Nanocellulose: A Review on an Agricultural Waste to a Valuable Pharmaceutical Ingredient

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DOI: https://doi.org/10.55248/gengpi.5.0224.0414

ABSTRACT

Cellulose was and continues to be the most prevalent biopolymer produced by all plant fibers, including agricultural waste. It is important to use this trash as a beginning material in the manufacture of new products. Nanocellulose is a subject of substantial scientific interest due to its excellent physicochemical properties, the ability to degrade and high mechanical strength. New nanocellulose helps to advance the rapidly growing field of environmentally friendly substances and nanocomposites. The present state of research on the separation of micro and nano fibrillated cellulose from plant sources is summarized in this study. Various pharmacological uses are discussed, including regulated, sustained, or quick drug delivery, stabilizing agents, and its usage as a safe and sustained environment for cell growth, allowing it to be used in the field of tissue engineering. Due to its compelling characteristics, including outstanding mechanical qualities, a large surface area, strong hydroxyl groups that can be used for transformation, and organic characteristics with fully recycled content, nanocellulose and its uses have recently gained considerable attention in both scientific and manufacturing domains. Additionally, with a focus on the characteristics of Bio nanocomposite materials, it summarizes recent advancements in several multifunctional nanocellulose applications. Additionally, a comprehensive discussion of numerous obstacles to the commercialization of nanocellulose and its economic elements for both current and future markets is included.

Keyword: Nanocellulose, Nanocomposites, Application, Agriculture waste management, Lignocellulose biomass.

1. Introduction

In recent years, efforts have been made to find more ecologically friendly alternatives because of the social and environmental effects connected with the use of fossil fuels [1].

For the creation of new generations of sophisticated nanomaterials, renewable and readily accessible resources are required, together with cutting-edge technology.

To replace petrochemicals with sustainable, renewable energy sources, more attention should be paid to the agricultural biomass waste that is generated. materials that degrade naturally and are readily available.[2]

Farmers worldwide harvest 39.35 million tons of natural fibers from plants per year, according to data from the Food and Agriculture Organization (OECD-FAO) and Organization for Economic Cooperation and Development (OECD-FAO) [3].

Due to their high lignocellulose content, which is often made up of three fractions: cellulose, hemicellulose, and lignin, wastes generated by agricultural activity have recently attracted attention from researchers. [4]

The family of nanocellulose can be broadly divided into three types: (1) cellulose nanocrystals (CNC), also known as microbial cellulose, nanocrystalline cellulose, and cellulose (nano) whiskers; (2) cellulose nanofibrils (CNF), also known as nano fibrillated cellulose (NFC), micro fibrillated cellulose (MFC), and cellulose nanofibers; and (3) bacterial cellulose (BC), also known as cellulose nanofibers [5-6].

The most prevalent organic material in nature, cellulose is produced by green plants through photosynthetic processes using carbon dioxide, water, and sunlight. [7]

Due to its straightforward chemical structure and ability to be easily manipulated, cellulose can be seen as a renewable and biodegradable source of energy and a raw material for the manufacturing of a variety of fibers, films, and functional polymers. [8-10]
Lignocellulose materials are very desirable because of their biodegradability, low density, and superior mechanical qualities. They are one of the most significant natural sources for producing high added-value materials or biopolymers. [11-12]

To convert leftover biomass into cellulose nanofibers and nanocrystals, various treatments have been used, including olive tree pruning, argon press cake, apple pomace, and vine shoots.

Numerous sectors, including biomedicine, membrane filtration, mechanical reinforcement of matrices, and food packaging, have exploited nanocellulose-based products. Applications for products [13].

Research on a variety of goods and applications, including nanocomposites, gels and aerogels, viscosity modifiers, films, barrier layers, fibers, foams, energy applications, and filtering membranes, has recently been sparked by nanocellulose [14].

<table>
<thead>
<tr>
<th>Cellulose-based frameworks</th>
<th>Measurements (nm)</th>
<th>Dimensions (nm)</th>
<th>Component proportion (L/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microfibril</td>
<td>&gt;10000</td>
<td>2-10</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>MFC</td>
<td>&gt;1000</td>
<td>10-40</td>
<td>100-150</td>
</tr>
<tr>
<td>Cellulose whisker</td>
<td>100-600</td>
<td>2-20</td>
<td>10-100</td>
</tr>
<tr>
<td>MCC</td>
<td>&gt;1000</td>
<td>&gt;1000</td>
<td>~1</td>
</tr>
</tbody>
</table>

Table no 1: Nanocellulose products dimension [15].

2. Sources

Cotton and wood are regarded as the most accessible and traditional sources of cellulose, along with untreated agricultural wastes such as palm and banana rachis, cotton seeds, sugar cane, rice straw, wheat straw, bamboo cane, and flax bast that are collected from the field.

Plant cellulose is thought to be the main source of cellulose due to its availability and inexpensive cost, despite the benefits of non-plant cellulose in terms of purity. The most prevalent natural polysaccharide is cellulose, which was originally produced from wood in 1838 by treating it with nitric acid. [16]

According to the source cellulose is fundamentally present in the secondary cell wall of the plant as elementary fibrils or nanofibrils with a diameter ranging between 10 and 100 nm and a micrometric length. [17]

Cellulose, hemicellulose, and lignin make up the majority of the three types of polymers that make up the LCB’s cell wall structure, (figure 1) This explains why the plant cell wall is rigid, strong against compression, resistant to rot, and impermeable to water. [18]

The equatorial shape of the glucose residues helps cellulose develop as extended rod-like straight strands. Additionally, crystalline and amorphous areas of the cellulose chains are organized. Van der Waals forces, inter- and intramolecular hydrogen bonding, as well as 1,4-glycosidic bonds are the sources of the crystalline area, whereas the amorphous region results from the breakdown and defects of hydrogen bonds. [19]

The dimer of glucose called cellobiose, which is made up of two anhydro-glucose units (AGU), is another component of the cellulose chain. Depending on the source or the pre-treatment (chemical or mechanical), the cellulose chain’s length and molecular weight can change. The degree of polymerization (DP) is determined by the number of AGUs present in each chain. Nearly 10,000 and 15,000 AGU units, respectively, make up the DP of wood and cotton. [20]
The individual cellulose chain ends with a reducing moiety, where the hemiacetal group may present an open-chain aldehyde form, while the other end lacks such reducing qualities and is named non-reducing end [21].

Mechanical breakdown or defibrillation is the main concept for obtaining individual cellulosic fibers in the nano-dimensions; width diameter less than 100 nm and length of few micrometers, which are the common and accepted dimensions. Led by Turbak et al. [22] and Herrick et al. [23], the first isolation of NFC was performed by their teams in 1983 using Gaulin laboratory homogenizer.

Their teams used the Gaulin laboratory homogenizer in 1983 to conduct the first NFC isolation. The ultrafine grinder was first used to grind a pulp suspension with a very low concentration (approximately 2%) after which optical microscopy was used to determine the appropriate number of passes to reach the ideal dimensions.

After being ground, the suspension was further defibrillated by homogenization careful, repeated homogenization can be used to create a diluted dispersion of a highly fibrillated and gel-like feature [24].

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Figure 1: Scheme of the main components of lignocellulose biomass.

Figure 2: Illustration showing the preparation of nanocellulose, and the several pharmacological uses covered throughout the examination.
3. Classification of cellulose

Figure 3 A diagram showing how nanocellulose and its derivatives are categorized, modified, printed, and used in biomedicine.[25]

3.1 Cellulose nanocrystal (CNC)

It is well known that CNC may be isolated by acid hydrolysis utilizing mineral acids like phosphoric, sulfuric, or hydrochloric acid and techniques such enzymatic processes [26-30].

When cellulose fibers are hydrolyzed, the amorphous portion is split, creating a hard, highly crystalline, and rod-like nanostructure. The incorporation of acid leads to the charge on the surface of CNC during the acid hydrolysis process, facilitating the rapid formation of colloidal dispersion [31].

The proportion of crystalline cellulose can range from 50 to 90% depending on the source, and the elastic moduli are found to be between 105 – 168 GPa [32,33]. Tunicates, which have a length of 100–300 nm and a diameter of 5–50 nm, may be used to make the longest form of CNC [31].

Asymmetrical hematic phases are produced at concentrations by CNC, which exhibits a shear-thinning characteristic and behaves like liquid crystals [34]. For additive manufacturing, hydrogen bond networks that enable stress transfer when CNC is applied to polymer materials are particularly exciting [35].

Different acids can be employed to achieve acid hydrolysis, with sulfuric acid (H2SO4) being the most used hydrolytic agent. The process of esterification between the hydroxyl groups on the surface of cellulose and the anionic sulfate ester groups causes the creation of a negative electrostatic layer, which then makes it easier for nanocrystals to disperse in water.

The acid hydrolysis technique typically uses temperatures between 40 and 80 °C for 10-120 min, 60 to 70 percent H2SO4, and 5 to 15 g of fiber per 100 cm³ of acid dissolution [36].

The cellulose chain is penetrated by hydronium ions during the acid process, which hydrolyzes the glycosides linkages in the amorphous parts and releases the individual crystalline sections [37].

These nanocrystals are made entirely of cellulose and have high crystallinity (54–88%) [38,39], albeit the features of these nanocrystals differ depending on the kind of plant and extraction technique.

The residual free acid molecules and other contaminants should be eliminated after acid hydrolysis by dilution with water and washing using dialysis and centrifugation methods. To further stabilize the NCC particles in homogenous suspensions, specialized mechanical processing like sonication may be required.

However, due to the large quantity of water used in the washing process for neutralizing the nanocellulose suspension, the acid hydrolysis process suffers from a high inclination for corrosion, a low rate of recuperation, and high acid wastewater production [40].

The primary microscopic methods used to investigate the morphological properties of CNC are atomic force microscopy (AFM), transmission electron microscopy (TEM), scanning electron microscopy (SEM), or light scattering methods like small angle neutron scattering (SANS), polarized and depolarized dynamic light scattering, or dynamic light scattering (DLS) [41].

It is important to note the use of cellulose nanocrystals in the production of bio composite packaging materials among its many other uses [42,43].
3.2 Cellulose nanofibers (CNF)

CNF is produced using by-products from cane sugar, corn, rice, barley, bananas, and wheat. The most typical sources of nanocellulose used to produce CNF are wood and wood pulp [44]. Isolating CNF is most frequently done by mechanical treatment. However, there are alternative approaches as well [45,46], including enzymatic and pharmacological therapies.

The micro-fluidizer operates at a constant speed in contrast to the homogenizer, which maintains a constant process mass. When refining is done using a disc filter, the threads are linked through a space between the spinning and stationary discs [47]. Researchers are now interested in cellulose nanofibers (CNF), also known as microfibrillated cellulose, cellulose microfibril, or microfibrillar cellulose, due to the intriguing nanocomposite possibilities they have.

The cellulose fibers must undergo a mechanical disintegration process to delaminate the fiber and isolate the nanometric fibers, which is essential to create these structures. To assure the efficacy of the nano fibrillation process, this procedure uses a lot of energy. Various pretreatments have been designed to endure cellulose fiber before its nano fibrillation to lessen it and improve the process efficiency [48]. There are several ways to extract glucose (monosaccharide) from cellulose. The usage of cellulasises, enzymes that catalyze the breakdown of cellulose polymer into smaller polymer branches, namely cellobiose (dimer) and glucose, is one of the most promising.

Endoglucanases, exoglucanases, and cellobiohydrolases (CBH) are the three classes into which these enzymes have traditionally been grouped. In comparison to those obtained merely by mechanical treatment, the generated CNF (10–20 nm) exhibits better homogeneity [49]. A chemical reaction between monochloroacetic acid and cellulose in the presence of sodium hydroxide results in partial carboxymethylation, a process in which the hydroxyl groups of the cellulose chain are replaced by carboxymethyl groups (CH₂COOH), in two successive phases. Carboxymethylation makes the surface of the fibrils highly charged and makes it easier for them to release during the disintegration process. Finally, 5–15 nm diameter and greater than 1 m length nanofibers may be produced [50].

The main barrier to commercial success has been the extremely high energy consumption, which translates to about 25,000 kWh per ton in the manufacturing of MFC because of the necessary several runs through homogenizers. [51] Saito and others [52] Before the initial mechanical treatment, a few pretreatments were applied to reduce the degree of polymerization and weaken the hydrogen connection. Mechanical refinement, alkaline hydrolysis, solvent-assisted pretreatment, organic acid hydrolysis, 2,6,6 tetramethylpiperidine-1-oxyl (TEMPO)-mediated oxidation, enzymatic disintegration, periodate-chlorite oxidation, oxidative sulfonation, cationization, ionic liquid, carboxymethylation, deep eutectic solvents, and acetylation are some of these pretreatments [53].

Nanofibrous structure products were produced using the TEMPO reagent. The cellulose degradation is increased when this procedure is coupled with sonication action, resulting in fibers that are distinguished by their longitudinal rupture and simplifying the subsequent defibrering steps [54].

3.3 Bacterial nanocellulose (BNC)

The other types of nanocellulose, such as CNC and CNF, are made through a top-down method (cellulose molecules of higher dimensions are broken down to produce nanocellulose), whereas bacterial nanocellulose (BNC) is made through a bottom-up method (glucose molecules are metabolized to produce nanocellulose) [55].

BNC is formed as floccus, which subsequently develops into fiber and intertwines to make pellicles. Bacterial species include Acetobacter, Azotobacterial, Pseudomonas, and Sarcinaventriculi and can generate BNC. BNC is produced by the fermentation of glycerol and glucose found in the natural or artificial medium (in which the bacteria is grown). Conditions during culture, such as oxygen supply, pH changes, etc., have an impact on the mechanical properties, crystallinity, and form of the generated BNC [56].

A very important component of the synthesis of BC is the choice of microorganism strains. Currently, static fermentation and submerged fermentation are the two primary techniques that have been employed for the manufacture of BC [57].

BNC is typically produced as fibers with a diameter between 10 and 100 nm and crystallinity between 75 and 96%. It is biodegradable [58,59]. Numerous methods have been employed to determine the single fiber's mechanical properties, with Young's moduli greater than those of CNF and CNC at 78 to 114 GPa[60,61]. Particularly high purity (pure cellulose), a nanofiber network structure, and a high-water content of 99% in the form of physically and thermally stable hydrogel bodies are characteristics of BNC [62].

Due to BNC's single fibers' tens of nanometer thickness, scanning electron microscopy (SEM) is an excellent tool for examining its morphological characteristics. This approach has the fundamental benefit of not requiring the creation of extremely thin sections, as is necessary for transmission electron microscopy (TEM).

Furthermore, photographing three-dimensional BNC objects is made much easier by its exceptionally high depth of field. Research on biotechnological techniques spanning from agitated to static cultivation approaches, utilizing methodologies ranging from batch or fed culture methods to continuous
culture methods, has been sparked by the demand for high-quality BNC. The tools employed can include spinning disk reactors, bubble columns, and aerated fermenters [63].

A more uniform BC and equally distributed oxygen to bacterial cells would also come from fermentation agitation. The generated BC, however, is less crystalline and strong mechanically than static fermentation [64].

The development of cellulose nonproduction strains [65], irregular BC granule or pellet morphologies, and physical BC characteristic alteration are only a few of the submerged fermentation problems that the researcher is still working to solve. Additionally, due to the buildup of self-protection metabolism, hydrostatic pressures and excessively high rotation speed may encourage bacterial production of gluconic acid [66].

### 3.4 Microcrystalline cellulose (MCC)

In the manufacture of food, microcrystalline cellulose (MCC), a refined form of wood pulp, can be employed as a texturizing, anti-caking, emulsifying, extending, and bulking agent.

As an alternative to carboxymethylcellulose, it can also be used in vitamin supplements. Its approval as a thickener, stabilizer, or emulsifier is given the E E460 designation in the European Union.

Abrasive, absorbent, anti-caking, aqueous viscosity-increasing, binder, bulking, emulsion-stabilizing, slip-modifying, and texturizing properties of MCC are also used in the cosmetic sector and may be found in a variety of hair and skin care products in addition to cosmetics.

Other popular methods for estimating the thermal behavior of MCC under thermal stresses include differential thermal analysis (DTA), differential scanning calorimetry (DSC), and thermogravimetric analysis (TGA). Noting that the source and isolation method have a significant impact on MCC fiber diameter.

Since the amorphous cellulose is destroyed, leaving the MCC, acid hydrolysis is the primary method of getting MCC. The factors that have the greatest influence on the hydrolytic process are the fiber-acid ratio, the kind and concentration of the acid, and the temperature and duration of the hydrolysis process. [67]

There are many ways to extract MCC from lignocellulosic wastes. For example, sisal fibers have been treated with sodium chlorite, followed by NaOH and acid hydrolysis [68], while waste cotton fabrics have been subjected to mercerization with 12% NaOH at room temperature for two hours, acid hydrolysis, and then treatment with NaOH [69] or phosphotungstic acid to create a new, environmentally friendly way to make MCC [70].

The ability to obtain MCC by an enzymatic radiation method has also been described [71]. On the other hand, a promising mechanical pulping technique that has seen widespread application is the steam explosion treatment procedure [72].

### 4. Isolation of Nano fibrillated cellulose

The purification of the biomass, which comprises of the two sub-steps of pulping and bleaching, is the primary stage prior to fibrillation. The goal of pulping is to get rid of non-cellulosic components like lignin and hemicelluloses.

Alkali [73] and organic solvents [74] are only two examples of chemicals that may be used as pulping agents. Alkali can also be coupled with sulfur compounds to speed up the pulping process [75].

To extract pectin and waxes, a stage of extraction might come before pulping. Bleaching, which is a component step in the pulping process, happens after pulping. Hydrogen peroxide and sodium chlorite are the two bleaching substances that work the best. [76-77]

The extraction of cellulose and its mostly acid-based purification are the primary topics of discussion in the bibliography.

In general, acid hydrolysis would be used to make cellulose nanocrystals following alkaline treatment and purification, whereas mechanical treatments that end in a high-pressure homogenization procedure are used to produce cellulose nanofibers. Bacterial nanocellulose may also be produced via fermentation techniques.[78]

### 4.1 Chemical Treatment

When semi crystalline cellulose fibers are hydrolyzed with mineral acids, the crystalline areas are released, resulting in the formation of cellulose nanocrystals.[79]

Pre-treatments are often employed to get rid of everything that isn't cellulose, such hemicelluloses, lignin, fat, wax, and pectin around the cellulose structure, to make it easier for the crystalline area to be liberated.

Controllable pretreatment needs to adhere to a few criteria, including: 1) lowering energy use and associated costs; 2) preventing the production of hazardous wastes; and 3) preserving the core cellulose structure while separating out non-cellulosic impurities. A few in-depth research studies described the chemical pretreatment procedure and its pertinent aspects. With either acid or alkali, this preparation may entail hydrolysis.[80]
4.2 Alkali Treatment

Lignin and the residual pectin and hemicelluloses are solubilized during moderate alkali purification. To prevent unwanted cellulose degradation and to guarantee that hydrolysis only takes place at the fiber surface so that intact nanofibers may be retrieved, alkali extraction must be carefully managed. [81-85]

4.3 Oxidation pre-treatment

TEMPO-mediated oxidation is a potential surface modification technique that may introduce carboxylate and aldehyde functional groups into solid native celluloses under aqueous and mild conditions to solve the aggregation issue brought on by the presence of native cellulose -OH groups. [86-87]

4.4 Grinding

To fibrillate cellulose fibers, several researchers have sought to employ modified commercial grinders with specially crafted disks. In such machinery, the cellulose slurry is transferred between two grind stones: one that is stationary and the other that rotates at a rate of roughly 1500 rpm.

The shearing forces produced by the grinding stones are what cause the fibrillation mechanism in grinder therapy. This breaks down the cell wall structure, which is made up of hydrogen bonds and multi-layered nanofibers. Nanosized fibers are then separated from the pulp in this way. [88]

4.5 Cryocrushing

Liquid nitrogen is used to freeze the fibers before they are subjected to strong shear stresses in the cryocrushing process, which produces nanofibers. Making ice crystals inside the cell wall is the aim of cryocrushing. [89]

Ice crystals inside the frozen fibers press on the cell walls, causing them to break under the shock of high impact pressures and releasing microfibrils. [81]

Cryocrushing fibers from flax, hemp, and rutabaga that had been chemically treated allowed Bhatnagar and Sain [85] to produce nanofibers with an estimated diameter of 5-80 nm.

4.6 Enzymatic pre-treatment

A variety of cellulases, not just one, break down cellulose in nature. These can be divided into three groups: cellobiohydrolases of the A and B types; endoglucanases of the C and D types. While endoglucanases typically need some structural disorder to destroy cellulose, cellobiohydrolases may target extremely crystalline cellulose.

Endoglucanases and cellobiohydrolases have potent synergistic actions that speed up MFC degradation. When compared to nanofibers made by submitting pulp fiber to severe acid hydrolysis, MFC made from enzyme-pretreated cellulosic wood fibers had a more advantageous structure, having a higher average molar mass and a greater aspect ratio. [90]

The first stage in the three-step process of enzyme hydrolysis is the mechanical or chemical treatment of the biomass to disrupt its interconnecting structure. By increasing the polymers' surface area, this process makes the enzymatic treatment more effective. [92,93]

In contrast to those produced by mechanical treatment alone, research found that the combination of acidic treatment and enzymatic hydrolysis produced nanofibrils with a low aspect ratio and molecular weight. [94]

To ensure ongoing enzyme activity, the second and most important step involves exposing the treated biomass to the enzymes in a buffer solution. [95]

Every enzyme has a specific mechanism of action, thus combining them results in the optimal level of hydrolysis and cleavage of the polymer into smaller pieces. [96]

The enzymatically prepared fibers go through a mechanical process in the third and final phase, which produces NFC. Xylanase pretreatment and subsequent ultrafine grinding of rice straw pulp for soda and sulfite processing enhanced fibrillation and used less energy, according to prior research. [97]
5 Preparation of nanocellulose

Single cellulose fibers with widths of 25 to 30 mm are bundled together to form cellulose fibers. Microfiber bundles with widths ranging from 0.1 to 1 mm make up one single cellulose fiber. Microfibers are made up of nanofibers, which range in size from 10 to 70 nm in diameter and have lengths of thousands of nanometers.[99]

The term “cellulose microfiber” refers to a fiber made up of continuous cellulose chains with minimal amounts of lignin and hemicellulose and having a minimum corresponding length of 2 to 20 microns.[100]

Purely crystalline cellulose chains with lengths of a few microns and widths between 5 and 40 nm have traditionally been referred to as cellulose nanofiber.[101]

5.1 Source

5.1(a) Wood

Researchers first used cyclic mechanical treatment in a high-pressure homogenizer to create MFC from wood pulp in the 1980s, which is when mechanical extraction of nanofibers from wood began.

The wood pulp and a substance in which the fibers had been split into their sub-structural microfibrils were disintegrated because of the homogenization process. Strongly entangled, disordered networks of cellulose nanofiber made up the MFC gels that were produced. Research into MFC synthesis frequently begins with bleached Kraft pulp.[102]

5.1(b) Agricultural Crops and By-Products

The most significant industrial source of cellulosic fibers is unquestionably wood. Despite this, it is difficult to provide all consumers with the necessary amounts of wood at an affordable price because of rivalry from other industries, including construction goods, furniture, pulp and paper, and energy combustion. Therefore, it is anticipated that demand for fibers from crops like flax, hemp, sisal, and others, especially from their by-products, will rise.

These agricultural byproducts are now either burnt or utilized to produce low-value goods like animal feed or biofuel. Crop leftovers can be excellent sources of natural nanofibers since they are renewable.[103]
5.1(c) Bacterial Cellulose

As extracellular structures, cellulose fibers are released by certain bacteria from the genera Acetobacter, Agrobacterium, Alcaligenes, Pseudomonas, Rhizobium, or Sarcina in addition to their plant origins. Acetobacterxylinum, a species of acetic acid-producing bacterium that is Gram-negative, is the most effective generator of bacterial cellulose.[104]

6. Modification of nanocellulose

It's generally known that bio-based nanocellulose has mostly been employed in paper or bio nanocomposites because of its mechanical reinforcement and barrier capabilities; nevertheless, new uses, notably medication delivery, are anticipated and encouraged.[105]

The cationic surfactant N-hexadecyltrimethylammonium bromide, diluted in water, may be physically adsorbed to the TEMPO-NFC to provide hydrophobic behavior.[106]

To prevent the phenomenon of nanofibrils aggregating upon drying and their poor dispersive characteristics in most non-polar media, modification methods are also important [107].

Other methods, such solvent exchange in ionic liquids [108], silylation [109], and grafting [110], have been used to improve the hydrophobic nature of NFC.

We may draw the conclusion that surface modification of nanocellulose is commonly used in research to increase its mechanical characteristics and the interaction between them with the goal of modulating the hydrophobicity and surface roughness. [108,111-113]

To maintain the stability of the nanofibrils, the processing environment must be moderate. The stability and effect of any loaded medication may also be altered by these alterations; like directing drug release, Table 2 lists a variety of surface modification approaches used to investigate the potential of nanocellulose in the pharmaceutical industry

<table>
<thead>
<tr>
<th>Methodology for modifying surfaces</th>
<th>Concept and supporting elements</th>
<th>Important takeaways</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adsorption</td>
<td>• Electrostatic interaction between polyelectrolytes • Uncharged materials such as resins using hydrogen bonds and Vander Waals forces.</td>
<td>• To create organogels in dimethyl sulfoxide, nanocellulose was first carboxylate, and then octadecyl amine was adsorbed. • The organogels received various medications before being heated and cooled. The usage of octadecyl amine, whose surfactant capabilities stabilized the extremely hydrophobic drug particles, may have contributed to the generated organogel ability to maintain the drug release. This nanocellulose organogel can therefore be utilized as a drug carrier for carefully controlling the release of a medication.</td>
<td>[114–115]</td>
</tr>
<tr>
<td>Silylation</td>
<td>• Making use of coupling agents like triethoxyvinylsilane and alkoxysilane. • The hydrocarbon chains found in silane combine chemically with nanocellulose to form silane agents. • The chemical reaction is enhanced by the presence of water.</td>
<td>• Methyltrimethoxysilane was added to a suspension of nanocellulose to create a silylated nanocellulose sponge, which was then freeze-dried. • Depending on the silylation amount, the resulting sponge had different water contact angles. • Silylation agents are poisonous and costly, hence their usage in the drug delivery industry is restricted.</td>
<td>[116–118]</td>
</tr>
<tr>
<td>Esterification</td>
<td>• Reacting hydroxyl groups on the surface of nanocellulose with an acid anhydride, an organic acid, or an acyl halide is the most popular approach for making nanocellulose hydrophobic.</td>
<td>• Different reaction conditions were used to carry out the esterification of CNC with succinic anhydride. • The results showed that decreasing the response time by 240 minutes (about 4 hours) allowed the surface-modified CNC to attain thermal stability. • This method produces a stable nanocomposite that works well as a drug carrier.</td>
<td>[119-122]</td>
</tr>
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</table>
Carbanylation • Carbanylation via amidation provides a more stable link as compared to esterification. • These developments open the door for numerous applications in drug delivery.
• Carbanylation of NFC in toluene to produce (NFC_C18NCO) enhanced the antibacterial properties with a synergistic effect after the addition of TiO2 nanoparticles without affecting their biodegradability in comparison to the neat NFC.

[123-124]

Functionalized CNF reactions • The surface of nanocellulose can be altered by carboxylation during TEMPO oxidation.
• Different kinds of cyclodextrins were used to create TEMPO-NFC/cyclodextrin-based scaffolds that were loaded with raloxifene hydrochloride. Beta-cyclodextrin-based scaffolds had the longest-lasting drug release, lasting 480 hours (about 3 weeks).

[125]

Polymer grafting • The "Grafting from" approach involves mixing nanocellulose with a solvent and a starting agent, then inducing polymerization on its surface.
• "Grafting onto" technique: nanocellulose is combined with an attaching agent and a polymer.
• Grafted cellulose nanocrystals were created by "grafting onto" polyphosphoesters. A negative charge on the bonded surface was employed to combine with doxorubicin. After releasing the medication into the cells and disrupting the electrostatic connection in the acidic environment inside the tumor cells, drug-loaded implanted cellulose nanocrystals demonstrated increased anticancer efficacy against HeLa cells. A pH-sensitive carrier with regulated drug release behavior is presented in this work.

[126-127]

Table 2 Different surface modification methods for nanocellulose

7. Pharmaceutical applications

As shown in Fig. 5, diverse pharmaceutical uses for nanocellulose-loaded drug delivery devices will be discussed in this study.

7.1 Controlled and sustained drug delivery

In the development of many forms of controlled or sustained drug delivery systems, such as nanocomposites, films, microparticles, gels, and scaffolds, NFC and CNC shown considerable relevance, providing an excellent and safe solution for commonly delivered medications.[128]

By freeze-drying, a distinct kind of porous nanocomposite aerogel was created from several NFC sources to serve as reservoirs for oral drug administration. The NFC aerogels included beclomethasone dipropionate nanoparticles that had been coated with amphiphilic hydrophobic proteins.[129]

Additionally, NFC was employed to create film matrices with outstanding mechanical qualities using a filtering technique appropriate for heat-sensitive medications. Itraconazole, indomethacin, and beclomethasone were evaluated as three model medications.[130]
Further, pH sensitive beads made with magnetic nanocellulose and sodium alginate in the presence of calcium ions demonstrated improved controlled ibuprofen release [131]. In another study, controlled-release dexamethasone-loaded hydrogel beads were created using chitosan in addition to nanocellulose and alginates [132].

7.2 Rapid drug delivery

The use of NFC and CNC in the development of fast drug delivery systems has been utilized in a variety of studies for the preparation of drug delivery systems, such as tablets and nanoparticles.[133]

The attached CNC/chitosan oligosaccharide was used to make procaine hydrochloride loaded nanoparticles, which delivered the medication within 1 hour at pH 8. The produced particles suggested the use of a biocompatible nanocarrier for transdermal application [134].

7.3 Stabilizing agent

Another key function for NFC and CNC is as a stabilizing agent. NFC derived from a food industry waste product, the mango teen fruit, was utilized to stabilize oil-in-water Pickering emulsions containing vitamin D3. This action might be attributed to NFC’s capacity to block lipases or bind to other components involved in lipid breakdown, such as bile salts [135].

However, NFC’s lipid-inhibiting capacity may be useful in the treatment of obesity. This study confirmed NFC’s capacity to be employed as a surfactant-free emulsion stabilizer,[136]

Another research looked into oil-in-water emulsions stabilized by CNC and NFC. Three distinct antimicrobial oils (cinnamaldehyde, eugenol, and limonene) were used to make these emulsions. Furthermore, CNC derived from corncob cellulose was utilized as a stabilizer in the Dlimonen Pickering emulsion.[137]

7.4 Cell culture

NFC hydrogels were employed as a cell culture safe environment. These hydrogels can be used in a variety of applications, including tissue engineering, medication delivery, and cell treatment. [138]

Because they are plant-based, they have the required immunological qualities. Another study found that NFC has a positive ability for hepatic cell culture and tissue engineering, as evidenced by improvements in metabolic activity and cell shape, as well as the expression and localization of hepatic markers [139].

7.5 Food Packaging

The protection of the environment has encouraged the exchange of conventional packaging made of polyethylene or copolymer-based materials with biodegradable and renewable components [140], which ensures food quality while minimizing trash output. In this way, nano clays, kaolinite, or graphene (common fillers of plastic polymers) have been replaced with bio-based materials to improve active packaging, which includes adding antimicrobial nanoparticles to plastic films to prevent food contamination [141] or using layered composite films for more flexible packaging [142].

Nanocellulose is combined with two types of polymers: thermoplastics and thermosets. The usage of this disposable and sustainable material in place of its plastic equivalent will certainly help to the reduction of greenhouse emissions [143].

7.6 Foodstuffs

Bacterial, micro fibrillated, regenerated, and vegetal nanocellulose has been used as a fat substitute or oil emulsion stabilizer in food items [144]. Furthermore, a new study is predicated on the use of this polymeric nanostructure to preserve natural antioxidants such as polyphenol chemicals that prevent food degradation using adsorption desorption procedures [145].

The use of BNC derived from agricultural wastes has been studied to create packaging materials with components that release or absorb substances from or into the packaged food or the surrounding environment, thereby extending shelf-life and maintaining or improving packaged food condition [146].

7.7 Biomedical Applications

Nanocellulose-based composites are extremely biocompatible and low in toxicity, which is why they are used in so many biological applications [147]. Changes to the surface of nanocellulose are required to bind medicines, non-ionic compounds having hydrophobic properties, to the. According to current study [148], increasing its hydrophobic nature to assist drug bonding might therefore manage its sluggish release.

Bacterial nanocellulose may also create multi-layered hydrogel tubes with the addition of chemicals. Tubular nanocellulose can be employed as a restorative material for the bile duct, ureter, and esophagus [149].
Because of the antibacterial and non-toxic features of hydrogels, nanocellulose-based hydrogels have been used in wound dressing applications. Similarly, combining nanocellulose with water or biological fluids produces hydrogels with qualities comparable to human tissues; as a result, they are frequently employed in scientific fields such as tissue engineering and in vitro diagnostics [150].

7.8 Wood Adhesives

The most common adhesives in wood adhesive technology are synthetic formaldehyde-based adhesives such as phenol-formaldehyde resin, urea-formaldehyde resin, and melamine-formaldehyde. Furthermore, the use of cellulose nanoparticles in the formulation of wood adhesives increases their adhesive bonding efficiency and durability in both wet and dry circumstances, acting as a reinforcing agent [151,152]. Nanocellulose is used in traditional adhesives, particularly wood adhesives, since it introduces a sustainable, plentiful, and inexpensive nano-biomaterial for property enhancement [153,154].

7.9 Cosmetic

Because of its outstanding qualities, BNC has numerous potential uses in cosmetics, namely as a support for skin-active chemicals or as a structuring ingredient in cosmetic formulations [155]. Thus, a film created from bacterial cellulose generated in a modified medium was effectively employed to create sheet masks with moisturizing and anti-inflammatory properties for acne-prone and inflammatory skin. This substance, when applied to the skin via bacterial cellulose, does not produce a distinct and disagreeable odor, as is typical of commercial cosmetics containing it [156].

7.10 Electrical and Optical Materials

These methods enable the creation of materials with unique surface characteristics and functionalities, particularly for electrochemical, electrical, and optical applications [157]. The primary goal may be to synthesize chiral hematic compounds from cellulose nanocrystals in conjunction with other polymers or silica, allowing some component to be selectively deleted afterwards or employed as a nanocomposite. By selectively removing a portion of the initial nanocomposite, chiral mesoporous material is produced, which can host components or act as a template to develop additional chiral materials [158]. Electronics applications include chiral plasmonic, sensitive hydrogels, anti-reflective coatings, optical filters, adaptable electronics, and soft actuators. Conversely, cellulose nanocrystals have been used to create optical materials such as surface plasmons, UV blocking and fluorescence, and low refractive materials [43].

7.11 Textile

Nano cellulose materials have found considerable uses in the textile area, particularly for medical applications, due to their molecular structure and enormous active surface. Another method is to make ethyl cellulose nanocomposites with Spiro oxazine as a light stabilizer. During the high temperature paste printing process, cellulose nanoparticles retain photochromic capabilities without changing physical properties [159].

7.12 CO₂ Capture

Two of the primary approaches for CO₂ adsorption involve the chemical modification of nanocellulose or the incorporation of inorganic particles into nanocellulose; these nanomaterials, particularly functionalized nanocellulose aerogels, can be used as adsorbents or constituents of membranes to selectively retain CO₂ [160]. CO₂ retention by physical absorption has also been shown using aerogels saturated with acetate-functionalized crystalline nanocellulose solution [161].

8. Conclusion

The primary purpose of this work is to give a summary of how nanocellulose promotes different uses. The primary goal of this was on investigation and advancements in BNC, NFC, and NCC. This extraordinary biomass produced by plants has not yet been extensively studied in the literature. Therefore, additional study into the possible uses of these materials in medicine is recommended. A lot of tests on cellulose formulations with sustainability Various scientists and companies conducted several research studies to enhance the production and marketing of nanocellulose. Applications for surface-modified nanocellulose and nanocellulose-based mixes in biology include biosensors, blood vessel replacement, bone rebuilding, and wound healing. When most polymer chains are physically or chemically connected, they produce multilayer network patterns like hydrogels and aerogels.
9. Future perspective

Future study should concentrate on the dangerous effects of chemicals routinely used to increase the effectiveness of dressings, which may have a negative impact on the healing process. In the years to come, it is critical to examine the problems connected with nanocellulose and related biomaterials for use in tissue engineering and other biomedical applications. The in vivo and in vitro evaluation of nanocellulose biodegradation patterns should be handled and investigated carefully. Recent research investigations have concentrated on cellulose at the nano-level because to the fact that it is an eco-friendly material with unique qualities that allow it to be utilized as a flexible construction with nanomaterials that incorporate nano-dimensional particles (discontinuous phase) into a reference matrix (continuous phase) are known as nanocomposites.

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