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Bismuth-Complex-Incorporated Nanocellulose Sheet for Biomedical Application: A Review on New Nanocellulose Composites

Kirubanandan Shanmugam[1]*, P Dhanasekaran[2], Deepa Priya R[3], Narendhar Chandrasekar[4], Ramachandran Balaji[5]

[1]Saveetha School of Engineering, SIMATS, Thandalam, Chennai 602107, Tamil Nadu, India
[2]Department of Chemical Engineering, Erode Sengunthar Engineering College, Erode 638057, Tamil Nadu, India
[3]Department of Biotechnology, Aarupadai Veedu Institute of Technology, Paiyanoor, Chennai 603104, Tamil Nadu, India
[4]Department of BioNano Technology, Gachon University, Seongnam-si 13120, Gyeonggi-do, Republic of Korea
[5]Department of Biotechnology and Chemical Engineering, National Taipei University of Technology, Taipei 106, Taiwan Province of China

Corresponding author: Kirubanandan Shanmugam, Kirubanandan.shanmugam@gmail.com

Abstract: Antibiotic resistance is one of the major issues in the medical field and a potential threat to human health. However, newly emerging antimicrobial compounds failed to combat antimicrobial resistance developed by bacterial pathogens. Recently, a bismuth-based complex has been developed to eradicate antimicrobial-resistant microorganism infections. The complex is known as organobismuth (III) phosphinate, which is said to be a potential broad-spectrum antimicrobial agent. This complex has been incorporated into the nanocellulose suspension to fabricate a biomedical composite for various applications. The composite can be fabricated by two methods namely vacuum filtration and spray coating. In this paper, the surface and topography of the composite are investigated and discussed in terms of SEM micrographs and their antimicrobial potential. This review focuses on the organo-bismuth nanocellulose composite and its biomedical application in the future.

Keywords: Bismuth complex; Nanocellulose; Nanocomposite; Spray coating; Vacuum filtration; Antimicrobial activity; Antifungal activity

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1. Introduction

Bismuth is a stable naturally occurring element that is situated in Group 15 of the periodic table. It has an atomic mass of 209 and an atomic number of 83. It is a soft and silvery metal with a density of 9.78 g/cm^3. Pure bismuth is found in trace amounts in the earth's crust. According to reports, the crustal quantity of this substance is only 8 ppb. It is the 69th most abundant element, less prevalent than indium, cadmium, and platinum and just half as widespread as gold. The electron configuration of [Xe] $4f^{14}\ 5d^{10}\ 6s^2\ 6p^3$ allows bismuth to accept an electron pair easily due to the presence of empty orbits. It has two main oxidation states (+3 and +5). Bismuth is found naturally as bismuthinite (Bi_2S_3) and bismite (Bi_2O_3). Besides, it is a by-product of refining lead, copper, tin, silver, and gold [1,2]. It has a melting point of 271 °C and a boiling point of 1560 °C. Bismuth in the oxidation state of 3 behaves as a Lewis acid when attached to an electronegative atom, thus it is used as an important catalyst in various industrial applications. Due to the Lewis acidity of the bismuth (III) compounds, intramolecular and intermolecular bonds can occur, enabling the formation of extended bismuth structures (coordination number of 3–10). For example, bismuth nitrate pentahydrate [$Bi(NO_3)_3.5H_2O$] has a coordination number of 10. Compositions of bismuth (IV) and other bismuth compounds can exist in the solid state, also known as alkali metal bismutates. In three-coordinate ternary and alkyl-bismuth(III) compounds, the Bi(III) center adheres to the octet rule, resulting in a coordination geometry of a trigonal pyramid. This geometry is consistent with valence shell electron pair repulsion theory [3].

2. Antimicrobial potential of bismuth-based compounds

Bismuth has been used to treat digestive diseases throughout history. Different gastrointestinal conditions have been treated using phenolic salts like salicylates as well as inorganic bismuth salts such as bismuth carbonates, phosphates, silicates, subcarbonates, and subnitrates [4,5]. Bismuth complexes typically have low solubility in several popular solvents. BSS or bismuth-containing substances, such as Pepto-Bismol De-Nol (also known as colloidal bismuth subcitrate or CBS), and its derivatives have been utilized for digestive system issues. Syphilis, rheumatoid arthritis, diarrhea, and other gastrointestinal conditions can all be treated with bismuth salicylate. Moreover, bismuth subcitrate is effective against *Helicobacter pylori*, so it is used to treat ulcers. Additionally, disodium pentaiodobismuthate tetrahydrate ($Na_2BiI_5.4H_2O$) and cacodylate ($Bi[Me_2As(=O)O]_3.8H_2O]$) are bismuth-based that were used as antisyphilitic medications in the past [5]. Bismuth's aliphatic carboxylate salts have also been used to treat syphilis, appendicitis, and tonsillitis. The types of salt include butylthiolaurates, camphorates, citrates, dipropylacetates, ethylcamphorates, potassio(sodio)tartrates, and succinates. Additionally, the therapy of intestinal ulcers is aided by colloidal tripotassium dicitrato bismuthate and micronized bismuth subnitrate. Some bismuth compounds have shown low toxicity and antibacterial properties at extremely low doses. However, the development of antibiotics decreased the demand for this heavy metal and its derivatives. Five mixed thiolatobismuth (III) complexes were examined and were hypothesized to have antibacterial capabilities. At a maximal tolerance limit of 20 g mL^{-1}, all five complexes were reported to be non-toxic to the mammalian COS-7 cell line. According to their research, heteroleptic bismuth (III) complexes were more potent against bacteria than their homoleptic counterparts [6]. Additionally, bismuth compounds also showed antibacterial activities against gram-negative bacteria like *E. coli* [7]. Other studies have also shown that drugs containing bismuth (III) are more effective in inhibiting gram-positive bacteria. This is because gram-negative bacteria have a double membrane that acts as a barrier against the entrance of antimicrobial drugs [8].

Bismuth thiols are thought to inhibit mucus production by reducing the concentrations of 16 strains of *S. epidermidis*. Therefore, they can be a promising tool for inhibiting bacterial colonization on certain surfaces [8,9]. Besides, bismuth thiols have been reported to be bacteriostatic and bactericidal and have unique biofilm inhibitory properties. Another study investigated cyclic organic bismuth compounds and the results showed that eight-membered ring compounds were more active against bacteria than six-membered ring compounds. Therefore, cyclic organobismuth compounds and bismuth thiol compounds have previously been identified as effective antibacterial agents with potential for various medical applications. Hydrogel-coated polyurethane rods treated with bismuth-2-3-dimercaptopropanol (BisBAL) inhibit *S. epidermidis* for more than a month, thus it can be used in internal medical devices. In addition to its antimicrobial properties, bismuth also has anticancer and anti-leishmanial (skin type) properties. It has been proposed that bismuth binds to proteins with metal binding sites, e.g., thiol (cysteine) containing protein structures [9,10].

3. Organobismuth compounds

There has been continuous research on bismuth complexes as antibiotics. Despite being a heavy metal, bismuth has been used in medicine for more than 200 years and is currently regarded as a low-toxic metal. In addition, our recent studies have demonstrated that low μm–high nm concentrations of bismuth complex (e.g., bismuth-based complex sulfonates) and low μm hydroxamates are significantly more effective than the carboxylate-based drug formulations that are currently used. Bismuth (III) thiolate derived from small heterocyclic thiones exhibits remarkable broad-spectrum antibacterial activity, including anti-MRSA and anti-VRE activity (low μm concentrations) [8-10].

Organophosphorus compounds are well-known for their antibacterial properties, particularly phosphinic acids, such as R1R2P (=O)OH. Like sulfonic acids, phosphinic acids have a low pKa value, and they form ligands with metals through their oxygen atoms and are expected to form similar labile complexes. While there have been some reports of organo-phosphinatic bismuth compounds, there have been no reports of their biological activity. The antibacterial activity of bismuth(III) complexes is known to be strongly ligand-dependent. There is significant potential to investigate synergistic effects between Bi(III) and phosphinatic ligands against multidrug-resistant bacteria. It is anticipated that the activity of these complexes could be comparable to, if not better than, analogous sulfonatic complexes. Bismuth compounds are safe for pharmaceutical formulations as it is low in toxicity and non-carcinogenic [11-15].

4. Nanocellulose as a base bionanomaterial

Nanocellulose is a fibrous biomaterial made of cellulose, which is found in the cell walls of plants, lignocellulose, and agricultural biomass [16,17]. The unique property of nanocellulose is that it has been processed down to the nanoscale, giving it some extraordinary mechanical and barrier properties. One of the most notable aspects of nanocellulose is its exceptional strength-to-weight ratio. It is stronger than steel, yet incredibly lightweight, making it a fantastic candidate for various applications. It can be used as a base material in the production of biodegradable films, coatings, and even textiles. Additionally, nanocellulose has exceptional barrier properties, making it an excellent choice for packaging materials. It can help extend the shelf life of perishable products and reduce food waste. Moreover, researchers are exploring the potential of nanocellulose as a reinforcement material in composite materials, such as in the automotive and aerospace industries. It could help make vehicles lighter, more fuel-efficient, and environmentally friendly. With its versatility and eco-friendly nature, nanocellulose holds great promise for the future functional nanomaterials in medicine [18].

Nanocellulose is a plant-based natural biopolymer with a range of properties, including biodegradability, renewability, cost-effectiveness, and non-toxic properties. It has a unique hydrophilic structure, is biocompatible, is easy to chemically modify/functionalize with the hydroxy groups of cellulose, has a high surface area, and can form nanocellular fiber morphologies. Nanocellulose can be categorized into cellulose nanofibers (CNF), Microfibrillated cellulose (MFC), nanocrystalline cellulose/cellulose nanocrystals (NCC/CNC), and bacterial nanocellulose (BNC) [19].

CNFs are made up of nano-sized cellulose fibers with a high aspect ratio. These fibers are usually 5–60 nm in diameter and several micrometers in length. CNF is typically obtained by high shear fibrillation. The fibers are sometimes pre-treated chemically or enzyme-treated before fibrillation. Nanocellulose is composed of crystalline and amorphous, rigid nanoparticles that are formed by acidic hydrolysis of CNFs. These nanofibres are shorter than the nanofibrils (100–250 nm) of plant cellulose and have a diameter of 5–70 nm. BNC is a type of cellulose produced by aerobic bacteria. BNC is a more crystalline, stronger form of cellulose and has a fiber diameter of 20–100 nm. However, large-scale industrial manufacturing of BNC is yet to be developed. The processing techniques required for BNC production vary depending on the type of bacteria and production parameters [16-19].

5. Microfibrillated cellulose (MFC)

In this review paper, the terms "MFC" and "nanofibers" will be used interchangeably. MFC is primarily derived from wood cellulose, which is a highly abundant biomass. The film of MFC can act as a barrier material due to its nanoscale pores. The wood-based cellulose fibers are fibrillated and freed as individual microfibers with a high aspect ratio. One of the major challenges in the commercialization of MFC is its high production cost (approximately 25,000 kWh per ton of MFC). However, a great deal of research is being conducted to reduce this cost by performing pre-treatment such as physical treatment, chemical treatment, and enzyme degradation to make the production of MFC more energy-efficient [19].

5.1. Production of MFC

MFCs are produced by breaking down cellulose pulp through high shear forces, with or without pre-treatment to fibrillate the cellulose. Pre-treatment techniques break down the cellulose with biological or chemical means. Chemical pre-treatment includes TEMPO oxidation, carboxymethylation, etc.; mechanical pretreatments include homogenization, grinding, and microfluidization. The bundle length of the mechanically treated fibers is greater than that of the pre-treated ones, which are thinner and generally shorter. Pre-treated nanocellulose fibers thus have an increased aspect ratio. The pretreatment has no effect on the MFCs' degree of crystallinity, which instead gets lower with each pass through the high-shear homogenizer. However, pre-treated fibers must undergo mechanical processing to become less crystalline. Optically transparent films can be created from nanofiber aqueous dispersions if they have a dense network and gaps between them that are tiny enough to prevent light scattering. These suspensions are pseudoplastic, meaning that they become more viscous when subjected to shear strain. The separation of the cellulose fibers is aided by forming charged groups on the fibers. Aqueous MFC at low concentrations has the ability to gel. MFCs are mainly used as a reinforcing filler in paper and polymer composites, a smooth coating material for paper surfaces, a nanofiller for glues and resins, and additives in paints and cosmetics [19].

6. Forms of nanocellulose as biomaterial

Depending on the intended applications, nanocellulose can be utilized as films, hydrogels, aerogels, solids, and in combination with other materials to create composites.

6.1. Nanocellulose films

MFC suspensions can be processed into sheets and films through various methods like vacuum filtration, casting, spraying, or MFC coating onto a base such as paper. Incorporating MFC into paper can enhance its wet and dry strength or serve as a reinforcement agent. MFC holds promise in diverse applications such as food packaging, different types of packaging, substrates for printed electronics, and sensor applications. Films and sheets made from MFC exhibit impressive mechanical, optical, and barrier properties [19].

6.2. Nanocelluose hydrogels

A hydrogel is a three-dimensional network formed by physically entangling polymers that can absorb substantial amounts of water and are chemically crosslinked. This network can be filled with water or combined with natural, synthetic, or hybrid polymers, particularly those with hydrophilic properties. Chemically crosslinked hydrogels establish their three-dimensional structure through covalent bonding. In the case of cellulose-based hydrogels, hydrogen bonding plays a significant role in their formation.

Hydrogels are highly hydrated, have excellent biocompatibility, and have a wide range of potential uses in biomedical and pharmaceutical applications. Hydrogels can be used in manufacturing soft contact lenses and soft tissue medical implants, protein and drug delivery, and tissue engineering, to name a few. Antimicrobial hydrogels find applications in various medical fields such as medical implant coatings and wound dressings. These hydrogels can be created by immobilizing or dispersing antimicrobial agents within the gel matrix or by using materials inherently possessing antimicrobial properties. Additionally, scientists have been attempting to replace polystyrene-based foam with starch-based foam, but the mechanical properties of the latter pose significant limitations. Stronger alternatives include pure MFC aerogels or starch foams reinforced with MFC [20].

6.3. Nanocellulose fibers as a matrix for antimicrobial agents

Researchers have been exploring nanocellulose due to its exceptional qualities, primarily its eco-friendly, sustainable, and renewable nature. Nanocellulose's attributes, such as high mechanical strength and biodegradability, make it a perfect candidate for reinforcing agents in nanocomposites, as well as in the production of paper and packaging materials. A key element in ensuring food safety, consumer health, and reducing environmental pollution is the material used to package food. Different metal nanoparticles and polymers have been used to create an antimicrobial packaging material. A recent study that examined the impact of silver and cellulose nanofiber coating on base paper revealed that higher concentrations of silver nanoparticles had a stronger antibacterial effect, eventually showing a 100% elimination of bacteria at concentrations of 20 ppm or higher. Another study found that the best antibacterial activity against *E. coli* and *S. aureus* was produced by coating paper with MFC and adding only 2.5% nano-ZnO. They could also be utilized in high-end medical applications like artificial implants and wound dressings [19,20].

A review was done on a free-standing antimicrobial nanocellulose film developed by incorporating an organobismuth complex into a nanocellulose fibrous matrix. In order to produce nanocellulose films that have antibacterial capabilities and are renewable and biodegradable, the non-toxic compound phenyl bismuth bis(diphenylphosphinato) was added to the films by dispersing the compounds into the nanocellulose suspension. The effects of the fabrication approach on the antibacterial sheets prepared with various loadings of the organobismuth complex were discussed. The complex was shown to be generally distributed throughout the nanocellulose matrix, with sporadic clumping behavior on the surface, according to morphological analyses of the sheets. The inclusion of the bismuth complex in the structure also had an impact on its physical properties, necessitating a trade-off between the loading level and material performance for commercialization. The composite sheets were effective at preventing the growth of fungus and bacteria, even multidrug-resistant bacterium strains. The report also demonstrated the bismuth complex's ongoing release throughout time, with the effective lifetime varying with loading. Using a weakly soluble bismuth complex dispersed into a nanocellulose matrix, this work detailed the creation and characterization of a sustainable and environmentally friendly antimicrobial composite film that has the potential to be used as a biomaterial for biomedical applications [21-25].

7. Fabrication methods for bismuth-nanocellulose nanocomposite

There are two common methods for the fabrication of bismuth nanocellulose composites, namely vacuum filtration [26] and spraying [27–29]. Vacuum filtration is a common process for fabricating free-standing nanocellulose films. In this process, the nanocellulose suspension containing an organic bismuth complex is poured into the column and there is a metallic mesh at the bottom of the column. The water in the nanocellulose suspension is drained through the mesh when applying a sufficient vacuum at the bottom of the column. As a result, the nanocellulose fibers form a sheet on the metallic mesh and the wet film is peeled from the mesh after couching with a blotting paper. The wet film is peeled and dried using a drum drier. The retention of nanocellulose fibers on the mesh depends on the type of mesh and their pore sizes. Small mesh sizes lead to longer drainage time for dewatering from the suspension. In the filtration process, the drainage time increases exponentially with nanocellulose suspension. Therefore, the time taken for wet film formation on the mesh varies from 10 minutes to 24 hours [26]. The time taken for the filtration process can be shortened to 10 minutes by fibrillation of nanocellulose via high-pressure homogenization, ball-milling, and acid hydrolysis of cellulose nanofibers. As filtration time progresses, the wet film's basis weight and thickness tend to increase on the mesh. This prolonged filtration leads to a buildup of the wet film, causing resistance to subsequent filtration. Moreover, after drying, the resulting nanocellulose film might display imperfections such as filter markings, impacting the film's overall uniformity and surface smoothness.

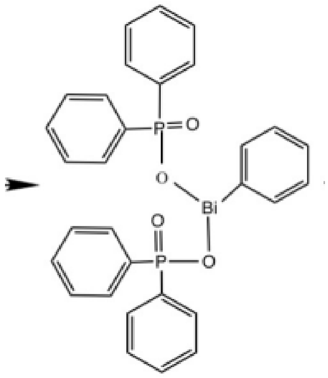

Figure 1. Organobismuth compounds are used for incorporation into nanocellulose for biomedical applications [30,31]

8. Nanocellulose-bismuth composite via vacuum filtration

In a study of the fabrication of composite, a Celish grade, KY-100G nanocellulose sample was obtained from a Japanese company, Daicel Corporation. The average diameter was determined to be 73 nm, and the aspect ratio was estimated to be in the range of 125–142. The material, which had a solids content of 25% and was never dried, was dispersed into the deionized water with a dissolution rate of 0.2 wt %. This process was achieved by agitation with a 3 L disintegrator. The bismuth papers were filtered using Whatman Grade 541 hardened ashless filter papers, with a diameter of 185 mm. AQUA+TECH, Switzerland graciously provided a cationic polyacrylamide (CPAM) polymer with a high molecular weight (13 MDa) and charge density of 40 wt% (F1, SnowFlake Cationics). It is widely known that this polymer can hold onto inorganic particles within a matrix of cellulose nanofibers. The CPAM was dissolved in deionized water at a rate of 0.01 wt% for eight hours at ambient temperature using a magnetic stirrer to create a polymer solution. The cellulose-bismuth suspension was created through a two-step procedure. After carefully combining the CPAM-bismuth suspension with the

MFC suspension, the bismuth complex was added. Following that, the suspension was passed through a vacuum filtration apparatus and left to filter naturally. The thin coating that developed on a piece of Whatman filter paper was removed using blotting sheets and a dryer set to 105°C. Alterations in the amount of bismuth(III) phosphinate solution were made for each sample to achieve the required loading of the bismuth complex while maintaining a constant MFC content of 1.2 dry grams (equivalent to 60 g/m^2 of film) [26,31].

Figure 2 shows the scanning electron microscopy (SEM) micrograph of the pure nanocellulose films prepared via vacuum filtration. The image reveals the cellulose nanofibers are well interconnected through the formation of hydrogen bonds between hydroxyl groups of the nanofibers [26,31]. Normally, the cellulose nanofibers matrix acts as a scaffold for tissue regeneration and a reservoir for antimicrobial agents. This nanocellulose matrix can mimic the microenvironment for the cell fate process [20].

Bismuth complexes can be used as antibacterial agents for polymeric materials in packaging, surface coatings, and medical devices. SEM was performed to determine the presence of bismuth in the sheet (especially on the surface) and to determine how the complex was distributed throughout the cellulose nanofibre matrix. **Figure 3** clearly shows that the bismuth complexes are intertwined with the cellulose network. Backscattered electron images were utilized to examine the dispersion of the particles in the sheet, even though the bismuth phosphinate particles can be easily identified by their needle-like morphology. The bismuth-containing particles were quite evenly distributed throughout the nanocellulose [31].

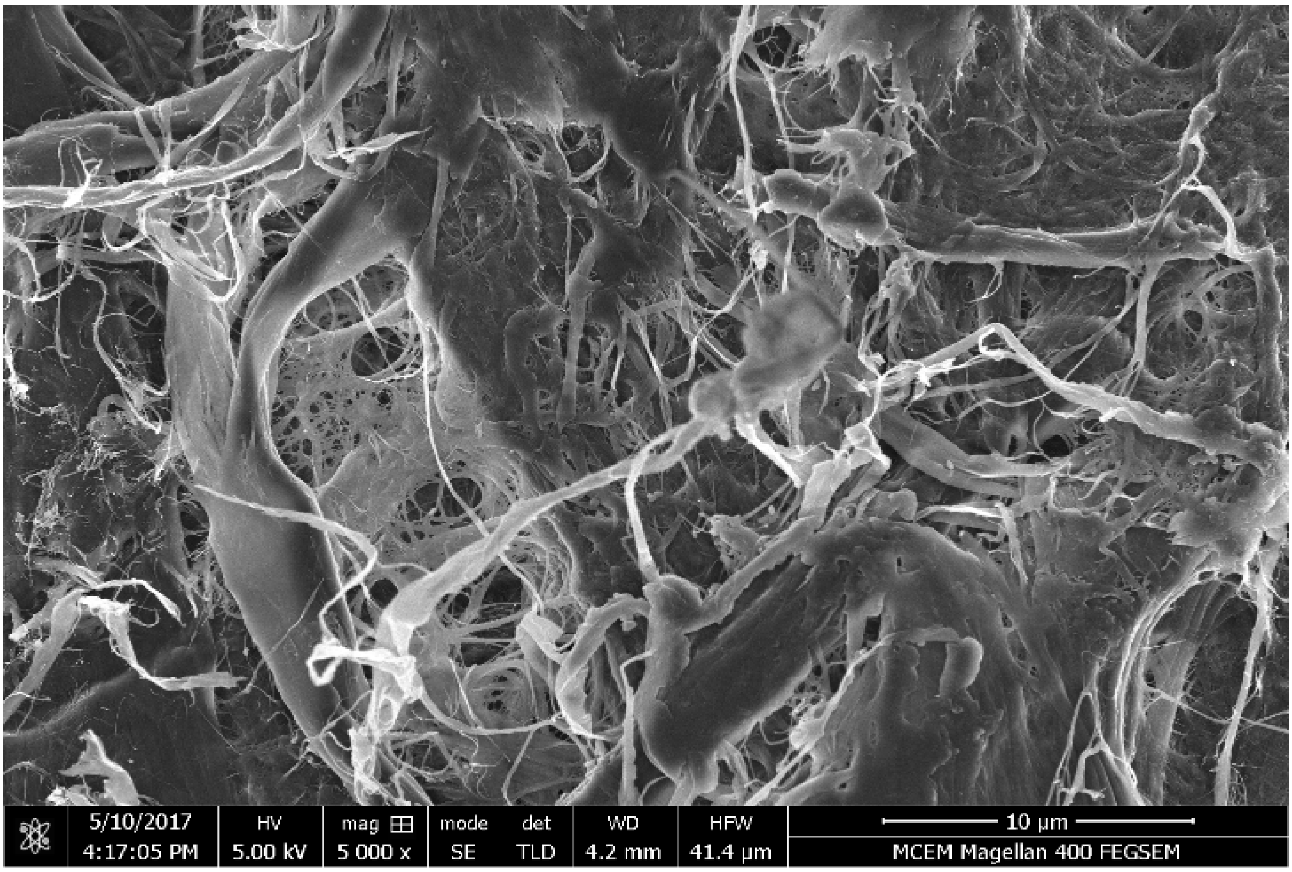

Figure 2. Vacuum-filtered pure nanocellulose films

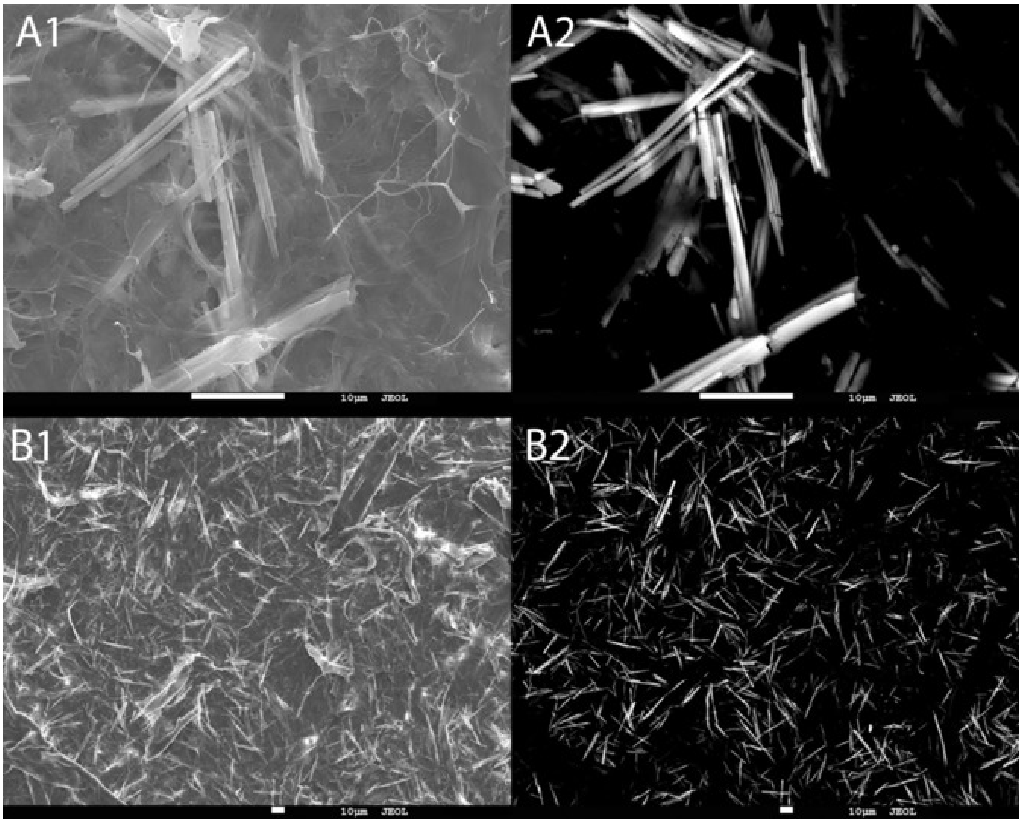

Figure 3. Bismuth-nanocellulose composite prepared via vacuum filtration [31]

9. Spraying process

Spraying cellulose nanofibers on the surface of polished metals is a novel approach to the fabrication of free-standing nanocellulose films. The operation time for the spraying process is independent of nanocellulose suspension concentration and the time taken to fabricate the wet film is less than 1 minute [27,28]. The procedure of the spraying process includes the formation of a spray jet of cellulose nanofibers from the nanocellulose suspension and then the atomization of the sprayed jet into the mist of the cellulose nanofiber suspension. The atomization consists of the disintegration of liquid lamella and the jet of nanocellulose suspension. The fine droplets formed from atomization coalesce on the contact surface and a film is formed on the base surface. The spraying of these nanofibers onto the solid surface causes the coalescence of sprayed droplets due to the film-forming properties of the polymers via hydrogen bonding. The film formed on the surface can be peeled from the substrates after drying [28-30].

In a study, organobismuth compounds dispersed in nanocellulose suspension were used in the spraying process to fabricate free-standing films. The suspension was hydrophobic and diluted to 2.0 wt% fiber content for spraying. The process was carried out in a high-speed disintegrator at a speed of 15000 revolutions and then dispersed through a small mixer at a speed of 3000 rpm to get a homogenous suspension that was free from fiber aggregates. Suspensions with different concentrations of organobismuth compounds were prepared to fabricate the film with different loading of bismuth composites. The nanocellulose suspension was sprayed on the polished square steel plates with dimensions of 220 mm x 220mm. The stainless-steel plate was kept on the conveyor moving at a constant speed. The suspension was sprayed using a Professional Wagner spray system (Model number 117) at 200 bar from a height of 30 ± 1 cm. A spray tip of 517 type was used, with a fan width of 10” and an orifice diameter of 0.017”. The conveyor was maintained at a speed of 1 ± 0.2 cm/s. The spray gun was set at an angle to minimize the wastage of the suspension. After spraying, the MFC on the plates was dried under constraint at the edges until it was dry enough to be peeled off. The sheets were then peeled from the plates and stored at 23°C and 50% RH. **Figure 4** shows the spray system for the fabrication of the free-standing nanocellulose films and composites [27-28,30].

Figures 5 and **6** show the spray-coated nanocellulose–bismuth composite, and its thickness and the basic weight of the sheet can be tailored by changing the consistency of the nanocellulose suspension and the speed of the conveyor [28,30]. Spray-coated films have unique surfaces, in which the rough surface is exposed to air and the smooth surface is exposed to the stainless-steel plate. This feature may help control biofilm adhesion on the wound if the sheet is used as a wound dressing.

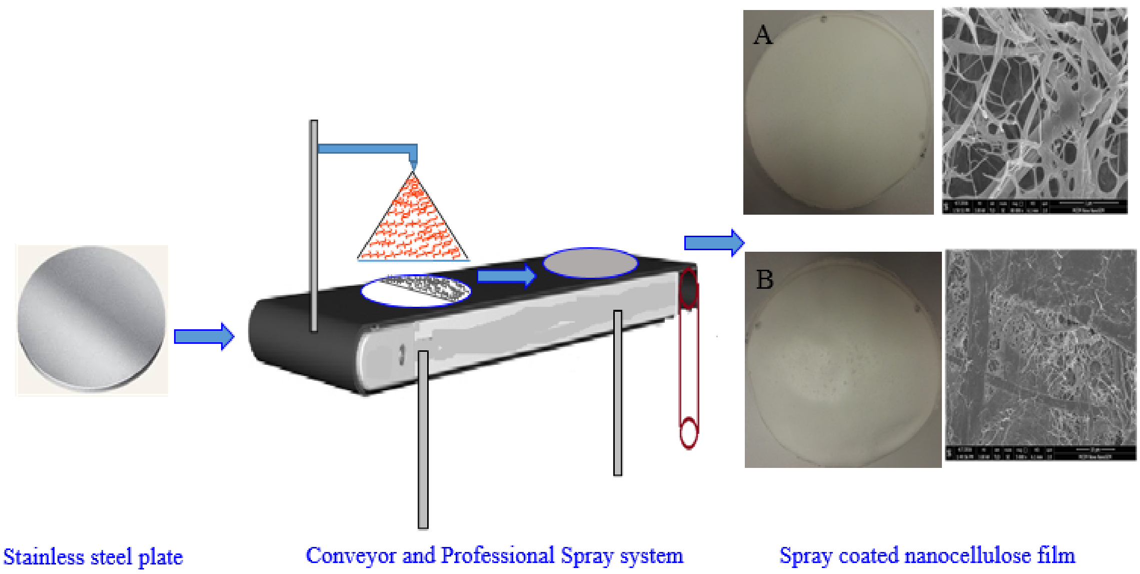

Figure 4. Spray system for fabrication of free-standing NC films [27]

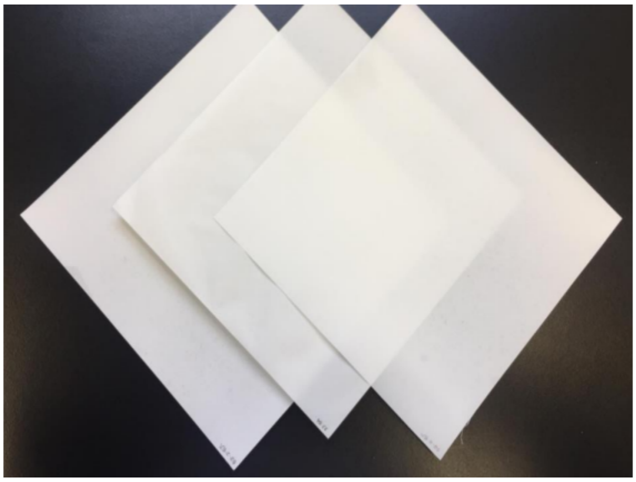

Figure 5. Sprayed nanocellulose-bismuth sheet for biomedical applications

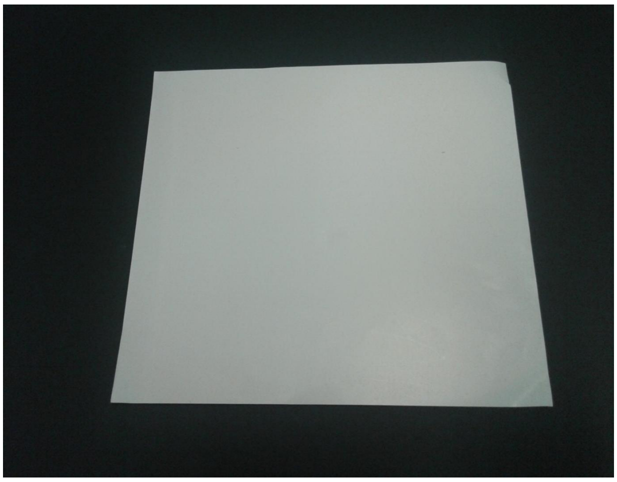

Figure 6. Sprayed nanocellulose-bismuth composite for biomedical applications

10. Structure and morphology of the composite

Figures 7 and **8** are SEM micrographs of pure nanocellulose film and nanocellulose–bismuth composites prepared via the spray coating process. The SEM micrographs reveal the bismuth complex substances distributed into the cellulose nanofibrous matrix. **Figure 7** is an SEM micrograph of pure nanocellulose film confirming that the cellulose nanofibers are well entangled and form a fibrous matrix acting as a reservoir for antimicrobial agents. In addition to that, the cellulose nanofibers mimic the structure of the extracellular matrix and capacity to induce the cell fate process. So that the film can be used as a base biomaterial for tissue engineering scaffolds and drug delivery devices. **Figure 8** shows the SEM micrograph of a nanocellulose-bismuth composite, confirming that the bismuth complex exists as cylindrical particles and rods in the matrix. It is also revealed that the bismuth inorganic complex varies in size and is randomly oriented in the fibrous matrix. These complexes can act as potential antimicrobial agents against both gram-positive and gram-negative bacterial pathogens [30].

11. Antimicrobial property

Bismuth phospinate-nanocellulose composites have been evaluated for their antimicrobial performance against bacterial species. It has been proven that the bismuth-phosphinate complex is more potent against gram–positive bacteria compared to gram-negative bacteria.

Figure 9 displays the antimicrobial efficacy of the bismuth-nanocellulose composite containing 4.00 wt% of the bismuth complex within the nanofiber matrix. The produced sheets demonstrated a noteworthy zone of inhibition against pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), and *S. Aureus*. Variations in the size of the inhibition zones have been observed among the sheets, potentially due to differences in the release of the bismuth complex. The release mechanism and fabrication method of the sheets may indirectly influence the control of bismuth release [21,30,31].

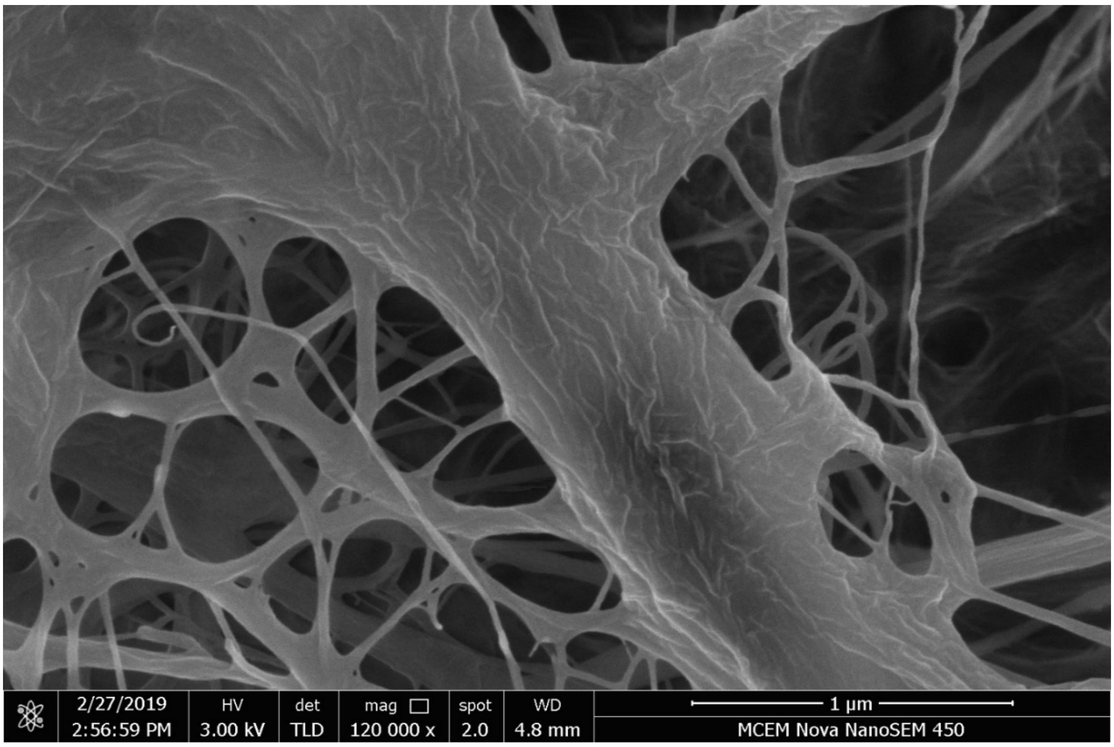

Figure 7. SEM micrograph of pure nanocellulose film via spraying process

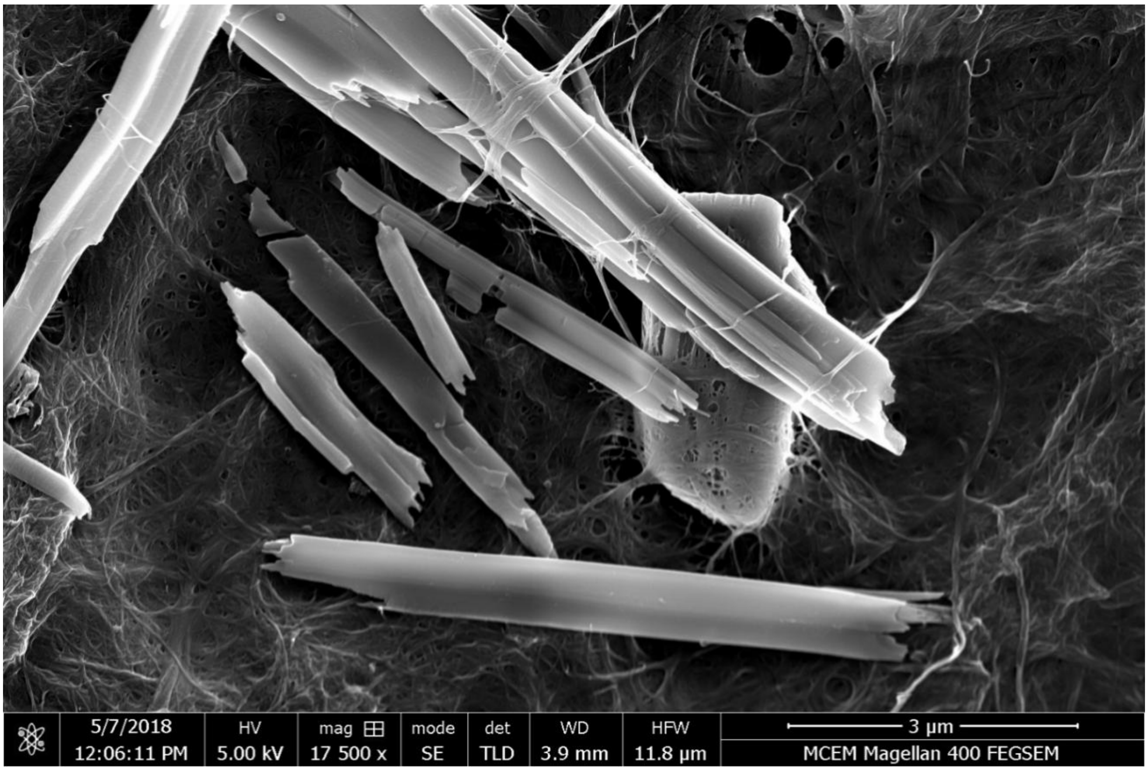

Figure 8. SEM micrograph of nanocellulose-bismuth composite via spraying

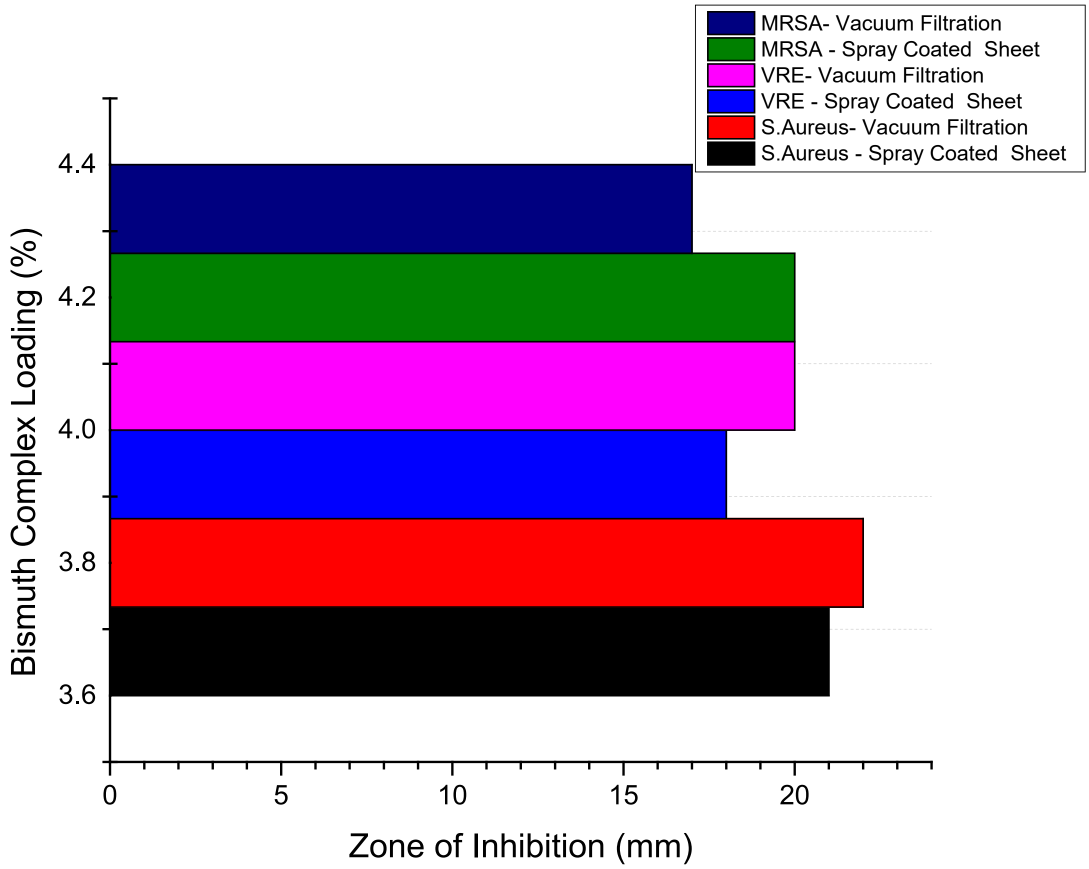

Figure 9. Antimicrobial potential of nanocellulose-bismuth composite

12. Anti-fungal activity of the composites

To investigate the potential use of the sheet as an antifungal barrier, preliminary antifungal tests were conducted. The bismuth-loaded sheets proved effective against three strains, including the troublesome *Candida glabrata* and *Candida albicans*. When the bacterial and fungal plates were compared, the results showed a narrow range of inhibition comparable to that of the adaptable and difficult-to-*kill P. aeruginosa* and *E. coli*. The anti-fungal activity of nanocellulose-bismuth composite was attempted to find the anti-fungal efficacy against 3 strains such as *Candida glabrata* and *Candida albicans*.

13. Biomedical application of the composites

Bismuth-nanocellulose composites demonstrate versatile applications in medical fields. These composites serve as effective wound dressings for infected dermal wounds and burns, utilizing leached bismuth complexes to exhibit potent antimicrobial actions against pathogens. They function as drug delivery devices to combat various bacterial and fungal skin infections, serving as topical bandages or surgical sutures for infected wound treatment and control. The bismuth complex's capability to eradicate bacterial infections and inhibit biofilm formation is particularly beneficial. Moreover, these composites are valuable in treating diabetic ulcers and fostering stem cell growth for tissue engineering. Utilizing cellulose nanofibers to simulate the extracellular matrix facilitates cell fate processes and offers a conducive microenvironment for cell growth. Additionally, the composites serve as a reservoir for growing keratinocytes and fibroblasts, aiding in the development of artificial skin substitutes via tissue engineering strategies [20].

14. Conclusion

Given its potent antimicrobial properties against both gram-positive and gram-negative bacterial pathogens, bismuth complexes have been integrated into nanocellulose sheets to create antimicrobial composites for biomedical applications. Experiment results highlight the sheets' effectiveness against microbes, even at relatively low loadings of less than 5%. The findings suggest that spraying nanocellulose with phenylbismuth and incorporating the complex in nanocellulose suspension can produce biophilic sheets effective against challenging bacterial and fungal strains. The spraying process proves to be quicker for fabricating antimicrobial sheets compared to vacuum filtration. In conclusion, these antimicrobial sheets hold promise as valuable biomedical devices for a range of biomedical applications.

Disclosure statement

The authors declare no conflict of interest.

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