduction

The use of polymers has grown significantly in recent years as the pharmaceutical industry shifted away from unsustainable fossil fuel resources and looking toward a softer and more sustainable environmental approach. The increasing consumption of unsustainable fossil fuel resources for biomaterial research causes extreme global pollution and climate change. In today's more eco-conscious society, environmentally friendly biopolymers represent a sustainable alternative to fossil-based resources. Since the past few years, several new molecules have been discovered for the treatment of human ailments. These newly synthesized therapeutic agents have high molecular weight, hydrophobicity, instability, and biocompatibility issues and thus represent notable challenges for the selection of appropriate excipients for safe and effective formulation development. In this regard, cellulose is the amplest, cheap, and sustainable biopolymer in the environment. Cellulose is a principal component of plant cell walls in wood and other plant-based substances. Nanocellulose materials derived from cellulose are non-toxic, biodegradable, and recyclable, with no adverse effects on health and the environment (de Amorim et al. 2020). Cellulose nanofibers isolated from cellulose fibers represent a novel class of nanobiomaterials. Currently, there is an increasing interest in cellulose nanofibers research due to unique properties such as high specific surface area, high mechanical strength, reactive surface, biocompatibility, biodegradability, and nontoxicity including environmental and economic sustainability properties. Due to these specific properties, cellulose nanofibers are used in controlled drug delivery, as a formulation excipient, wound healing dressing materials, anticancer, antimicrobial, transdermal drug delivery and skin tissue engineering (Galkina et al. 2015). Interestingly, crude materials for sustainable production of cellulose nanofibers are almost limitless.

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Turbak and coworkers have first discovered the cellulose nanofibers in the year 1983 (Turbak et al. 1983). There is a famous Swedish saying that 'a dear child has many names,' and this is true for cellulose nanofibers or cellulose nanofibrils. Cellulose nanofiber is known by different names such as micro-fibrillated cellulose, nanofibrillated cellulose, nanocellulose, and cellulose microfibrils. These multiple nomenclatures used in the literature generally lead to misinterpretations and ambiguities. According to the definition by the Technical Association of the Pulp and Paper Industry, cellulose nanofiber is a type of cellulose nanofiber that holds both crystalline regions and amorphous regions, with dimensions of 5–30 nm in width and aspect ratio usually greater than 50. Therefore, cellulose nanofibers need not to be merged with other cellulose materials such as cellulose nanocrystals or microcrystalline cellulose (Thoorens et al. 2014). Cellulose nanofibers are commonly fabricated from cellulosic material obtained from various botanical sources such as wood, hemp, and cotton. The isolation of cellulose nanofibers from cellulosic material is performed by mechanical delamination along with some chemical or enzymatic pretreatment of cellulose fibers. The most common pretreatment steps are milling, pulping, and bleaching. The presence of hydroxyl groups in cellulose helps in the formation of hydrogen bonds. This leads to the formation of micro-fibrillated structure, crystalline as well as amorphous fractions and cohesive properties of cellulose polymer (Mishra et al. 2019). Cellulose nanofibers have gained wide attention as sustainable packaging material for food and pharmaceuticals to increase their shelf life (Löbmann et al. 2017; Qasim et al. 2020). In conclusion, cellulose nanofibers are a novel versatile excipient for the formulation of pharmaceutical dosage forms and an excellent biomaterial for biomedical applications due to their unique physiochemical properties (Fig. 1). This review sets the scene for the discussion of cellulose nanofibers pharmaceutical applications as an excipient in formulation development, controlled drug delivery, anticancer, antimicrobial, and transdermal drug delivery. Furthermore, work published over the past 5 years also recorded for cellulose nanofibers-based hydrogel preparation methods, focusing on the new three-dimensional printing method. Additionally, miscellaneous biomedical applications of cellulose nanofibers are also highlighted.

Fig. 1 Application of cellulose nanofibers. Cellulose nanofibers offer numerous therapeutic applications by incorporating active pharmaceutical ingredients. Drawing was performed using www.biorender.com

Controlled and sustained drug delivery

To fulfill the increased consumption demand of drugs for the large global population, there is a strong need for the search of new alternative sustainable resources to develop safe, effective, and stable pharmaceuticals (Pandey 2019). Controlled and sustained drug delivery of pharmaceutical dosage forms represents a broadly investigated technology in the domain of pharmaceutical sciences. The delayed-release property of pharmaceutical formulations facilitates the increased efficacy of drug therapy by protecting the drug from the gastric environment, enhanced therapeutic activity, reduced toxicity, and bypass of the first-pass metabolism. Therefore, desirable drug delivery rates could be achieved by the incorporation of suitable polymers during formulation development. It inspires researchers to design novel and advanced polymers. Recently, cellulose nanofibers have drawn increasing attention due to their multidimensional properties such as high strength and stiffness, biocompatibility, biodegradability, nontoxicity, and renewability. Therefore, various forms of cellulose nanofibers have been developed, such as spray-dried particles, hydrogels, aerogels, and films. First time, Kolakovic et al. (2012a, b) investigated the ability of cellulose nanofibers to form porous microparticles in the spray drying process and simultaneously to encapsulate six model drugs (indomethacin, metoprolol tartrate, verapamil hydrochloride, nadolol, ibuprofen, and atenolol) inside the cellulose nanofibers carrier. Briefly, drug-loaded cellulose nanofibers microparticles were synthesized by a spray drying method. The microparticles were evaluated for size and morphology, drug loading capacity, and physical state of the entrapped drug as well as dissolution test to explain the release pattern of the drug from the matrix. The results obtained revealed that cellulose nanofibers microparticles facilitate sustained drug release by forming a tight fiber network and thus control drug diffusion from the formulation obtained. Dose dumping is a major drawback of sustained release drug delivery, which causes a large amount of drug released rapidly and leads to toxic effects of the drug on the patient. Therefore, to prevent possible dose dumping in another study, Kolakovic and coworkers developed cellulose nanofibers film-based matrix material for sustained drug

delivery of water-insoluble drugs such as indomethacin (analgesic), itraconazole (antifungal), and beclomethasone dipropionate (anti-inflammatory). The findings of the study demonstrated that indomethacin showed diffusion-limited release for 15–30 days. Similarly, itraconazole and beclomethasone exhibited zero-order release kinetics. The results showed that cellulose nanofibers film builds a tight fiber network and entraps the > 90% drug molecules within the matrix, thus facilitating sustained drug release for the three-month duration (Kolakovic et al. 2012a, b). The sustained release of the drug could be due to differences in solubility of the drug in the dissolution medium and the diverse effects of drug binding to cellulose nanofibers chains. Cellulose nanofibers-based films contain 23% hemicellulose in the form of xylan which might be relevant in novel drug delivery systems such as implants and topical skin patches. The carboxylic acid groups present in xylan impart a negative charge to cellulose nanofibers surface which may lead to repulsion between fiber or film layers, resulting in enhanced water permeation and more accelerated drug expulsion (Kolakovic et al. 2012a, b). Cellulose nanofibers, when blended with the surfactants, create highly stable air bubbles and dry foams. Utilizing this intrinsic property, Svagan et al. (2016) modify the release kinetics of the reference drug riboflavin. They have developed wet foams by incorporating cationic cellulose nanofibers and surface-active agents, lauric acid sodium salt together. Furthermore, the drug was suspended, in the wet stable foams followed by drying to get dry foams. This yields drug-loaded flexible cellular solid materials that showed diffusion-controlled drug release when subjected to drug release study.

In another study, Valo et al. (2013) developed drug-loaded nanoparticles enclosed in four different cellulose nanofiber aerogel systems for controlled drug delivery. They have reported that the cellulose nanofibers type affects the drug release pattern. Paulraj et al. (2017) have described the formulation of bioinspired microcapsules. The microcapsules composed of pectin, xyloglucan, and the layer fabricated cationic cellulose nanofibers-by-layer technique. The findings of in vivo evaluation study suggested that capsules have shown a stimuli-responsive permeability phenomenon and biocompatibility. Additionally, the viable cell staining investigation exhibited that the non-toxic microcapsules have the potential for cell proliferation. Thus, microcapsules proved themselves clinically worthful for colon-targeted drug delivery.

Novel formulation excipient

First time, Kolakovic et al. (2011) evaluated the property of cellulose nanofibers as a novel tableting material. In this investigation, the physical and mechanical attributes of spray-dried cellulose nanofibers have been studied and compared with the commonly used tableting material microcrystalline cellulose. Because chemical forms of both microcrystalline cellulose and cellulose nanofibers are almost indistinguishable, besides they differ in physical and mechanical properties. The novel spray-dried cellulose nanofibers have been evaluated for various density parameters, moisture content, and flowability characteristics. Additionally, tablet formulation also developed using cellulose nanofibers alone and in combination with microcrystalline cellulose by direct compression and wet granulation technique to evaluate the tensile strength. Results showed that cellulose nanofibers-based tablet formulation is possible by both wet granulation and direct compression because cellulose nanofibers particles displayed the ability to resist permanent deformation as well as less ductile characteristics. Drug release studies revealed immediate drug release (94% of the drug after 4 m) from direct compression tablets prepared with cellulose nanofibers, while wet granulated formulation did not show any notable variation.

Cellulose nanofibers also play a pivot role in formulation stabilization as a viscosity modifier. Paukkonen et al. (2017a, b) developed biopolymer-based oil-in-water emulsion formulations for sustained drug delivery of poorly water-soluble drugs naproxen and ibuprofen. Here, class II hydrophobin protein (*Trichoderma reesei)* was incorporated as an emulsifying agent to stabilize the oil/water interfaces of the emulsion droplets in the continuous aqueous phase. In the next step, cellulose nanofibers were also incorporated as a viscosity modifier to enhance the stability of the emulsions and encapsulate protein-coated oil droplets in the cellulose nanofibers-based fiber network. The potential of both native and oxidized cellulose nanofibers has been evaluated for this purpose. Results showed that 0.15% of oxidized cellulose nanofibers are optimal for sustained drug release formulation. Similarly, native cellulose nanofibers combined with hydrophobin proteins displayed a rapid drug release for naproxen and ibuprofen. The results delineate that both native and oxidized cellulose nanofibers grades are suitable emulsion stabilizers with low concentration for sustained and immediate drug release formulations, which may be an advantage over conventional surfactants used in pharmaceutical emulsion formulations.

Wound healing dressing material

The wound healing process consists of different phases, such as granulation, collagenization, collagen maturation, and scar maturation. Another relevant biological event angiogenesis also plays a vital role in the process of wound healing, as newly generated blood vessels facilitate the transportation of oxygen and essential nutrients to cells at the targeted site of the wound (Fig. 2). The bacterial infection in wounds

represents a severe obstacle for clinicians, especially in the wounds caused by thermal shock and in patients undergoing oncological therapy. Notwithstanding recent advancements in wound treatment, optimal strategies to promote wound healing and avoidance of bacterial infection are lacking. In an alternative approach, wound healing can be improved via an accelerated tissue regeneration of damaged tissue, especially in case of wounds caused by clinical surgery.

To promote tissue regeneration in surgical wounds, the use of human adipose mesenchymal stem cells has been recognized as an effective approach (Reckhenrich et al. 2014). Nevertheless, the efficiency of stem cell therapy depends on the targeted delivery of cells at the target site. Mertaniemi et al. (2016) utilized the plant-derived cellulose nanofibers with glutaraldehyde cross-linking to fabricate the human adipose mesenchymal stem cells-loaded threads to suture the wounds. Here, the cross-linking of cellulose nanofibers with glutaraldehyde enhances their mechanical strength by forming bridges within different threads. Interestingly, the generated threads were strong enough to pass through different tissues. Moreover, cellulose nanofibers cross-linked threads offer a suitable environment of adhering, migrate, and proliferate to stem cells. Results of the ex vivo suturing study revealed that cross-linked cellulose nanofibers sustained the human adipose mesenchymal stem cells uniform profile and functionality. In conclusion, in vivo human adipose mesenchymal stem cells may have the ability to engraft the sutured tissue accelerating wound healing.

Cellulose nanofibers have been studied as a dressing material for non-healing and chronic wounds due to their huge capacity to absorb fluids and to form translucent layers. Moreover, the translucency of cellulose nanofibers film enables one to assess the development of the wound without removing the dressing (Sun et al. 2017). The wound healing potential of cellulose nanofibers was evaluated in a clinical trial on burn patients (Hakkarainen et al. 2016). Briefly, a cellulose nanofibers wound dressing was applied to split-thickness skin graft donor sites. The cellulose nanofibers dressing showed rapid epithelialization between 11 and 21 days and seemed to be effective for skin graft donor site treatment. These attributes of cellulose nanofibers dressing may be due to their biocompatibility, easy and prolonged attachment to the wound bed until complete healing.

In another study, pretreated bleached sulfite cellulose nanofibers, obtained from softwood dissolving pulp, exhibited hemostatic potential when cross-linked with calcium ions, particularly when incorporated with kaolin or collagen (Basu et al. 2017a, b). Similarly, Powell et al. (2014) fabricated cellulose nanofibers derived from *Pinus radiata* pulp fibers in the form of films. These cellulose nanofibers abolish the growth of major wound pathogen *Pseudomonas aeruginosa*, resulting in higher bactericidal effect than commercial wound dressing product Aquacel®. Similarly, the same cellulose nanofibers in other pharmaceutical formulations such as suspension and aerogels revealed significant activity against *Pseudomonas aeruginosa* PAO1. The wound

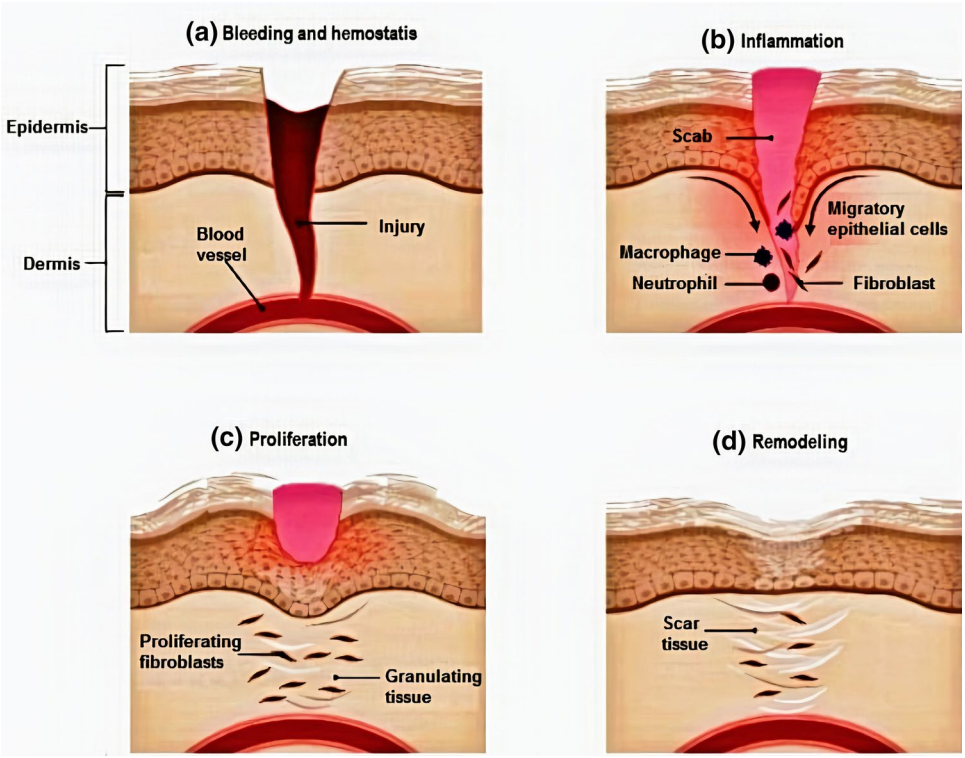

Fig. 2 **a** A wound causes the formation of the clot (dark red area); **b** recruitment of macrophages (blue) and neutrophils (round blue); **c** collagen and fibroblasts rebuilt the tissue inducing endothelial cells proliferation and vessel generation; **d** skin stem cells generate mature skin cells to obtain the wound closing. (Drawing was performed using Web site http://www.biorender.com)

healing properties of cellulose nanofibers can be improved by chemical modifications and by attaching various ions. Therefore, to explore this strategy, Basu et al. (2018) synthesized softwood pulp-derived cellulose nanofibers tempered by cross-linking agents, such as divalent calcium and copper ions. Results obtained showed that cross-linked hydrogels were more effective against *Pseudomonas aeruginosa*, while copper-cross-linked hydrogel formulations exhibited an antibacterial effect against *Staphylococcus epidermidis*. Additionally, Ca2 + cross-linked cellulose nanofibers hydrogels serve as a carrier for drug delivery applications in chronic wound healing.

Transdermal drug delivery

Cellulose nanofibers serve as carriers for topical and transdermal drug delivery of antibiotics that cannot be orally administered to the patients, for example, a gentamycin-grafted nanocellulose sponge formulation, fabricated by multi-cross-linking of cellulose nanofibers with cellulose acetoacetate and (3-aminopropyl)triethoxysilane. The developed nanocellulose sponge formulation displayed remarkable antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus* (Xiao et al. 2018). Similarly, Liu et al. (2018a, b) fabricated a hydrogel drug delivery system, composed of softwood kraft pulp-derived cellulose nanofibers. These cellulose nanofibers were synthesized by '2,2,6,6 tetramethylpiperidine1-oxyl (TEMPO)'-mediated oxidation and polydopamine loaded with tetracycline, an antibiotic. The results showed that topical application of hydrogel on the excision wound of rats exhibited significant wound healing effects and effective against *Escherichia coli* and *Staphylococcus aureus*. Another unique approach for combating bacterial infections involves delivering antibacterial peptides, such as nisin, obtained from *the bacterium Lactococcus lactis*. Weishaupt et al. (2018) incorporated peptide nisin into '2,2,6,6-tetramethylpiperidine1-oxyl (TEMPO)'-oxidized nanofibrillated cellulose via electrostatic attraction between the negatively charged cellulose nanofibers surface and the positively charged nisin molecules. Nisin negatively charged cellulose nanofibers composites exhibited significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus* comparable to free nisin. In another study, Kontogiannopoulos et al. (2011) developed electrospun cellulose acetate nanofibrous meshes for potential wound dressings by incorporating potential antimicrobials and wound healing phytoconstituents such as alkannin, shikonin, and their derivatives. The result showed high drug entrapment efficiencies of nanofibrous meshes, ranging from 74 to 95%, and appropriate drug release profiles. It renders cellulose acetate nanofibrous meshes as remarkable alkannin, shikonin, and wound healing dressings.

Anticancer drug delivery

Cellulose nanofibers possess novel properties such as good flexibility, good elasticity, low density, low toxicity, and a relatively reactive surface for grafting specific groups. Thus, it represents the potential for an effective carrier for controlled drug delivery. Therefore, to explore these properties of cellulose nanofibers, Bhandari et al. (2017) fabricated cellulose nanofibers-based aerogel loaded with hydrophilic anticancer drug bendamustine. Bendamustine is an alkylating antineoplastic agent that is used in the treatment of chronic lymphocytic leukemia and non-Hodgkin's lymphoma. Cellulose nanofibers-based hydrogel exhibited pH-dependent swelling phenomenon being maximal at pH 7.4 and minimum at pH 1.2 in vitro. Prominently, the increased swelling at pH 7.4 triggers the increased drug release. The authors reported that drug-loaded cellulose nanofibers hydrogel showed peak plasma concentration in 5 h after oral administration and remain bioavailable up to 24 h after administration. This kinetic profile unquestionably reveals the excellent potential of cellulose nanofiber hydrogel in improving the drug release pattern. Moreover, it delineates the probability to develop a controlled drug delivery approach for the antineoplastic agents. Cellulose nanofibers are frequently isolated from different agricultural biomass and renewable waste. In this category, lemongrass waste after oil extraction is of limited use, such as animal feed and composting, which is not a cost-effective approach. The eco-friendly, enzyme-mediated cellulose nanofiber green synthesis using agricultural waste represents a cost-effective strategy to utilize agriculture waste (Filson et al. 2009; Kumari et al. 2019). Recently, Kumari et al. (2020) have reported an application of lemongrass waste-isolated cellulose nanofibers for controlled drug delivery of camptothecin. Camptothecin is a hydrophobic potent anticancer agent that acts by inhibiting topoisomerase I during the *S*-phase of the cell cycle. Camptothecin active lactone form rapidly hydrolyzes to the inactive carboxylate form under physiological conditions, thus limiting the delivery and therapeutic application of camptothecin in cancer therapy (Pandey A. 2020). Briefly, the different composition formulations of camptothecin-loaded cellulose nanofibers complex (10:3, 10:5, and 10:7) were prepared and evaluated for encapsulation efficiency, binding capacity with cellulose nanofibers, and in vitro drug release profile at different physiological pH conditions. Results showed that in the 10:3 composition ratios of cellulose nanofibers, camptothecin exhibited the highest encapsulation efficiency and significant binding with cellulose nanofibers. Further, the highest extended-release profile was observed at pH 7.4, suggesting the release of the drug via a diffusion mechanism. In conclusion, the results

delineate that that enzyme-mediated cellulose nanofiber represents a novel carrier for the controlled drug release formulation without any synthetic excipients.

Cellulose nanofibers have also augmented interest in the development of colon-specific drug delivery systems for the treatment of colon cancer and inflammatory diseases. Usually, films derived from natural polymers are incorporated, but these films lack adequate mechanical barriers and thermal attributes. Therefore, to overcome these limitations and to enhance the low oral bioavailability of anticancer drug methotrexate, Meneguin et al. (2017) fabricated nanocomposite films of resistant starch and pectin by incorporating cellulose nanofibers. The addition of cellulose nanofibers to polymeric film significantly improved the film strength, perhaps due to the intrinsic rigidity of cellulose nanofibers. Furthermore, cellulose nanofibers improved the film mucoadhesion property when evaluated in an ex vivo bioadhesion test by employing porcine colonic mucosa sections. Additionally, the barrier properties of films also improved toward water penetration because high water permeability decreases the film stability on the colon mucosa and alter drug release. Subsequently, the results of an in vitro study exhibited that cellulose nanofibers-enriched polymeric film notably enhances the methotrexate delivery from the film.

Metastasis is the major obstacle in the successful cancer therapy of many types of melanoma because extracellular matrix degradation plays a vital role in cancer metastasis. It has been reported that nanofibers can mimic the structure of extracellular matrix proteins and restrict the cancer cell movement if they are inserted around the tumor region (Kumar et al. 2015). Based on these considerations, Nurani et al. (2017) fabricated cellulose nanofibers and examined their anti-metastatic potential. Due to the ability to form matrices, cellulose nanofibers are also loaded with the anticancer drug metformin. Briefly, metformin surface-modified cellulose nanofibers were developed by the attachment of metformin on the surface of cellulose nanofibers through electrostatic interaction. The findings of the study suggest that metformin-loaded cellulose nanofibers significantly reduced the migration of melanoma cells. Additionally, the adequate adhesion of the melanoma cells with metformin-loaded cellulose nanofibers reduces the melanoma cell invasion. Therefore, metformin surface-modified cellulose nanofibers offer a unique strategy for the inhibition of melanoma metastasis.

In another study, injectable cellulose nanofiber gel of anticancer drug doxorubicin was developed for localized chemotherapy of melanoma and to overcome melanoma cell movement. Alizadeh et al. (2018) formulated doxorubicin surface-modified injectable gel by the electrostatic attachment of doxorubicin molecules on the surface of cellulose nanofibers. The prepared gel formulation showed a nanofibrous structure confirmed by using field emission scanning electron microscopy. Doxorubicin cellulose nanofiber gel exhibited a sustained drug release pattern when evaluated in vitro at different physiological pH ranges (6.5–7.4), thus validating its promising application for localized chemotherapy. The results of the cytotoxicity study proved that gel formulation exerts a more cytotoxic effect against melanoma cancer cells than the free drug. Moreover, it also significantly suppresses melanoma cancer cell migration. This attribute may be due to the physical barrier property of cellulose nanofibers.

Antimicrobial drug delivery

Cellulose nanofibers avail a permeable porous network structure in the fabrication of biomaterials. This porous network is useful for the effective delivery of therapeutic agents into the wound. Moreover, it also serves as an efficient physical barrier against any external infection (Andersen et al. 2007). However, cellulose nanofibers possess no antimicrobial activity and cannot limit wound infection. Cellulose nanofibers-based antimicrobial biomaterials are fabricated by the combination of cellulose nanofibers and antimicrobial agents by utilizing physical or chemical strategies. The literature reveals that among various antimicrobial substances, silver has been most extensively investigated for antibacterial activity and practiced for several decades to prevent microbial infection (Rai et al. 2009). To explore the antibacterial potential of silver nanoparticles, Martins et al. (2012) manufactured cellulose nanofibers and silver nanoparticles-based composite, using an electrostatic assembly method. Here, polyelectrolytes were used as macromolecular linkers between cellulose nanofibers and silver nanoparticles. Briefly, fluorescent silver nanoparticles were immersed in cellulose nanofibers materials dispersed in poly(methacrylic acid). Results showed that fluorescent silver nanoparticles provided fluorescence as well as antibacterial activities for the composites. In another study, Liu et al. (2013, 2014) described the synthesis of sodium alginate-based cellulose nanofibers antibacterial composites prepared with the addition of antibacterial agents such as chitosan–benzalkonium chloride or chitosan–methylisothiazolinone. Both nanospherical shape antibacterial agents adsorbed on the surface of cellulose nanofibers for a few minutes, under the influence of hydrogen bonds and electrostatic interactions. These composites exhibited adequate mechanical strength and significant antibacterial activity against *Staphylococcus aureus*. In another novel approach, Roemhild et al. (2013) have investigated especially the antibacterial effect of cellulose nanofibers with surface derivatization. Results showed that electrospun nanofibers composed of amino-modified cellulose nanofibers revealed remarkable antimicrobial

activity against *Staphylococcus aureus and Klebsiella pneumonia* strains.

Cellulose nanofibers-based hydrogels

Hydrogel was first invented in the 1960s, enriched with the capability of retaining the aqueous environment in a three-dimensional network, and represents a class of drug carrier materials for pharmaceutical and biomedical applications. A hydrogel is a heterogeneous combination of two (or more) phases, among which the dispersed phase is water and the solid phase is a solid three-dimensional network (Nascimento et al. 2018). Hydrogels are multidimensional materials as they can self-assemble into different forms including microgels/microspheres, nanoparticles/nanogels, films and membranes, fibers/nanofibers, and sponges/nanosponges, thereby resulting in the formation of 2D and 3D networks such as spheres, scaffolds, ribbons, and sheets (Crini et al. 2019). Generally, hydrogels synthesized by chemical reaction of a mixture of monomers and cross-linkers have low tensile strength and toughness, while hydrophilic cellulose nanofibers with the charged interface have the potential to be used as strengthening agents or even building blocks of hydrogels. Cellulose nanofibers-based hydrogels are biodegradable and highly hydrophilic and possess good mechanical strength. Cellulose nanofibers-based hydrogels are extensively utilized in wound dressings, drug delivery, tissue engineering, hygiene products, food additives, and numerous biomedical purposes (Ahmed 2015; Sharma et al. 2018). Hydrogels with self-healing attributes provide significant features such as the less short invasive delivery mode by injection at the target site without gel fragmentation. Self-healing hydrogels with strong tissue adhesion properties remarkably promote wound healing. They also act as a carrier for the delivery of therapeutic agents to the damaged tissue area, contributing to a local treatment effect. Moreover, the self-healing hydrogels may provide an extracellular matrix-like 3D environment for embedded cells and thus hold promises for tissue engineering applications (Cheng et al. 2019). In an eye-catching work, Laurén et al. (2014) have demonstrated that an injectable technetium-99m-labeled cellulose nanofibers hydrogel, providing for the identification of the localization of cellulose nanofibers hydrogels and time-dependent in vivo investigation of drug delivery. In another study, Paukkonen et al. (2017a, b) have demonstrated the drug-releasing performance of (2,2,6,6-tetramethylpiperidine-oxyl)-oxidized cellulose nanofibers hydrogels subjected to freeze-drying. Results showed that lyophilization has no effect on drug release pattern from redispersed cellulose nanofibers hydrogel formulation. Thus, the oxidized cellulose nanofibers hydrogels are stable in dry form and only reconstituted when required, ultimately beneficial to patient administration. Since the last decade, cellulose nanofibers-based stimuli-responsive hydrogels gained the attention of researchers because they offer a need-based drug release toward specific stimuli such as pH and temperature. For example, Masruchin et al. (2018) reported the synthesis of twofold sensitive composite hydrogels constituted of '2,2,6,6-tetramethylpiperidine-oxyl TEMPO'-oxidized cellulose nanofibers and thermolabile poly(N-isopropyl acrylamide) for drug release. Briefly, the pH-responsive characteristics of such hydrogels can be obtained by regulating the carboxyl charge level of the cellulose nanofibers, and the swelling ratio of hydrogels is temperature-dependent. The literature regarding the addition of cellulose nanofibers in hydrogel is relatively rare. Very recently, cellulose nanofibers (0.5–4.5 wt%) were incorporated into methacrylate-functionalized carboxymethyl cellulose followed by ultraviolet cross-linking to generate mechanically robust hydrogels. The fibrous structure of cellulose nanofibers may presumably change the rheological behavior and modify the self-healing ability of the hydrogel network (Hossen et al. 2018). Table 1 summarizes the various approaches for the direct incorporation of cellulose nanofibers in different polymer matrices for hydrogel preparation, with a focus on current new methods such as 3D printing including their specific pharmaceutical and biomedical applications.

Miscellaneous biomedical applications

Cellulose nanofibers have outstanding properties such as a high aspect ratio, a low density, high mechanical properties, tensile strength, stability, biocompatibility which strengthen cellulose nanofiber research and development as a substitute for medical biomaterials, for replacement of blood vessels, soft tissue, and nucleus pulpous. The research investigations of cellulose nanofibers as blood vessel replacement are most attractive and useful, as revealed from the results in various preclinical experiments before clinical research. Similarly, the studies on cellulose nanofibers as soft tissue, cardiac tissue, and nucleus pulpous replacement biomaterial and most reports are still in the primary stage and chiefly concentrate on the comparison of various properties between cellulose nanofibers-based biomaterials and real organs. The search for biomaterials to be employed for soft tissue replacement should not only provide comparable mechanical properties as the tissue it replaces but also enhance life span, biocompatibility, and stability. Cellulose nanofibers also exhibit excellent enzyme immobilization properties facilitated by a high number of functional groups on the surface support. Table 2 summarizes some biomedical applications of cellulose nanofibers.

Table 1 Preparation methods for cellulose nanofibers-based hydrogels and their applications in drug delivery, wound dressing, and tissue engineering, with a focus on current new methods such as 3D printing

Materials	Functional groups of cellulose nanofibers	Preparation method for hydrogel	Application	References
Cellulose nanofibers	Carboxylic acid groups, quaternary ammonium groups	Homogenization	Drug delivery	Hujaya et al. (2018)
Cellulose nanofibers	Carboxylic acid groups (by TEMPO oxidation)	Metal cation cross-linking, freeze-drying	Drug delivery	Paukkonen et al. (2017a, b)
Cellulose nanofibers	Carboxylic acid groups (by TEMPO oxidation)	Metal cation cross-linking, coextrusion	Drug delivery	Zhang et al. (2018)
Cellulose nanofibers, xyloglucan, pectin	Quaternary ammonium groups	Homogenization	Drug delivery	Paulraj et al. (2018)
Cellulose nanofibers, poly(N-isopropylacrylamide)	Carboxylic acid groups (by TEMPO oxidation)	Free radical polymerization	Drug delivery	Masruchin et al. (2018)
Cellulose nanofibers	Carboxylic acid groups (by TEMPO oxidation)	Metal cation cross-linking	Wound dressing	Basu et al. (2017)
Cellulose nanofibers	Carboxylic acid groups (by TEMPO oxidation)	3D printing	Wound dressing	Xu et al. (2018)
Cellulose nanofibers, gelatin, silver amide nanoparticles	Carboxylic acid groups (by TEMPO oxidation)	Homogenization	Wound dressing	Liu et al. (2018a, b)
Cellulose nanofibers, hemicellulose	Carboxylic acid groups (by TEMPO oxidation)	In situ sorption	Wound dressing	Liu et al. (2016)
Cellulose nanofibers	None (without pretreatment)	Controlled fibrillation and homogenization process	Wound dressing	Koivuniemi et al. (2020)
Cellulose nanofibers, polydopamine	Carboxylic acid groups (by TEM PO oxidation)	Metal cation cross-linking	Wound dressing	Liu et al. (2018a, b)
Cellulose nanofibers	Carboxylic acid groups (by TEMPO oxidation)	Metal cation cross-linking	Tissue engineering	Zander et al. (2014)
Cellulose nanofibers, polyacrylamide	None (by delignification)	Free radical polymerization	Tissue engineering	Kong et al. (2018)
Cellulose nanofibers	Carboxylate moieties (by enzymatic treatment)	Homogenization, neutralization	Tissue engineering	Doench et al. (2018)
Cellulose nanofibers, gelatin methacrylamide	None (without pretreatment)	3D printing	Tissue engineering	Shin et al. (2017)
Cellulose nanofibers, alginate	None (by enzymatic treatment)	3D printing	Tissue engineering	Markstedt et al. (2015)
Cellulose nanofibers, alginate	_	3D printing	Tissue engineering	Martínez Ávila et al. (2016)
Cellulose nanofibers, alginate	Carboxylic acid groups (by TEMPO oxidation)	3D printing	Tissue engineering	Abouzeid et al. (2018)
Cellulose nanofibers, alginate or hyaluronic acid	None (by enzymatic treatment)	3D printing	Tissue engineering	Nguyen et al. (2017)
Cellulose nanofibers, chitosan	Carboxylic acid groups (by TEMPO oxidation)	Network formation through a dynamic Schiff base reaction	Neural regeneration effects	Cheng et al. (2019)
Cellulose nanofibers/polyvinyl alcohol/sodium alginate	Carboxyl and aldehyde moieties	3D printing	Bone tissue engineering	Abouzeid et al. (2020)

TEMPO 2,2,6,6-tetramethylpiperidine1-oxyl

Conclusion

This review is a collection of literature about potential pharmaceutical applications of cellulose nanofibers such as controlled and sustained drug delivery, novel formulation excipient, anticancer, transdermal, antimicrobial drug delivery, and wound healing dressing material. Cellulose nanofibers-based hydrogels also reviewed for effective and

Table 2 Miscellaneous biomedical applications of cellulose nanofibers and advantages related to crucial attributes of cellulose nanofibers such as physical mechanical properties, high surface area, biocompatibility, and biodegradability

Materials	Advantages	Application	References
Cellulose nanofibers, polyurethane	Improved elastic, physical, mechanical properties, and low thrombogenicity	Blood vessel replacement	Cherian et al. (2011)
Cellulose nanofibers	Improved mechanical properties and stress relaxation behavior	Soft tissue ligament, meniscus, and cartilage replacements	Mathew et al. (2012)
Carboxy-methylated cellulose nanofibers hydrogel	Adequate swelling ratio and improved mechanical properties	Nucleus pulposus replacement	Eyholzer et al. (2011)
Cellulose nanofibers /polypyrrole composite	Effective removal of small uremic toxins in blood, improved thrombogenic properties	Hemodialysis membrane	Ferraz et al. (2013)
Cellulose nanofibers, polyvinyl alcohol-based hydrogel	High water content and similar mechanical properties to native tissues	Ophthalmic tissue engineering	Tummala et al.(2016)
TEMPO-oxidized cellulose nanofibers	Remarkable stability and good biocompatibility with cardiac myoblast cells	Cardiac tissue engineering	Ajdary et al. (2019)
Cellulose nanofibers, poly(lactic acid)) and poly(butylene succinate)	Sustainable biodegradation behavior and improved mechanical property	Vascular tissue regeneration	Abudula et al. (2018)
Cellulose nanofibers-based ink for 3D printing	Realistic mimicking of actual neural tissue	Neural tissue engineering for brain study	Kuzmenko et al. (2018)
Cellulose nanofibers-based hydrogel	Excellent rheological properties and cellular biocompatibility	Three-dimensional liver cell culture	Bhattacharya et al. (2012)
Cellulose nanofibers, ethylene diamine-based nanoparticles	Improved biocompatibility	Drug delivery in colorectal cancer	Chenampulli et al. (2019) and Makvandi et al. (2020)
Cellulose nanofibers matrix	Support structure in enzyme immobilization	Biocatalyst	Sulaiman et al. (2015)
Cellulose nanofibers	Immobilization and recognition of enzyme/protein	Alkaline phosphatase, anti-hydrocortisone antibody	Arola et al. (2012)
Cellulose nanofibers/polypyrrole composite	High surface area of porous structure	Capture of DNA oligomers	Razaq et al. (2011)
TEMPO-oxidized cellulose nanofibers, alginate gel	Non-cytotoxic, improved bioadhesion	Tissue repair or wound healing applications	Siqueira et al. (2019)

TEMPO: 2,2,6,6-tetramethylpiperidine1-oxyl

biocompatible drug delivery including skin and bone tissue engineering. Furthermore, biomedical applications of cellulose nanofibers recorded for blood vessel, nucleus pulposus replacement, enzyme immobilization, ophthalmic, cardiac, and neural tissue engineering. Cellulose nanofibers are enriched with significant mechanical properties, a highly reactive surface including biocompatibility, and biodegradability, which enable cellulose nanofibers a promising biomaterial for pharmaceutical and biomedical applications. However, most of the cellulose nanofibers-based hydrogel's therapeutic applications in the biomedical domain are at the laboratory-level research. Limited clinical trial investigations have been performed for the in vitro treatment. For example, Hakkarainen et al. (2016) studied the potential of the cellulose nanofibers wound dressing in a clinical trial on burn patients. Findings suggested that cellulose nanofibers wound dressing does not exhibit any allergic signs or inflammatory response. Recently, Koivuniemi et al. (2020) have performed a single-center clinical trial on 24 enrolled patients to evaluate the performance of cellulose nanofibers-based wound dressing for skin graft donor site wound healing. The outcomes revealed that cellulose nanofibers dressing exerts a significant wound healing effect comparable to copolymer dressing. These clinical investigations delineate the potential of cellulose nanofiber dressing as a novel, green sustainable material for wound treatment without animal or human-origin components. Apart from this, cellulose nanofibers toxicology assessment is also a critical issue for its frequent clinical applications. Technology transfer or large-scale production of cellulose nanofibers-based hydrogels is also the main obstacle in their manufacturing. Recently, the novel 3D printing technique has emerged as a likely pathway to ensure the scaling up of the fabrication of cellulose nanofibers-based hydrogels. This review

demonstrated that the cellulose nanofibers alone and cellulose nanofibers-based hydrogels have great potential in numerous pharmaceuticals as well as biomedical applications, and they have paved the way for more advancement in natural biomaterial research investigations. From both scientific and economic viewpoints, cellulose nanofibers, the resource and boon provided by nature, are on the threshold of a breakthrough driven by recent extraordinary activities in the field of biomedical applications.

Author contributions Not applicable.

Funding Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The author has declared no conflict of interest.

Consent to participate Not applicable.

Consent for publication I hereby give my consent for the publication of manuscript.

Ethical approval Not applicable.

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