Cellulose-Based Materials for Biomedicine

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Received: 09-Jun-2023, Manuscript No jphc-23-101992; **Editor assigned:** 12-Jun-2023, PreQC No. jphc-23-101992 (PQ); **Reviewed:** 15-Jun-2023, QC No. jphc-23-101992(Q); **Revised:** 22-Jun -2023, Manuscript No. jphc-23-101992 (R); **Published:** 27-Jun-2023, DOI: 10.35248/2332 2594.23.13(6).509

Abstract

Nature contains a variety of biomaterials, but none of them completely satisfies the requirements. Biopolymers based on cellulose, an environmentally favourable material, have improved substantially to meet the majority of consumer demand and get around many environmental issues. An overview of the state of the art in cellulose knowledge and technological biological applications is what this review tries to do. The chemical makeup of cellulose makes it easy to modify and combine with various substances, including nanoparticles, without having to make laborious efforts. Biomedical applications such as antibacterial agents, antifouling, wound healing, medication delivery, tissue engineering, and bone regeneration have all exploited cellulose-based polymers. They improved the applications to be less expensive, biocompatible, and biodegradable, as well as simple to shape and manufacture into various forms and to have the right chemical, mechanical, and physical qualities. bliography of current research findings for both basic and applied studies.

Keywords: •Cellulose • Biomedical • Wound healing •Drug delivery • Antibacterials •Tissue engineering

Introduction

Anhydroglucose monomer is linked to other molecules in cellulose via - (1-4) bonds (($C_6H_{10}O_5$)n; n is the degree of polymerization; n=10000-5000 depending on the source used to extract cellulose). Plants, seaweeds, sugarcane bagasse, tunicate, marine algae, and bacteria can all be used to make it. Over a few hundred billion tonnes of cellulose are produced annually. Over time, the market's demand has been rising steadily. High stability in acidic environments, chirality, high tensile strength, good elastic modulus (130 GPa-150 GPa), low density or lightweight (density of 1.6 g/cm^3), high biodegradability, and an abundance of hydroxyl functional groups on their surfaces all contribute to the excellent mechanical, physical, and chemical properties of cellulose. Cellulose also has good wettability and high tensile strength. As a result, it was used for a variety of applications, including those based on energy, the environment, and health. Advanced biomedical uses exist for cellulose-based materials. Antibacterial agents, wound dressing, medication delivery, tissue engineering, artificial blood vessels, and UV radiation protection were among the applications documented. Cellulose can develop into a variety of materials, including membranes Three-Dimensional (3D) scaffolds, hydrogels, aerogels, and aerogels. They display a number of traits that make biomedical applications appealing. They provided decent binding qualities. Both organic and inorganic-based compounds can be conjugated with them.

Cellulose nanoparticles

Microfibrillated Cellulose (MFC), Microcrystalline Cellulose (MCC), Nanofibrillated Cellulose (NFC), Cellulose Nanocrystals (CNCs), microfibrils, and Bacterial Cellulose (BC) are some of the different kinds of cellulose that have been sold. It is attainable in the micro- and nano-scale regimes. Microsize Cellulose Particles (MCC) are cellulose particles having a length up to 1 m and a width greater than 1 m. Wood is frequently treated mechanically or chemically to create MFCs. Individual fibres known as microfibrils have dimensions of >10 m in length and 2 m–20 m in breadth. 50% to 90% of cellulose nanoparticles are crystallised. Hydroxyl groups are cellulose's most frequent functional group. By means of TEMPO-mediated oxidation, which produces TOCNF, NFC can be further oxidised to carboxylic functional groups. A variety of techniques, such as adsorption or chemical modification through the creation of covalent bonds, can be used to alter the surface of cellulose. For the material's characterisation, cellulose's surface charge is a crucial factor. The strong charge of the cellulose colloids ensures great stability and inhibits nanoparticle agglomeration

Applications of cellulose nanoparticles as antibacterial agents

Comparatively to other natural biopolymers as cationic chitosan, cellulose demonstrates no intrinsic biocidal action. Nevertheless, it can be employed as an antibacterial agent in a variety of ways, such as surface modification and conjugation with antibacterial substances including organic and inorganic chemicals.

Pure cellulose with modification for antibacterial agents

Pure cellulose can be surface-modified with a variety of functional groups, such as carboxylic groups, aldehydes, amines, alkyl amines, and quaternary ammonium groups, to enhance its antibacterial characteristics. Organic compounds having photosensitizing characteristics can be used to change the functional groups of cellulose. The table below provides an overview of some of the antibacterial substances that use cellulose-based polymers. Researchers looked at the 2,3-Dialdehyde Nano Fibrillated cellulose's (DANFC) antibacterial efficacy against Methicillin-Resistant *Staphylococcus aureus (MRSA) and S. aureus*. Utilising a chemical reagent such as sodium periodate ($NaIO_4$), dialdehyde was produced by oxidation cleaving the C2 and C3 bonds in the D-glucose monomer of cellulose. Increasing the oxidation duration of DANFC improves its antibacterial properties. The aldehyde groups in DACNF generate a decrease in pH value (5.7-6.2), which has an antimicrobial effect. Dialdehyde microcrystalline cellulose (DAMC) has also been shown to have antibacterial properties. The most effective antibacterial action against *S. aureus, Bacillus subtilis* (*B. subtilis*), *E. coli*, and *Salmonella typhimurium* was demonstrated by DAMC with aldehyde levels of 5.14 mmol/g. For *S. aureus, B. subtilis, E. coli,* and *S. Typhimurium*, it showed Minimum Inhibitory Concentration (MIC) values of 15 mg/mL and 30 mg/mL, respectively. Ginger nanofibers, also known as GNFs (ginger nanofibers), were processed using high-pressure homogenization and acid hydrolysis to remove the cellulose .GNFs' antimicrobial effectiveness was evaluated .For *B. cereus, E. coli, S. aureus, S. Typhimurium*, the MIC values of GNF were 142 g/mL, 131 g/mL, 180, and 310 g/mL, respectively. High antibacterial activity is displayed by cellulose containing carboxylic groups. A gel of TOCNF (0.2-0.8 wt% in water) stopped a wound's growth that was infected with the bacteria *P. aeruginosa* from spreading. Through processing, such as autoclaving, the physical, chemical, and antibacterial activities of carboxylate CNF can be changed. Pure cellulose nanoparticles' antibacterial properties could be explained by a number of processes, such as a reduction in the bacteria's mobility, encircling and entrapping them via the development of a network, and a lowered pH due to the rise in aldehydes groups in CNFs. But further research needs be done to determine the crucial factors influencing the antibacterial activity of pure cellulose nanoparticles.

With the right functional groups, pure cellulose exhibits strong antibacterial properties. However, it is necessary to take into account the existence of alien species that may produce inflammation and antibacterial activity, such as endotoxins or lipopolysaccharides. The endotoxin level in the CNF generated by the modified TEMPO-mediated oxidation process utilising sodium hydroxide as a pre-treatment was 45 Endotoxin Units (EU) per g of cellulose . At low doses, this value might not be harmful.

Photoactive cellulose for antibacterial agents

They required the presence of photosensitizer molecules that either generate reactive species (i.e., photodynamic treatment) such as Reactive Oxygen Species (ROS) or absorb light radiation and convert it to thermal energy (photo thermal therapy). Pure cellulose is devoid of photosensitizer's characteristics. In order to absorb light, it is typically modified with tiny molecules through covalent and non-covalent interactions. Most of these photosensitizers are substances that are inert against bacteria. However, they are efficient in killing germs when using low-cost light sources like Light-Emitting Diode (LED) bulbs.

Using CNC and a material based on hairy Aminated Nanocrystalline Cellulose (ANCC), Photodynamical Inactivation (PDI) against bacteria has been demonstrated. Xanthene, BODIPY (Dipyrrometheneboron difluoride), chlorine, phthalocyanines, protoporphyrin-IX , and porphyrin are examples of molecules that can be used to modify cellulose and produce reactive oxygen species when exposed to light CNC was chemically changed into CNC-Por by cationic porphyrin using a Cu(I)-catalyzed reaction.

Cationic cellulose for antibacterial agents

Cationic cellulose demonstrates inherent antibacterial action, much like Chitosan (CTS). The high binding affinity between the positive charge of these polymers and the negative charge of the bacterium cells underlies the antibacterial effect of cationic biopolymers. Due to unfriendly phosphate groups in peptidoglycan and phospholipids, the surface of bacterium cells, both Gram-positive and Gram-negative, is negative. According to this theory, cellulose can have significant antibacterial action by being positively charged Additionally, cationic CNCs can be employed as immune-modulators Quaternary ammonium compounds, such as 3-chloro-2-hydroxypropyl-tri-methyl ammonium chloride, Poly(Isopropanol Dimethylammonium) Chloride (PIDMAC), quaternized Poly(2-(Dimethylamino Ethyl) Methacrylate)(PDMAEMA), and Cetyltrimethylammonium Bromide (CTAB), can be used to modify Benzalkonium chloride , 3-Chloro-2-Hydroxypropyl-Trimethyl Ammonium Chloride (CHPTAC) , pyridinium/N-chloramine, and quinolinium silane salt .The antibacterial activity of cationic cellulose can be attributed to a number of mechanisms, including the destabilisation of bacterial intercellular membranes caused by Ca^{2+} or Mg^{2+} ion exchange, membrane disruption caused by the release of potassium ions, the formation of ROS, an increase in amine groups, or an increase in lipophilicity caused by the use of amino-alkyl groups.

Organic-modified cellulose as antibacterial agents

Chemically modifying cellulose with organic bioactive compounds, such as antibiotics, antimicrobial peptides, N-halamines, aminoalkyl groups, bacteriophage, and polymers, can increase its antibacterial activity.

Antibiotic-modified cellulose

Antibiotics are frequently used to treat germs. Antibiotics such as the beta-lactam benzyl penicillin, ciprofloxacin, tetracycline hydrochloride, silver sulfadiazine (Ag SD), 3-pentadactylphenol , Allicin, and amoxicillin were grafted onto cellulose. Through the creation of ester bonds, antibiotics like penicillin can be covalently changed with cellulose. The covalent modification of cellulose offers strong durability and effective antibacterial characteristics. It has been observed that the cationic cellulose filter paper has antibacterial activity for the treatment of water. As a Cationic Polyelectrolyte Binder (CPE), PIDMAC was applied to the cellulose filter paper. Additional amphiphilic block copolymer micelles containing the antibacterial and antifungal compound triclosan were added. Through the block copolymer Polystyrene-Blockpolyacrylic Acid (PS-b-PAA), the micelles interacted with the CPE.

Cellulose-inorganic nanoparticles for antibacterial agents

Inorganic nanoparticles such metal oxides, metallic nanoparticles, and Metal-Organic Frameworks (MOFs) were used to modify cellulose. The majority of these materials have inherent antibacterial properties that enable them to function well against both Gram-positive and Gram-negative pathogens. High antibacterial activity can be found in carbon nanoparticles. With cellulose, they were conjugated. Antimicrobial activity against *E. coli* and *S. aureus* was reported for a composite of BC and graphene oxide (GO). The antibacterial activity of GO/BC nanocomposites was enhanced by electrostatic modification. The sharp edge of carbon nanosheets like GO acts as a knife to cut the cell's membrane, creating a rupture of the outer envelope, which is the primary cause of the antibacterial action of the sheets. High antibacterial activity can be seen in metal oxide nanoparticles like Zinc Oxide (ZnO) nanoparticles. A composite made of hydrophobic Polysulfone (PSf) and Cellulose Acetate (CA) was modified with 0.1 weight percent of ZnO NPs. ZnO NP-containing membranes demonstrated effective antibacterial action against *E. coli* . An in-situ technique was used to create ZnO nanoparticles. Using ammonium hydroxide, Zn^{2+} ions were adsorbed into cellulose prior to precipitation .For antibacterial action, cellulose was added to other metal oxide nanoparticles, such as TiO2 nanoparticle faujasite, and Montmorillonite (MMT) .

High antibacterial activity was demonstrated by cellulose acetate/TiO2 nanoparticles. Water contaminated with microorganisms (*E. coli,* Enterococci, and Clostridium) was purified using a Faujasite-cellulose composite membrane. Offering 100 colonies/100 mL, it demonstrated good eradication efficiency. The cellulose membrane's incorporation of MMT made it possible to modify it with a number of metal ions, including Na, Ca, and Cu. The maximum antibacterial activity against the tested bacteria was demonstrated by BC/Cu-MMT composites. Ag NPs, or silver nanoparticles, are potent antibacterial substances. For antibacterial action, they were extensively modified using cellulose nanoparticles. Ag NPs were created and then electrospun onto Cellulose Acetate (CA) fibre . During the process, silver ions that had been reduced by photons into Ag NPs were adsorbed. High antibacterial activity was shown by the produced materials against *S. aureus, E. coli, K. pneumoniae, and P. aeruginosa*. Interfacial Polymerization (IP) was used to create a polyamide Nanofiltration (NF) membrane made of polyamide and CNC/silver (CNC/Ag) . The membrane containing 0.01 weight percent CNC/Ag demonstrated 99.4% antibacterial efficacy against *E. coli* viability.

Cellulose-based materials for antifouling

The bioactivity, antibacterial, and antifouling capabilities of pure cellulose nanoparticles containing residual lignin or carboxylic functional groups are advantageous. As a result, they are frequently utilised as a membrane coating for antifouling purposes. For antifouling use, a membrane made of TOCNF, poly(vinyl alcohol), and Polyethersulfone (PES) was created. Against *E. coli,* the TOCNF/PVA@PES membrane shown strong antifouling. Zwitterionic poly (cysteine methacrylate, or PCysMA) grafted onto a micro/nanocellulose membrane had outstanding antibacterial and antifouling capabilities. It demonstrated an efficacy of 85% in reducing S. aureus biofilm formation. In comparison to commercial membranes like Millipore GS9035, cellulose nanoparticles-based membranes exhibit strong antifouling efficacy with high reflux.utilising a polyamide containing CNC/Ag (0.01 wt.%) membrane, the CNC/silver/polyamide membrane demonstrated high antifouling activity of 92.6% utilising humic acid with antibacterial activity of 99.4% against *E. coli* viability. For photocatalytic antifouling, a membrane made of CMC/GO/Magnesium Oxide (MgO) nanoparticles was created. Because it produces electrons and reactive oxygen species (ROS), it can be employed as an antifouling membrane. The oxidation of organic contaminants is thus possible. The basis of photocatalytic disinfection with photoactive materials is the production of free radicals in the presence of light.

Cellulose nanoparticles for wound dressing

To prevent microbial infection during burn therapy, extra precautions should be taken. Re-epithelialization must occur quickly during the first 10–14 days of wound healing to avoid problems. Chronic wounds may experience vital physiological changes or trigger tumour growth, both of which greatly increase the rate at which tissues or organs are destroyed. For diabetic individuals who are susceptible to developing chronic ulcers, this

circumstance is crucial. As a result, the dressing stops being viewed as a supplement and instead turns into an important active component during the healing process. To promote a quick and efficient healing process, the dressing should provide a warm and moist environment. In order to avoid infections, it should also be biocompatible, simple to separate, a thermal insulator, and have antibacterial activity.

Drug and gene delivery using cellulose-based materials

Drug delivery has advanced thanks to cellulose-based polymers They can be coupled with nanomaterials like Magnetic Nanoparticles (MNPs) to provide applications with multiple functions. They can be utilised to encapsulate drugs. Because of the functional groups in Carboxymethyl Cellulose (CMC), a selective release of an anticancer drug like 2,4-dihydroxy-5-fluorpyrimidin (5-FU) was made possible by treatment with folate. Folic acid surface modification of cellulose promotes selective cell absorption and binding via cellular mechanism controlled by the folate receptor . For the drug administration of hydrophobic medications including docetaxel, paclitaxel (PTX), and etoposide, cellulose serves as an efficient vehicle Curcumin (CUR) treatment for prostate cancer cells was made more effective by hydroxypropyl methylcellulose. Comparing CUR alone to CUR-conjugated cellulose, significant apoptotic alterations were observed. Comparing cellulose to other carriers including -cyclodextrin (CD), poly(lactic-co-glycolic acid) (PLGA), MNPs, and dendrimer, cellulose likewise demonstrated the maximum cellular absorption. For the medication delivery of CUR, TOCNF and MOFs such Zeolitic Imidazolate Frameworks(ZIF-8)were used.