Nanocellulose-Based Passivated-Carbon Quantum Dots for Antimicrobial Applications

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Passivated-carbon quantum dots (P-CQDs) have been attracting great interest as an antimicrobial therapy tool due to their bright fluorescence, lack of toxicity, eco-friendly nature, simple synthetic schemes, and possession of photocatalytic functions comparable to those present in traditional nanometric semiconductors. Besides synthetic precursors, CQDs can be synthesized from a plethora of natural resources including microcrystalline cellulose (MCC) and nanocrystalline cellulose (NCC). Converting MCC into NCC is performed chemically via the top-down route, while synthesizing CQDs from NCC can be performed via the bottom-up route. Due to the good surface charge status with the NCC precursor, researchers focused on synthesizing CQDs from nanocelluloses (MCC and NCC) since they could become a potential source for fabricating carbon quantum dots that are affected by pyrolysis temperature. There are several P-CQDs synthesized with a wide spectrum of featured properties, namely functionalized carbon quantum dots (F-CQDs) and passivated carbon quantum dots (P-CQDs). There are two different important P-CQDs, namely 2,2′-ethylenedioxy-bis-ethylamine (EDA-CQDs) and 3-ethoxypropylamine (EPA-CQDs), that have achieved desirable results in the antiviral therapy field.

Keywords: microcrystalline cellulose; nanocrystalline cellulose; carbon quantum dots

1. Nanocelluloses (NCs)

The most prevalent renewable organic substance on Earth is cellulose. It can be extracted from plants, algae, and bacteria. Higher plants have primary and secondary cell walls that are made up of cellulose, hemicelluloses, lignin, and pectin. The distinctions between primary and secondary cell walls in terms of chemical make-up and structure are what give rise to the plant kingdom's variety.

Several distinct types of nanoscale cellulosic fillers are possible due to the hierarchical and multilevel structure of cellulose. In addition to its nanocrystalline forms, cellulose also exists in an amorphous state that is randomly arranged in a spaghetti-like configuration, giving it a lower density. On the other hand, because they are vulnerable to intense acid attack, amorphous parts can be eliminated while leaving crystalline regions intact under certain circumstances.

As shown in Figure 1, the anatomical structure of a typical wood tissue is clear (Figure 1a), besides showing some macerated fibers (MFs), as presented at Figure 1b, which are the famous natural resource of the cellulose precursor for the MCCs and NCCs products. Furthermore, cellulosic microfibrils are confirmed to be a consequence of crystalline and amorphous regions.
Cellulose-rich sources such as wood contain amorphous regions (Figure 1c) of cellulosic microfibrils that are degraded by acid hydrolysis to produce highly crystalline nanoparticles. Self-organization into a chiral nematic (cholesteric) liquid crystal phase with a helical configuration is a remarkable feature of NCCs. With the help of this remarkable property, dried NCC film can be utilized for security documents, mirrorless lasing, and liquid crystal displays (LCDs and LEDs). Size, dimensions, and other NCCs' geometrical properties are also influenced by the composition of the cellulose precursors.

The amorphous regions are less dense than the crystalline domains and are constructed in a random manner like a spaghetti pattern (Figure 1c). As a result, the crystalline regions may remain unharmed while the amorphous regions are vulnerable to acid attack. Depending on their precursors, the majority of cellulosic materials contain crystalline and amorphous areas in varying proportions. The way that the cellulose molecules are organized has a significant impact on the physicochemical characteristics of the material. The majority of chemical reagents can only enter amorphous regions and can interact with crystallite surfaces to create MCC and/or NCCs (Figure 1d–k).

The MCC is a partially hydrolyzed cellulose. It can be obtained industrially from wood or lignocellulosic residues including linters, flosses, stalks, straw, rags, or shells of agricultural crops. The MCC is favorable in pharmaceutical, food, and cosmetic industries due to its high content of crystalline domains of the cellulose microfibrils. The MCC is one of the most important tableting excipients due to its outstanding dry binding properties of tablets for direct compression.

The nanometer range encompasses sizes larger than a few atoms and smaller than the visible light spectrum. Due to their distinct mechanical characteristics, chirality, sustainability, and accessibility, colloidal NCCs rods with high aspect ratio (100–250 in length and 4–10 nm in width) have gained significant popularity in international markets.

Illustrating the large scale of the NCCs noticed in Figure 1, it is arisen from a so-called novel crystallographic phenomenon termed as crystal growth (Figure 1a–j). When NCC particles are approaching each other in an acidic aqueous atmosphere at a relatively warm temperature condition, they are susceptible to agglomerating electrostatically up to microscale particles, termed as pseudo-microcrystalline cellulose (PMCCs), which differ from ordinary MCCs in terms of their origin. For more illustration, the PMCC is agglomerated directly from NCC upon its crystal growth, while the ordinary MCCs are ingrained directly from cellulosic microfibrils harvested from plant’s cell wall. Despite both PMCCs and MCCs
being situated within the microscale zone, they differ in their internal construction, especially crystallographic properties, namely crystallinity index (CI), crystallite size (CS), and lattice spacing (LS). It is worth mentioning that the NCCs have higher CI and CS, and lower LS than the MCCs, as examined by XRD.

For the sulphate groups (Figure 1e), grafted as a result of the acid hydrolysis of cellulosic microfibrils or MCC using sulfuric acid, researchers think that these functional groups may play an essential role in the agglomeration (upon crystal growth) and dissociation of micrometric particles (upon ingrain the NCCs from MCCs). Before synthesizing the CQDs from the SNCCs, they are desulphated using sodium hydroxide, as is seen in Figure 1k [18].

The nature of the cellulose precursors as well as the hydrolysis circumstances, such as duration, temperature, ultrasound treatment, and material purity, affect the geometrical properties of the NCCs, such as size, dimensions, and form [13][14][15]. The rod-like structure of the charged NCCs creates an anisotropic liquid crystalline phase above a critical concentration [4].

For the medicinal applications of the NCs, cellulose nanocrystals have the potential to be cutting-edge nanomaterials, according to Marpongahtun, et al. [14]. Due to their exceptional qualities, including good mechanical capabilities, low density, and an inherent renewable nature, nanocelluloses have gained a lot of attention in recent years [4]. These qualities make them ideal candidates for use as reinforcing nanofillers for various polymers. Additionally, CNCs have a number of benefits as starting materials for the creation of carbon structures, including a high fixed carbon content, low cost, and the exceptional ability to assemble into various morphologies (such as single nanoparticles, films, filaments, or aggregates). Then, specific carbon structures can be created by thermally decomposing these various CNC assemblies [16][17][18][19][20][21].

2. CQDs

The CQDs are small carbon nanoparticles (less than 10 nm in size) with some form of surficial passivation [22][23][24]. They possess the following properties: brightly fluorescent, non-toxic, ecofriendly, made with simple synthetic techniques, and have photocatalytic skills comparable to those of nanoscale semiconductors [11][25][26]. They have also attracted a lot of attention because of their stable photoluminescence properties, wide ranges of excitation and emission spectra, excellent biocompatibility, and little cytotoxicity effects on biological components. C-Dots are crucial in a number of applications [11]. The chemical modification of CQDs by adding organic molecules to their surfaces has created a novel class of materials with unique characteristics [23][28]. Valuable applications cover chemical and biological sensing, bioimaging, nanomedicine, photocatalysis, and electrocatalysis [25]. Among their unique properties is also their photo-catalytic antimicrobial function [27][29]. The CQDs with visible light illumination were found to be highly effective in inhibiting *Escherichia coli* cells, which can be attributed to their photodynamic effect [30].

3. P-CQDs

The surface modification of CQDs is an important target for selective application such as bioimaging and can be performed by either passivation (Figure 2a–d) or functionalization (Figure 2e) processes. The passivation process is the infliction of an outer layer of a shield material over a core material via a chemical reaction. This process is performed by constructing a core-shell model combined from passivation agents (such as EDA and EPA) that surround the hard fluorescent core of the CQDs and improve fluorescence emissions [31]. The process of surface functionalization (Figure 2e) involves adding functional groups to the surface, such as carboxyl, carbonyl, and amine groups, which can act as surface energy traps and change the fluorescence emission of CQDs. Surface chemistry or interactions such as coordination, interactions, covalent bonding, etc., can result in surface functionalization. The oxygenous characteristic of carbon quantum dots makes covalent bonding with functionalizing chemicals possible.
Figure 2. Schematic construction of surface modification of carbon quantum dots (CQDs): a surface passivation. (a) The spherical core and the thin layer shell of CQDs, (b) chemical structure of 2,2'-ethylenedioxy-bis-ethylamine (EDA) and 3-thoxypropylamine (EPA) which will be grafted on the CQD surface, (c) passivated CQDs, where MW is molecular weight of the surface molecule, TG is the terminal group of the surface molecule, FGY is fluorescence quantum yield, and PS is particle size. (d) 3D-illustration schematic model for the grafted EDA and EPA, and (e) surface functionalization.

Functionalized carbon quantum dots have superior photoreversibility, high stability, strong biocompatibility, and minimal toxicity when compared to naked carbon quantum dots. Occasionally, a small number of molecules can serve as both passivating and functionalizing agents, requiring no extra post-synthesis modifications. To compete with their rivals, such as organic dye molecules and inorganic semiconductor quantum dots, carbon quantum dots must have a high emission quantum yield. In addition to surface passivation and functionalization, one can use the heteroatom and nitrogen doping of carbon quantum dots to increase the quantum yield by up to 83%.

4. Applications of CQDs

4.1. Industrial Field

CQDs have numerous applications in industrial fields due to their enormous surface area, high electric conductivity, and quick electric charge transfer, as well as high physiochemical properties including crystallization, dispersibility in different liquids, and photoluminescence. In particular, the small size, superconductivity, and rapid electron transfer of CQDs endow the CQDs-based composites with improved electric conductivity and catalytic activity. In addition, CQDs have huge surficial functional groups that could facilitate the preparation of electrical active catalysts, which plays an important role in electrochemistry due to promoting charge transfer within and/or between molecules of these composites. By adjusting the size, shape, surface functional groups, and heteroatom doping of CQDs, it is possible to tailor their distinctive electrical and chemical structures. Rich organic groups that have been grafted onto the surface of CQDs make it possible for water molecules to easily adsorb there while also providing active coordinating sites for metal ions to produce CQD hybridized catalysts. The engineering of the electronic structures of the nearby carbon atoms within CQDs is greatly aided by the heteroatoms (such as N, S, and P) doped in CQDs.

Moreover, CQDs have been utilized to fabricate thin-film composite membranes for forward osmosis derived from oil palm biomass into polysulfone, which increased water flux and improved antibacterial performance and nanofiller, packaging sheets, and lubricant additives.

Furthermore, there are many applications of CQDs in the field of electrocatalysis such as the reduction and/or evolution of oxygen, hydrogen, or CO₂, as well as bifunctional catalysts, drug delivery, bioimaging, biosensing, optronic, solar cells, light-emitting diodes (LEDs), and fingerprint recovery.
4.2. Medicinal Field

The CQDs were reported to have medicinal therapeutic effects. It was indicated that all these biomass-derived CQDs contain the nitrogen element, which might be from the proteins, amino acids, and nucleic acids in the biomass. Furthermore, metal-containing CQDs (Figure 3) are divided into four types that can be used as antimicrobial agents: metal ion-doped CQDs, metal nanoparticle-decorated CQDs, Cd/metal oxide nanocomposites, and CQD/metal sulfide nanocomposites. For photoresponsive CQD, photosensitive agents (photosensitizers) are sensitized by light in the presence of oxygen to generate ROS, such as free radicals and singlet oxygen.

![Figure 3](image_url) Scheme illustrating the different types of antimicrobial CQDs for biomedical and industrial applications.

Bacterial Field

Several mechanisms were proposed to illustrate the effects of CQDs on typical bacterial cells. The antimicrobial CQDs have been leveraged for coating the surface of orthopedic implant materials. Positively charged CQDs (p-CQDs) effectively combat multidrug resistant (MDR) bacteria and can prevent the formation of biofilms, whereas n-CQDs significantly enhanced bone regeneration.

Incorporating water-dispersible and photoluminescent CQDs into bacterial nanocellulose (BNC) film was found to have protective activities against microbes, oxidants, and ultraviolet, making it suitable for food packaging. The behavior of this biocomposite can be revealed by the hydrogen bonding interaction between CQDs and the surficial carboxyl, hydroxyl, and carbonyl groups of BNC, leading to the formation of the CQD–BNC film.

Bacterial biofilm (BB) is a key issue in the medical industry. The BBs were found to be colonized and to damage a wide range of medical implants and devices.

In addition, biofilms have major efficacy in many industries including oil, gas, and water production due to causing metal corrosion in engineered systems.

In the complex process of biofilm formation, microorganisms grow and attach to surfaces in an irreversible manner. They also secrete extracellular polymeric substances (EPS) that help the formation of an extracellular matrix (ECM) and alter the phenotype of the organisms in terms of growth rate and gene transcription.

Although numerous conventional antimicrobial treatments have been employed to stop the development of mature biofilms or to remove them, these agents frequently require high dosages and are toxic, which poses serious risks to ecological and environmental systems as well as public health. Recent research on the newly created CQDs has had a substantial impact on efforts aimed at both prevention and eradication.

There are three general mechanisms illustrating the effects of CQDs on bacterial cells, namely electrostatic interaction, the disruption of the cytoplasm in which the internalization and intercalation occur in the bacterial membrane of the cytoplasm as a result of the charge alteration on the cell surface, and photodynamic inactivation with reactive oxygen species (ROS) production and DNA damage.

Viral Field
The semiconductor quantum dots can be used in labeling enveloped viruses for single virus trafficking. Due to the importance of human noroviruses (NoVs), researchers focused on novel technical therapy using CQDs. NoVs are known for acute gastroenteritis outbreaks. Great considerations were directed towards chemical and physical disinfection methods of human pathogens, especially norovirus (NoV) known as virus-like particles (VLPs) GI.1 and GI.4. This is due to the fact that there are currently no licensed vaccines or therapeutics for the prevention or treatment of human noroviruses. Moreover, a lack of well-defined infection models for such viruses, either in vitro or in vivo, has limited the development of their countermeasures. Finally, these viruses are known for their resistance against traditional sanitizers and disinfectants. However, most of these methods have been used for antibacterial applications and have been extended to be antiviral agents.

In the last couple of years, the use of nanoparticles as an antiviral strategy has gained much attention, which includes, but is not limited to, silver nanoparticles, gold-copper core-shell, TiO\(_2\) coupled with the illumination of low-pressure UV light, and passivated-carbon quantum dots (P-CQDs) which should be pithily considered. A group of viruses known as NoVs (family: Caliciviridae) is distinguished by their single-stranded RNA and lack of an envelope. They consist of six genogroups (GI-GIV), which can be further divided into various genetic genotypes based on the sequencing of their capsids. Examples of these are GI, which has nine genotypes, and GII, which has 22 genotypes. It is worth mentioning that human infection is caused by the genogroups GI, GII, and GIV.

Gastroenteritis is a common cause of morbidity and mortality among all ages of individuals, and it results from a large variety of bacteria, parasites, and viruses. Serovar is a distinct variation that may occur within a species of bacteria, virus, or immune cells, which can be used for classifying them according to their cell surface antigens.

It was reported by Patel et al. that developing protocols for direct serovar purposes will be an important area of studying NoVs due to these viruses having not yet been cultivated. Expressed VLPs from different NoV strains were found to be useful as immunogens to produce hyperimmune animal sera, and as antigens to assess serum antibody responses to infection. Identifying a cellular NoV receptor and researching potential host–cell interactions have both been performed using VLPs. Human histo-blood group antigens (HBGAs) have been shown to function as NoV infection receptors.

It is known that histo-blood group antigens (HBGAs) determine the host’s susceptibility to NoV infection. Protection from viral infection is provided by antibodies that prevent NoVs–HBGAs binding. The NoVs engage in strain-specific infection interactions with HBGAs in intestinal tissues as receptors or attachment factors. It is important to note that HBGAs are terminal assemblies of glycan chains that are complex and highly polymorphic carbohydrates. They mostly consist of the ABO, secretor, and Lewis groups. Moreover, HBGAs are widely distributed on the mucosal epithelia of the gastrointestinal tract, where they serve as anchors for NoVs to begin infection. According to earlier research, intestinal bacteria that express HBGAs or synthetic HBGAs may promote NoV infection in B cells.

References


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