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Nanocellulose in Drug Delivery Systems: A Comprehensive Review

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ABSTRACT

Research in medicinal chemistry lays a substantial emphasis on the development of efficient drug delivery techniques that make use of nanomaterials that are both biocompatible and inert. In comparison to the numerous primary materials that are now accessible, nanocrystalline cellulose stands out due to its biocompatibility and inert qualities. The surface of the object may also be modified using a wide range of various manufacturing processes. During the course of our investigation, we have gathered data on a number of different types of nanocellulose as well as the applications of nanocellulose that are associated with drug delivery systems. Throughout the course of this investigation, the key subjects of discussion include the methods of manufacturing nanocellulose as well as its applications in oral, transdermal, and localised drug delivery systems. Furthermore, it analyses the possibilities and restrictions that are given by nanocellulose that has been surface-modified.Because of their low cost, the fact that they may be reused, and the fact that they are biodegradable, natural polymers have been the subject of recent years' worth of substantial developments in the exploration of diverse uses.

Keywords: Nanocellulose, Transdermal drug delivery systems, Localized drug delivery systems

1 Introduction

In recent years, significant advancements have been made in exploring various applications of natural polymers, thanks to their affordability, reusability, and biodegradability. This has highlighted collagen, starch, alginate, gelatin, chitosan, elastin, and cellulose as promising biomaterials [1,2]. In drug delivery systems, the use of biocompatible, biodegradable, and bioavailable excipients is crucial [3].

Cellulosic nanomaterials, in particular, have garnered significant scientific interest due to their exceptional chemical, mechanical, structural, and biological properties, along with their high biocompatibility, biodegradability, and bioavailability [4].

Cellulose, the primary component of plant cell walls, is the most abundant organic compound in the world due to its structural integrity. It constitutes about 40% of all organic matter on Earth, with photosynthesis producing 75 to 100 billion tonnes annually [5]. Cellulose is also synthesized by algae, tunicates, and certain bacteria [6,7]. It can be extracted from any plant, including flax, bamboo, hemp, jute, cotton, wheat, kenaf, bagasse, ramie, sisal, softwood, hardwood, and coconut [8,9]. Cellulose is a natural polymer composed of long chains of glucose. Each cellulose fibril contains linear, water-insoluble polysaccharides made up of several hundred to thousands of β-1,4-anhydro-D-glucopyranose units connected by β-D-glycosidic bonds (1→4), as illustrated in Fig. 1. Each glucose unit has three hydroxyl groups at carbon positions C2, C3, and C6, with the primary hydroxyl group at C6 being more reactive than the others [10]. Cellulose consists of varying proportions of crystalline (highly ordered) and amorphous (disordered) regions, depending on the plant species source. Research by Nishiyama et al. revealed that native cellulose is a combination of two crystalline allomorphs, cellulose

Iα and Iβ [11, 12]. The hydroxyl groups' presence and ability to form hydrogen bonds significantly influence the crystalline structure and are crucial to cellulose's physical properties [13]. Cellulose indirectly plays a significant role in the human food cycle. Additionally, various industries such as veterinary foods, wood and paper, textiles and apparel, cosmetics, and pharmaceuticals utilize this polymer flexibly [13]. In pharmaceuticals, it is commonly used as an excipient. Recent and emerging applications of nanocellulose include its use in nanocomposites, Pickering emulsifiers, wood adhesives, and various new and developing biomedical applications. Finally, the challenges and potential of emerging nanocellulose-based materials are discussed [14]. There has been a growing focus on utilizing cellulose-based nanomaterials for environmental remediation, especially in water and wastewater treatment. These materials have been actively researched for various water treatment applications [16, 17]. Various derivatives have been developed to address solubility issues in typical solvents, making modification easy. In the 21st century, nanotechnology advancements have led to new insights into cellulose nano-sizing. Although numerous reviews have been published with a growing focus on the material, none can be deemed comprehensive due to the extensive body of work available.

In this review, we have outlined the use of nanocellulose in drug delivery systems, focusing on research not covered in recent reviews by Khine and Stenzel and Salimi et al. which discussed types of nanocellulose and its applications in drug delivery [18, 19].

Nanocellulose finds extensive use in various drug delivery systems such as nanoparticles, microparticles, tablets, aerogels, hydrogels, and in designing membrane drug delivery systems. Incorporating nanocellulose into drug formulations as a vehicle can effectively regulate drug release and enhance localized drug delivery, thus reducing overall consumption [20]. Its high surface-to-volume ratio facilitates improved cell binding and absorption, enhancing the effectiveness of these delivery systems [21]. Moreover, nanocellulose has demonstrated low toxicity risks, broadening its applications for various purposes [22].

2 Type of nanocellulose

Nanocellulose refers to materials derived from cellulose within the nanometer scale range. Moon et al. provided a detailed classification of cellulose particles [11]. Primarily, the Nanofibers class includes CNC or NCC, CNF or NFC, and BNC, while nanostructured materials comprise MCC and microfibrils (Fig. 2) [23, 24]. These types of nanocellulose share similar composition but differ in morphology, particle size, or crystallinity due to various sources and extraction methods [25, 26].

2.1 Cellulose nanofibers

Nanocellulose in the form of NCC is among the most extensively studied types. Ranby first reported the colloidal sulfuric acid-catalyzed degradation of cellulose fibers in 1951 [27]. NCC has been prepared from various sources including wood, cotton, sisal, tunicate, bacterial, microcrystalline cellulose, olive tree, and from biomass and waste materials [28–35]. NCC obtained from the acid hydrolysis of native cellulose exhibits various morphologies depending on the source and hydrolysis conditions [36]. The separation of NCC from cellulose relies on controlled sulfuric acid hydrolysis, yielding a relatively stable suspension [37]. Acid treatment primarily targets the amorphous regions of native cellulose, resulting in enhanced crystallinity. Apart from sulfuric acid, high-temperature hydrochloric acid, hydrobromic acid, and phosphoric acid have also been utilized to produce aqueous solutions at elevated temperatures. Arai et al. and Wang et al. have explored the production of cellulose nanomaterials with high crystallinity using acid hydrolysis [38, 39].

The typical acid hydrolysis process for cellulose involves treating cellulose with acids at high temperatures while

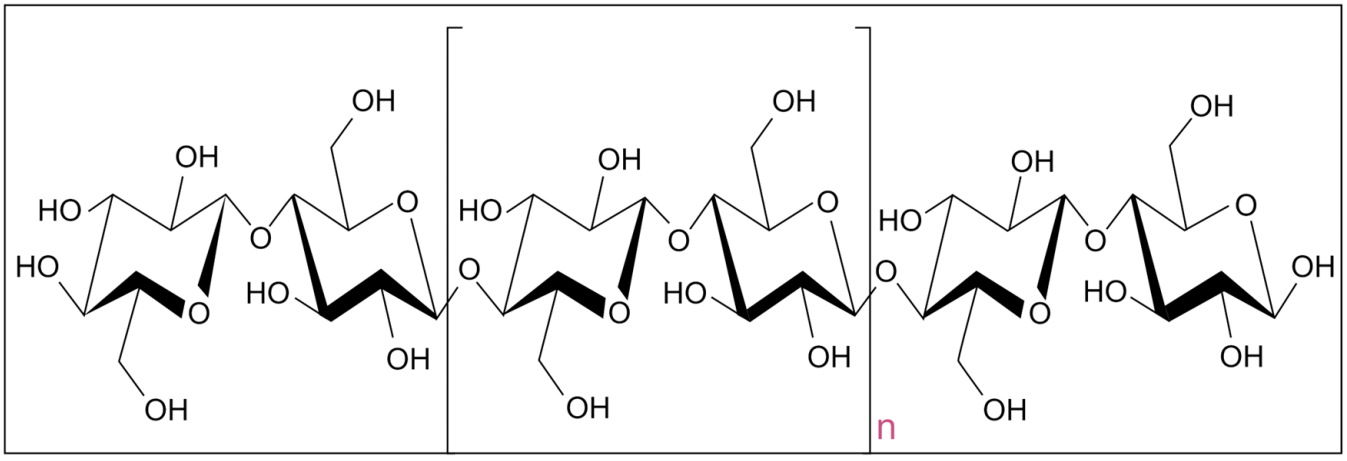

Fig. 1. The composition of cellulose's chemical structure [15].

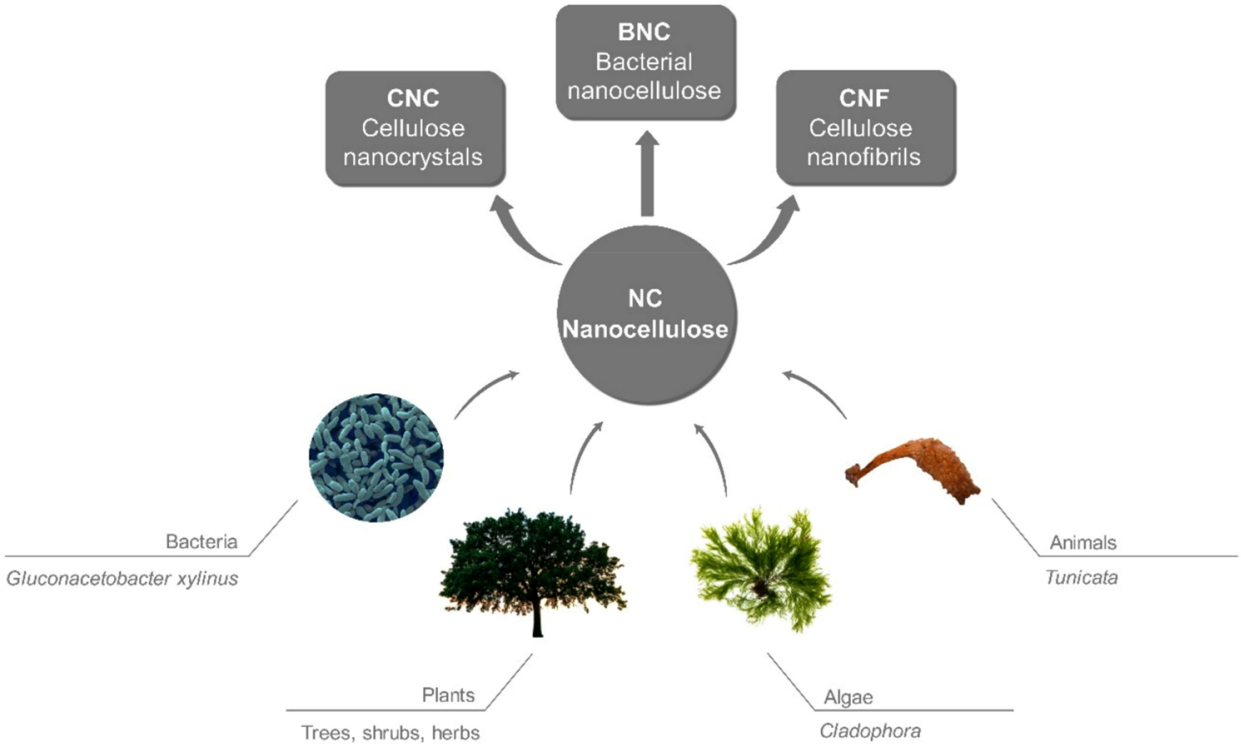

Fig. 2. Various nanocellulose sources and varieties [40].

continuously stirring. The reaction is then quenched by dilution in water, followed by centrifugation and washing with water to remove excess acid. Dong et al. presented a detailed method for cellulose hydrolysis using sulfuric acid [41]. In 2011, Qin et al. prepared surface c-NCC by oxidizing cotton linter pulp using the TEMPO-NaBr-NaClO method with ultrasonic treatment [42]. Leung et al. also reported the preparation of c-NCC by oxidizing cellulose using ammonium persulfate at 60 °C [43]. CNF can be obtained by pretreating cellulose fibers to facilitate disintegration followed by mechanical delamination. Turbak et al. first isolated CNF from bleached softwood fibers using high-pressure homogenization in 1983 [44]. Additionally, cellulose nanofibers have been obtained from pear and apple, Helicteres isora plant, oil palm tree, banana, Citrullus colocynthis seeds, and cassava peel [45–49]. Due to the high energy consumption required for the process, scientific and industrial interest declined. Therefore, alternative pre-treatments have been investigated more extensively, including enzymatic hydrolysis [50], partial carboxymethylation [51], TEMPO catalytic oxidation [52]. These methods have also been explored to reduce energy consumption in refining processes [53]. The benefit of TEMPO-mediated oxidation lies in its environmentally friendly and straightforward operation, cost-effectiveness, selective oxidation of primary alcohols, high product yield, preservation of crystallinity, morphological stability, and excellent aqueous dispersibility [54]. Following pre-treatment, fibers undergo mechanical disintegration processes such as high-pressure treatment, microfluidization, friction grinding, extrusion, cryopressure, and high-intensity ultrasonication [55]. Building on the work of Pääkkö et al., NFC has been isolated from various sources including curauá and sugarcane bagasse fibers, banana peel, and lignocellulosic biomass of lemongrass [56–58]. Various experimental techniques have been developed for the production of nanocelluloses, exploration of their properties, and methods for functionalization. In 2018, Kargarzadeh et al. compiled both traditional mechanical and chemical treatments used for preparing CNFs and CNCs, along with other promising methods and pre-treatment processes [59]. Nanomaterials derived from various cellulosic sources, including wood, have also been prepared. The transformation of cellulose into nanoscale materials imparts new properties, opening up numerous industrial applications across different fields. An overview of potential markets influenced by cellulose nanomaterials is provided [60].

BNC possesses unique characteristics compared to other types of nanocellulose. It is a promising natural polymer synthesized by bacteria, sharing the same molecular formula as cellulose extracted from plants. BNC is known for its excellent purity and water retention properties. Jozala et al. provided a review on bacterial nanocellulose production and its applications [61]. In this review, they discussed methods for producing bacterial cellulose using microorganisms such as static culture and stirred culture [62]. The optimal approach for developing these two forms of BNC depended on its final application, considering the varia-

tions in its physical, morphological, and mechanical properties. Cellulose derived from stirred culture exhibited low mechanical strength. Static culture required a larger cultivation area and a longer culture period [63]. Certain bacterial organisms have the capability to produce extracellular cellulose. Cellulose production has been observed in Gram-positive bacteria such as Sarcina ventriculi and Gram-negative bacteria including Rhizobium, Salmonella, Azotobacter, Aerobacter, Achromobacter, Agrobacterium, Alcaligenes, Pseudomonas, Acetobacter, and Gluconacetobacter xylinus. Gluconacetobacter, Agrobacterium, and Sarcina are among the most researched sources of cellulose among these species. BNC can be effectively synthesized through oxidative fermentation at a pH range of 3 to 7, maintaining the temperature between 25 and 30 °C, and utilizing saccharides as a carbon source in both synthetic and non-synthetic media. A study documented the production of BC by Gluconacetobacter xylinus PTCC 1734 in sugar beet molasses, cheese whey, and standard Hestrin–Schramm media. The synthesized BC was further hydrolyzed with sulfuric acid to produce BNC. Results indicated that treated sugar beet molasses resulted in the highest concentration and productivity of BC, followed by treated cheese whey [64].

2.2 Nanostructured materials

MCC can be prepared through acid hydrolysis [41]. This process effectively degrades the amorphous regions of cellulose, leaving behind MCC. Various methods have been documented for isolating MCC from lignocellulosic materials. For example, Moran et al. isolated MCC from sisal fibers using sodium chlorite treatment, followed by NaOH and acid hydrolysis [65]. Wang et al. isolated MCC from jute fiber through a process involving mercerization with 12% NaOH at room temperature for 2 hours, followed by acid hydrolysis and a final treatment with NaOH [66]. Trache et al. compiled a study detailing the acid hydrolysis-based separation of MCC from various sources [67]. Additionally, research documented the extraction of MCC from roselle fiber via acid treatment and compared the properties of the extracted MCC with commercially available MCC [68]. A review documented the preparation of MCC from Oolong tea waste using acid hydrolysis, revealing that the temperature and duration of hydrolysis significantly influenced the yield and degree of polymerization [69]. Hou et al. developed a novel and environmentally friendly method for synthesizing MCC from waste cotton fabrics using phosphotungstic acid [70].

MFC was first prepared by Herrick in 1984 and by Turbak et al. in 1985. Since then, numerous patents have emerged for MFC preparation from various cellulose sources. A study in 2010 summarized the synthesis and isolation of cellulose microfibrils, which involved enzymatic pretreatment followed by mechanical treatments [71]. Additionally, cellulose microfibrils were prepared from banana rachis using a combination of chemical and mechanical methods [72]. Su et al. investigated the characteristics of cellulose microfibril fractions isolated from fine particles of spruce wood using a combination of delignification, TEMPO-catalyzed oxidation, and sonication processes.

3 Drug delivery by surface modification of nanocellulose

The characteristics of an effective drug delivery system, including particle size, surface charge, modification, and biocompatibility, significantly influence the drug release and delivery process [73]. The large surface area and negative surface charge of NCC make it an excellent carrier for hydrophilic drugs, allowing for optimal dose control by attaching the drugs to the NCC surface [74]. The surface chemistry of NCC is governed by hydroxyl groups, which can be modified into other functional groups [75]. However, certain properties of nanocellulose, such as moisture sensitivity and low thermal stability in CNCs and CNFs, can restrict their applications [76]. Over the past decade, numerous techniques have been proposed to address these limitations. Methods for surface modification and fiber pre-treatment are now well-developed, allowing for the enhancement of specific properties. Additionally, the nanosized structure leads to a significant increase in hydrogen bonding-induced aggregation of these materials. Surface modification can be employed to introduce new steric or electrostatic effects to the particles [59]. Nanocrystalline cellulose is highly biocompatible due to its excellent biocompatibility, biodegradability, low ecological toxicity risk, low cytotoxicity, and increased surface area [26]. The material's properties are highly significant due to the abundance of active hydroxyl groups, which can undergo various chemical transformations. Modifications can be tailored to address drug side effects or specific requirements. Nanocellulose can be hydrophobically modified using different surfactants, whether long or short chain, linear or branched, cationic or anionic. Ionic liquids can also be utilized for modification. A range of ionic moieties can be employed to alter the surface of nanocellulose. For instance, phosphate substitution instead of sulfate can be done to mitigate inflammatory side effects. Several chemical modifications have been conducted on the hydroxyl groups of the crystalline surface of NCC. Under normal conditions, non-ionized and hydrophobic drugs do not adhere to the surface of unmodified NCC. These modifications serve as a linker to attach the drugs to the NCC surface. There are two main methods for these modifications:

1. Covalent chemical modification of NCC surfaces includes sulfonation, oxidation, cationization, silylation, esterification, carboxylation, and carbidation [77].

2. Application of surfactant-coated NCC suspension [78].

The negative charge of NCC was altered by a cationic surfactant known as CTAB, causing NCC to acquire hydrophobic properties for loading hydrophobic drugs onto the CTAB's domain. It was demonstrated that hydrophobic drugs were released more slowly from the modified NCC compared to unmodified NCC. These modifications enhanced the surface hydrophobicity of the NCC, facilitating the binding of hydrophobic drugs to the modified NCC. They have been investigated as sustained release drug delivery systems for luteolin and luteoloside, nonsteroidal anti-inflammatory drugs, and curcumin [79–81]. Putro et al. modified NCC using CTAB, SDS, and Tween 20, and compared the effects of these surfactants on the loading capacity and release rate of paclitaxel. Likewise, another research investigated the impact of natural surfactants like Triton X-100 and saponin on modifying cellulose and starch nanoparticles for hydrophobic drug loading and release [82]. Aulin et al. modified carboxymethylated NFC by applying varying amounts of a fluorosurfactant, specifically perfluorooctadecanoic acid (C17F35COOH) [83]. In 2011, the anionic surface of TEMPO NFC was easily altered with a cationic surfactant like CTAB. CTAB dissolved in water was applied to the surface of NFC films [84]. Surfactants such as CTAB, DDDAB, and DHDAB were utilized to regulate the water repellency of CNF [85]. Modifications of BNC through esterification, etherification, amidation, or phosphorylation offer options to adjust stability through covalent binding, electrostatic, or hydrophobic interactions for drug release. Covalently binding gentamycin to BNC enhanced interactions with cells and antimicrobial properties [86]. Drug immobilization has also been demonstrated for laccase and lipase on BNC [87]. Combining BNC with smart polymers through blending or grafting resulted in BNC derivatives with enhanced controllability and additional functionalities [88,89]. A recently published review covered nearly all patents related to cellulose nanomaterials published between 2010 and 2017. The data particularly emphasized the role of nanocelluloses in advancements related to polymeric composite materials, the importance of oxidative methods in patents related to plant nanocelluloses, and the exploration of innovative filtration devices, including CNC, papermaking compositions based on CNF, and medical devices involving BNC. Furthermore, the review of patent holders illustrated differences in the extent of innovation transfer to the industry among cellulose nanomaterials, with a notably higher presence of companies within CNF patents assignees compared to those of CNC and BNC [90]. Initially, nanocellulose was developed in 1949 by Ranby et al. [91]. Due to various advantages such as nano dimensions, high surface area, recyclability, bioavailability, biocompatibility, and tunable surface chemistry of different forms of nanocellulose, it has garnered attention in drug delivery in recent years [92,93]. Researchers have extensively explored various nanocellulose-based drug delivery systems. These have been commonly categorized into microparticles, hydrogels, gels, membranes, and films [94]. Moreover, drug delivery systems based on nanocellulose can be administered both externally and internally. Internal routes primarily include oral administration, while external routes mainly involve transdermal administration. Both internal and external routes have demonstrated local or systemic effects [21]. In a recent study, cellulose nanocrystals covalently bound with the drug doxorubicin were synthesized, serving as both a linker and a selective releasing agent. The study confirmed the controlled release of the chemotherapeutic agent [95].

4 Drug delivery systems using nanocellulose

Nanocellulose has emerged as a valuable carrier for various drug administration routes including oral, transdermal, and local. Studies have shown that the release time of drugs based on nanocellulose can range from a few minutes to several days [96].

4.1 Oral drug delivery

Numerous studies have investigated the oral delivery of various nanocellulose types. Jackson et al. and Burt et al. utilized NCC as a platform for specific anticancer medications like docetaxel, paclitaxel, and etoposide [73,97]. They modified the NCC surface by attaching a cationic surfactant CTAB, leading to a concentration-dependent increase in the zeta potential of NCC. The findings demonstrated a controlled drug release over several days. Mohanta et al. fabricated thin films using NCC and chitosan, a cationic polymer [98]. In this study, the amine groups of chitosan interacted with the sulfonate groups of NCC through electrostatic interactions. They loaded water-soluble (doxorubicin hydrochloride) and insoluble (curcumin) anticancer drugs into the films. The study revealed that the primary interactions between the drugs (doxorubicin and curcumin) and NCC involved hydrogen bonds and van der Waals interactions, leading to sustained release of both water-soluble and insoluble drugs Emaraa et al. investigated the impact of NCC and MCC carriers on the solubility of a poorly water-soluble drug [99]. They observed that increasing the load of NCC resulted in increased solubility. This indicates that NCC can serve as a suitable carrier for poorly water-soluble drugs. CNF is another intriguing material known for its unique physicochemical properties at various interfaces. CNF offers a large specific surface area facilitating positive interaction with drugs, along with mechanical properties that enhance the stability of dosage forms. Due to strong interactions between nanofibers and high crystallinity, CNF films exhibit excellent oxygen barrier properties, particularly at low humidity levels, enhancing the oxidative stability of oxygen-sensitive drugs during storage [100]. Therefore, CNF can be effectively utilized as a pharmaceutical excipient. CNF has been used in tablets, capsules, and particles for immediate release of drugs, and in the form of films for controlled drug release [101, 102]. In various stud-

ies, CNF combined with non-edible surfactants has been employed to encapsulate air bubbles using the Pickering method, resulting in stable air bubbles [103]. These three-dimensional closed-cell structures are promising for sustained drug release in pharmaceutical applications. Such aerogels can rapidly absorb liquid if the pockets are interconnected, leading to increased medication release due to the larger surface area [103]. Guo et al. developed beads using CNF/alginate and MCC/alginate for metformin hydrochloride release [104]. CNF enhanced swelling and mechanical properties, while alginate acted as the drug delivery matrix. The cumulative release from CNF/alginate beads was 10% higher compared to MCC/alginate and exhibited sustained release over the following 240 minutes.

In 2018, Patil et al. created a controlled release setup for dimethyl phthalate using nanocomposites of gelatinized corn starch and urea-formaldehyde with CNF [105]. CNF substantially hindered the initial release of dimethyl phthalate but effectively facilitated controlled drug release. They suggested that the network within the starch matrix created an indirect pathway, leading to prolonged release (approximately 80% to 95% of the drug was released within a week). Supramaniam et al. developed nanocellulose alginate magnetic hydrogel beads (m-NCC) for the controlled and prolonged release of ibuprofen over 30 to 330 minutes [106]. These m-NCC beads could potentially target, detect, and treat cancerous tissue using MRI, while also enhancing the mechanical strength and drug release properties. Thomas et al. formulated nano-sized alginate-cellulose nanocrystal hybrid polymers with higher EE, suitable for the controlled oral delivery of rifampicin. Therefore, rifampicin-loaded polymer nanoparticles show promise for the treatment of Mycobacterium tuberculosis [107]. Hivechi et al. conducted a study on the fabrication of polycaprolactone nanofibers reinforced with NCC and investigated the controlled release of TCH. They observed that increasing the NCC content in the PCL nanofibers led to a slower release of the drug [108].

Valo et al. prepared nanocellulose aerogel scaffolds derived from BC for oral administration, demonstrating sustained drug release properties. These nanocomposite structures have shown significant utility in various pharmaceutical nanoparticle applications [109]. Ahmad et al. developed biocompatible and mucoadhesive hydrogels by grafting poly (acrylic acid) onto BNC as enteric-coated systems. They demonstrated pH-responsive swelling behavior of the hydrogels, with controlled delivery of albumin observed at pH 6.8 [88]. Pavaloiu et al. investigated combinations of BNC with gelatin or composite films composed of BNC, poly (vinyl alcohol), and chitosan. These formulations showed delayed release of ibuprofen when the pH was increased from 1.2 to 7.4 [110]. BNC-alginate composites cross-linked with calcium chloride were found to enable dual-controlled drug delivery responsive to pH and electrical stimuli, releasing ibuprofen [111].

4.2 Localalized drug delivery

Local drug delivery systems offer the advantage of releasing the drug directly at or near the target site, which enhances system effectiveness and reduces the required dose. Consequently, systemic exposure is minimized, leading to reduced toxicity to healthy tissues [69]. Laurén et al. recommended CNF hydrogels as a promising matrix for the controlled release or local delivery of macromolecular proteins and peptide drugs in a study from 2014 [112]. In 2018, they also developed mucoadhesive drug release films using biodegradable and non-toxic polymers. They employed various combinations of mucoadhesive components, including CNF and ACNF, as film-forming agents. Functional bio-adhesion activators such as mucin, pectin, and chitosan were utilized for the release of metronidazole. The findings showed a quick release of the drug, which is beneficial for treating oral conditions like periodontitis. The rapid release ensures that the patch becomes inactive after detachment, which is advantageous for local drug administration since a quick and high local dosage is preferred. Moreover, a recent investigation described the fabrication of hydrogels from CNCs using salt-induced charge screening. In vitro studies demonstrated sustained release of the protein BSA, poorly water-soluble tetracycline, and readily soluble doxorubicin. A rapid release was observed for tetracycline within 2 days, while sustained release for BSA and doxorubicin lasted up to two weeks [113].

4.3 Transdermal drug delivery

The TDDS facilitates drug delivery through the skin directly into the systemic circulation, bypassing the gastrointestinal tract and liver metabolism, thereby achieving therapeutic concentrations. This approach reduces gastrointestinal and hepatic side effects and allows for therapeutic effects at lower doses. However, the conventional TDDS is limited in delivering larger drugs, restricting its application to smaller drugs only [114]. TDDS finds a significant application in skin tissue healing. According to the review by Fu et al. [115], BNC shows promising potential for skin tissue repair due to its unique structural, mechanical, and biocompatible properties, unlike plant cellulose. In a study conducted by Silva et al. , a BNC membrane-based TDDS was explored for delivering diclofenac sodium salt [116]. The permeation rate of diclofenac was comparable to commercial patches but lower than that of the gel. This technology offers potential for diclofenac release with the benefit of easy application and preparation. The monolayer structure allows for sustained release. Souza et al. developed bacterial cellulose membranes with gellan gum, which were loaded with the antifungal drug fluconazole for delivering human ASCs. The transferred ASCs can enhance wound healing both directly, by proliferating and differentiating in the host tissue, and mainly indirectly, through the secretion of vari-

ous bioactive molecules such as cell-adhesion mediators, immunomodulatory compounds, growth factors, and angiogenic factors [117]. Alkhatib et al. also proposed the use of an antiseptic octenidine delivered using a ready-to-use BNC/Poloxamer hybrid system for 8 days in the treatment of long-term skin wounds [118]. In addition to BNC, CNF also shows potential applications in TDDS. For instance, Sarkar et al. developed a CNF/chitosan transdermal film for delivering ketorolac tromethamine, where CNF served as a support [119]. This indicates that CNF has potential for controlled transdermal drug delivery systems. Kolakovic et al. also investigated the use of CNF as a matrix material for prolonged delivery of indomethacin, itraconazole, and beclomethasone in transdermal patches [96]. Film-like matrix systems were loaded with drugs ranging from 20% to 40% using the filtration technique. They found that the drug was continuously released for up to three months, indicating that CNF is a promising material for the controlled release of poorly water-soluble drugs.

Other formulations based on nanocellulose, such as GNP-NC and NFC/hydroxypropylmethyl cellulose nanocomposites, have also shown high potential for application in TDDS for controlled drug release [120, 121]. Bhandari et al. developed drug-loaded CNF aerogels suitable for loading water-soluble drugs through the physical adsorption method. After in-vitro characterization, both CNF and DCNF aerogels demonstrated suitability for drug delivery through the skin [122]. In 2019, Abba et al. developed BNC membranes loaded with crocin. The integrity of BNC remained intact even after the incorporation of crocin [123]. The results from direct dissolution and transdermal passage showed significant release and permeation profiles. Overall, all types of nanocellulose have demonstrated remarkable effectiveness in TDDS. Additionally, another study highlighted the suitability of nanofiber membranes as patches for TDDS. Prolonged release of PRX over several hours was observed when the loaded membranes were exposed to simulated human skin fluid, indicating their potential as drug delivery patches [124]. A recent investigation examined the long-term storage stability of BNC membranes loaded with both hydrophilic and lipophilic APIs such as caffeine, lidocaine, ibuprofen, and diclofenac. Among these, the caffeine-loaded BNC membrane was selected for in vivo cutaneous compatibility studies, which confirmed the good storage stability of the APIs-loaded BNC membranes. These findings underscore the potential of these topical delivery systems with different APIs. Additionally, Bacakova et al. provided a comprehensive review covering various applications of nanocellulose in skin tissue engineering and wound healing [125].

5 Limitations and Challenges

5.1 Production and cost issues

One of the primary challenges in the widespread adoption of nanocellulose for drug delivery systems is the scalability and economic feasibility of its production. Nanocellulose is typically derived from cellulose sources through processes such as acid hydrolysis, mechanical disintegration, and enzymatic treatments. Each of these methods has its own set of technical challenges that impact scalability [126].

The production of nanocellulose on a laboratory scale is well-established, but scaling up to industrial levels presents significant obstacles. For instance, the acid hydrolysis method, which is commonly used to produce NCC, involves the use of concentrated acids, leading to large volumes of acidic waste. Managing and neutralizing this waste on an industrial scale is both costly and environmentally challenging.

Mechanical disintegration methods, such as high-pressure homogenization and ultrasonication, require substantial energy inputs, making them less attractive for large-scale production. The equipment needed for these processes is also expensive and prone to wear and tear, further increasing operational costs. Enzymatic treatments, while more environmentally friendly, are slow and require expensive enzymes, limiting their feasibility for mass production [127].

The economic feasibility of producing nanocellulose at scale is another critical issue. The cost of raw materials, energy, and reagents, combined with the need for specialized equipment, results in high production costs. These costs must be balanced against the market price of nanocellulose-based products to ensure competitiveness. Currently, the cost of producing high-quality nanocellulose can be prohibitive, especially for applications in the biomedical field where price sensitivity is significant. Research efforts are ongoing to develop more cost-effective production methods. For instance, the use of biomass waste as a raw material for nanocellulose production has shown promise. Agricultural residues, forestry by-products, and other lignocellulosic wastes can be converted into nanocellulose, potentially reducing raw material costs and contributing to a circular economy. Advances in green chemistry and process optimization are also being explored to enhance the efficiency and sustainability of nanocellulose production [128].

5.2 Stability and storage

Another major limitation of nanocellulose in drug delivery systems is its stability and storage. Nanocellulose materials are prone to agglomeration and degradation over time, which can compromise their functionality and effectiveness as drug carriers. Nanocellulose particles have a high surface area and strong intermolecular forces, leading to a tendency to agglomerate. Agglomeration reduces the

available surface area for drug loading and alters the dispersion characteristics, impacting the release profile of the drug. Preventing agglomeration requires careful formulation and the use of stabilizers or surface modifications, which can add complexity and cost to the production process [129]. Nanocellulose is susceptible to degradation when exposed to environmental factors such as moisture, heat, and microbial activity. This degradation can result in the loss of mechanical properties and the release of degradation products that may be harmful or interfere with the drug delivery system. Ensuring the stability of nanocellulose requires the development of appropriate storage conditions, such as controlled humidity and temperature environments, which can be difficult to maintain, particularly in resource-limited settings. The shelf life of nanocellulose-based drug delivery systems is another critical consideration. To be commercially viable, these systems must maintain their efficacy over extended periods. However, the inherent instability of nanocellulose can lead to changes in particle size, morphology, and drug release characteristics over time. Ensuring a long shelf life requires rigorous stability testing and the development of formulations that protect the nanocellulose from environmental degradation [130]. Research is focused on enhancing the stability of nanocellulose through various strategies. For example, surface modifications such as coating with polymers or the incorporation of antioxidants can improve stability. Encapsulation techniques, where nanocellulose is embedded within a protective matrix, are also being explored to enhance shelf life and maintain functionality.

5.3 Regulatory and approval hurdles

The introduction of nanocellulose-based drug delivery systems into the market is hampered by significant regulatory and approval hurdles. The regulatory landscape for nanomaterials is complex and varies between regions, posing challenges for the commercialization of these innovative drug delivery systems.

Nanomaterials, including nanocellulose, are subject to stringent regulatory scrutiny due to their unique properties and potential safety concerns. Regulatory agencies such as the U.S. FDA, the EMA, and other national bodies require comprehensive safety and efficacy data for approval. This includes detailed characterization of the nanomaterial, assessment of biocompatibility, toxicity studies, and evidence of clinical efficacy [131].

The characterization of nanocellulose is particularly challenging due to its complex and variable structure. Regulatory agencies require detailed information on particle size, surface chemistry, crystallinity, and purity, which necessitates advanced analytical techniques and standardized protocols. The lack of standardized methods for nanocellulose characterization adds to the complexity and cost of regulatory compliance.

Obtaining the necessary safety and efficacy data for regulatory approval involves extensive preclinical and clinical testing. Preclinical studies must demonstrate the safety of nanocellulose in various biological systems, including its toxicity, immunogenicity, and potential for causing adverse effects. Clinical trials are required to establish the efficacy of the nanocellulose-based drug delivery system in humans, which are time-consuming and costly [132]. Regulatory agencies also require a thorough understanding of the pharmacokinetics and pharmacodynamics of the drug delivery system. This includes studying how the system behaves in the body, how it releases the drug, and the drug's absorption, distribution, metabolism, and excretion. These studies are essential to ensure that the nanocellulose-based system delivers the therapeutic payload effectively and safely.

Navigating the intellectual property landscape and choosing the appropriate regulatory pathway are additional challenges. Innovators must secure patents for their nanocellulose-based drug delivery systems to protect their inventions. However, the patenting process can be complex, especially for new materials with novel properties. Choosing the regulatory pathway is also critical. Depending on the intended use and the regulatory framework in the region, nanocellulose-based systems may be classified as drugs, medical devices, or combination products. Each classification has specific regulatory requirements, and navigating these pathways requires expertise and strategic planning [133].

6 Future Directions and Perspectives

The future of nanocellulose in drug delivery systems is promising, with numerous avenues for research and development that could significantly enhance the efficacy, safety, and versatility of these systems. This section explores potential future directions and perspectives, focusing on innovations in preparation techniques, expanded applications in medicine, and strategies to overcome current challenges.

One of the key areas for future research is the development of advanced manufacturing technologies for nanocellulose. Current methods, such as acid hydrolysis and mechanical disintegration, have limitations related to scalability, cost, and environmental impact. Innovations in green chemistry and sustainable production processes are essential to overcome these limitations. For instance, developing environmentally friendly solvents and catalysts can reduce the ecological footprint of nanocellulose production. Additionally, advancements in biotechnological methods, such as the use of genetically engineered microorganisms for cellulose production, could offer more sustainable and efficient alternatives [134].

Transitioning from batch to continuous production processes could significantly enhance the scalability and eco-

nomic feasibility of nanocellulose production. Continuous processes allow for the constant input of raw materials and output of nanocellulose, improving efficiency and reducing production costs. Research into optimizing these processes, including the integration of real-time monitoring and automation, is crucial for industrial-scale production.

Future research should also focus on novel surface modification and functionalization techniques to enhance the properties of nanocellulose for specific drug delivery applications. Techniques such as click chemistry, a powerful and versatile tool for functionalizing nanocellulose, can provide precise control over surface properties. Additionally, developing multifunctional nanocellulose systems that combine drug delivery with other therapeutic functions, such as imaging or sensing, could lead to the creation of more sophisticated and effective treatments [97]. Ensuring the stability and shelf life of nanocellulose-based drug delivery systems is crucial for their commercial viability. Future research should explore advanced stabilization techniques, such as the incorporation of stabilizing agents, encapsulation within protective matrices, and the development of robust packaging solutions. Additionally, understanding the degradation mechanisms of nanocellulose under various environmental conditions can inform strategies to enhance its stability.

Cost reduction is essential for the widespread adoption of nanocellulose in drug delivery systems. Future research should focus on optimizing production processes to reduce energy and raw material costs. Exploring alternative and abundant sources of cellulose, such as agricultural and forestry residues, could also lower production costs and promote sustainability. Additionally, developing efficient recycling and reuse strategies for nanocellulose could further reduce costs and environmental impact [40].

Regulatory approval remains a significant hurdle for nanocellulose-based drug delivery systems. Future efforts should focus on establishing standardized characterization methods and generating comprehensive safety and efficacy data. Collaborative efforts between researchers, industry stakeholders, and regulatory agencies are essential to develop clear guidelines and streamlined regulatory pathways for nanocellulose-based systems. Engaging in early and ongoing dialogue with regulatory bodies can help identify and address potential concerns, facilitating smoother approval processes.

The future of nanocellulose in drug delivery will greatly benefit from interdisciplinary collaboration. Combining expertise from materials science, chemistry, biology, medicine, and engineering can drive innovation and address complex challenges. Collaborative research initiatives, funded by both public and private sectors, can accelerate the development and translation of nanocellulose-based drug delivery systems into clinical practice. Additionally, fostering partnerships between academia, industry, and regulatory bodies can facilitate knowledge exchange and the commercialization of innovative solutions [135].

Nanocellulose-based drug delivery systems have the potential to play a significant role in personalized medicine. Future research should focus on developing customizable nanocellulose platforms that can be tailored to individual patient needs. This includes the ability to load and release specific drug combinations, adjust dosing regimens, and target unique molecular markers. Advances in microfabrication and 3D printing technologies could enable the production of personalized nanocellulose-based systems, enhancing treatment efficacy and patient outcomes.

As the production and use of nanocellulose increase, it is essential to consider the environmental impact. Future research should focus on developing sustainable production methods, minimizing waste generation, and exploring the life cycle of nanocellulose products. Additionally, assessing the environmental fate and impact of nanocellulose-based drug delivery systems is crucial to ensure their safety and sustainability [129].

7 Conclusion

Nanocellulose-based materials play a significant role in drug delivery systems. Conducting a literature survey is crucial for research as it provides insights into existing contributions. In this review, we offer a comprehensive overview of the types of nanocellulose and their applications in various drug delivery systems. By providing this information, readers can explore new ideas that haven't been previously discussed, thus minimizing time and energy wastage. In conclusion, structured nanocellulose finds broader applications in oral drug delivery systems, while nanofibrils have been predominantly used in transdermal drug delivery systems.

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