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Editorial

Nanocellulose as a promising sustainable material for biomedical applications

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In the recent few years, materials derived from natural renewable resources such as cellulose, chitosan, alginate, starch, collagen, elastin and gelatin have attracted much attention in various biomedical applications including scaffolds for tissue engineering, medical implants, vascular grafts, drug delivery, cancer targeting, cornea replacement, and biological detections [1–3]. Cellulose, a fascinating biopolymer, is by far the most abundant organic compound produced in the biosphere. It is biosynthesized by a variety of living organisms ranging from lower to higher plants, sea animals, bacteria and fungi. It is considered as an inexhaustive source of feedstock for the increasing demand for biocompatible and environmental friendly materials, products and devices. It is regularly regenerated by nature in relatively short period of time, where the bioproduction is estimated to be over 7.5×10^{10} metric tons annually [4,5]. Cellulose is commonly produced with a desired size by the top-down enzymatic, mechanical and/or chemical treatments of cellulosic precursors, in which cotton, wood, annual plants or other agricultural residues can be used. In contrast, cellulose can be obtained by a bottom-up approach, where cellulose is biosynthesized from glucose using the direct action of specific bacterial strains (e.g., *K. xylinus*) [6,7]. Owing to its physicochemical properties, renewability, biocompatibility, biodegradability, cellulose has served in a variety of applications during the past decades and continuously shows potential after adequate treatments (e.g., hydrolysis) or surface functionalization (e.g., grafting) [6,8], in several new applications such as electronic equipment, chemicals, automotive, spacecraft, energy storage in batteries and supercapacitors, and medical to cite a few [8]. Various suitable treatments have been developed to produce nanoscale cellulose [7]. Currently, the study of nanocellulose, material having at least one dimension in the nano-size (<100 nm), has attracted tremendous level of attention as revealed by the increasing number of scientific contributions and industrial investments in several fields [7,9,10]. The three-dimensional hierarchical structures that compose these cellulose nanofibers at different scales,

the combination of the physicochemical properties of cellulose, together with the various advantages of nanomaterials (e.g., a high specific surface area, aspect ratio) open new opportunities in several fields, ranging from electronics to medical applications. These nanoscale celluloses have unique properties including high elastic modulus, dimensional stability, low thermal expansion coefficient, outstanding reinforcing potential, hydrogen-bonding capacity and eco-friendliness [7,9,10]. Nanocelluloses can be devided in numerous main categories: cellulose nanocrystals (CNC), cellulose nanofibrils (CNF), amorphous nanocellulose (ANC), Cellulose nanoyarn (CNY) and bacterial nanocellulose (BNC) [11]. Different approaches have been developed to produce nanoscale cellulose from several natural sources resulting in particles with different physicochemical and mechanical properties, crystallinities and surface chemistries. The key parameters of various nanocelluloses are displayed in Table 1 [7–14].

Table 1. Types of cellulose nanofibers and their particle sizes.

Terminology and nomenclature of nanocellulose	Typical sources	Approximate dimensions	Advantageous properties
Cellulose nanocrystals, nanocrystalline cellulose, cellulose nanocrystals	Hardwood, Softwood, Annual plants/Agricultural residues, Bacteria, etc.	4–70 nm in width; 100–6000 nm in length	Low density, low coefficient of thermal expansion, high tensile strength, high surface area, elongated morphology, ease of bioconjugation
Cellulose nanofibril, nanofibrillar cellulose, nanofbrillated cellulose	Hardwood, Softwood, Annual plants/Agricultural residues, Bacteria, etc.	20–100 nm in width; >10,000 nm in length	Large specific area, significant barrier, mechanical and colloidal properties, low density
Bacterial nanocellulose, microbial nanocellulose	Low molecular weight sugars	10–50 nm in width; >1000 nm in length	Unique nanostructure, purity, higher-dimensional stability, greater mechanical strength, greater capacity to hold water
Amorphous cellulose	Wood pulp, cotton	20–120 nm in width; 50–120 nm in length	Increased content of functional groups and high sorption ability
Cellulose nanoyarn	Cellulose and cellulose derivatives	100–1000 nm in width; >10,000 nm in length	High surface area, high blotting ability

The most important methodology to produce CNC is commonly based on acid hydrolysis, but currently several other procedures have been established [7]. These treatments can eliminate the disordered (amorphous) domains of purified cellulose fibers leaving behind the crystalline regions. The obtained CNC consists of elongated, cylindrical and rod like particles with widths and length of 4–70 nm and between 100 nm and several micrometers [12]. CNF, however, are usually obtained by delamination of cellulosic pulps through mechanical or combined treatments [9]. These nanofibers are flexible and have entangled network structure with a diameter of approximately 1–100 nm, and consisting of alternating crystalline and amorphous regions. More recently, many research works

have focused on optimizing processes to lower energy consumption and other costs, and to improve quality, consistency, and yields [9]. On the other hand, BNC is typically obtained from bacteria (mainly *Komagataeibacter xylinus*), as a separate molecule and does not necessitate processing to eliminate contaminates. In the biosynthesis of BNC, the glucose chains are introduced inside the bacteria body and expelled out through minor pores existing on the cell wall. A 20–100 nm ribbon-shaped nanofibers with micrometer lengths, entangled to form stable network structures. BNC has opened several new applications such as immobilization of enzymes, bacteria and fungi, tissues engineering, heart valve prosthesis, artificial blood vessels, bone, cartilage, cornea and skin, and dental root treatment [10,15]. Another category, ANC, can be formed through acid hydrolysis of regenerated cellulose with subsequent ultrasound disintegration [11]. The prepared particles have spherical to elliptical shapes with diameters ranging from 80 to 120 nm, depending on the cellulose feedstock, isolation procedure and extraction conditions. Because of its amorphous structure, ANC exhibits specific characteristics, such as enhanced sorption, high accessibility, and increased functional group content. The main use of ANC is as carries for bioactive substances and thickening agent in different aqueous systems. CNY remains the less studied cellulosic nanofibers. It is commonly manufactured by electrospinning of a solution containing cellulose or cellulose derivative [11]. The produced eloctrospun nanofibers display diameters ranging from 100 to 1000 nm. CNY can be employed to create new types of wound dressings [16].

Cellulosic nanofibers show great promise as a cost-effective advanced nanomaterial for biomedical and pharmaceutical applications owing to their biocompatibility, biodegradability, low cytotoxicity, high sorption and absorption ability, porosity, small dimensions, a variety of shapes and enhanced specific surface, surface chemistry, rheology, crystallinity, self-assembly, high thermal stability and desirable mechanical properties. They exhibit high chemical resistance to dilute solutions of acids and alkalis, organic solvents, proteolytic enzymes and antioxidants as well [8,11,17]. These applications can include medical implants, tissue engineering, drug delivery, wound healing, cardiovascular applications, and diagnostics [18]. Emerging fields being developed to use nanocelluloses and their composites in novel ways in biomedical applications such as 3D printing and magnetically responsive materials are currently until investigation [1]. Moreover, with their chemical functionality, cellulose nanofibers can be easily modified to yield useful products. Covalent modifications such as esterification, oxidation, eherification, silylation and polymer grafting, as well as non-covalent binding are suggested in the literature in order to get more interesting properties and increase the number of applications [1,2,18–21]. These properties are useful in scaffold design by improving mechanical properties, cell adhesion, proliferation, differentiation and cellular patterning, where various shapes can be obtained. Another hot topic is the application of cellulosic nanofibers materials for drug delivery in the form of tablet coating, membranes or bionanocomposite delivery systems. On the other hand, the production of cellulosic nanofibers aerogels with porous structure have demonstrated the potential for wound dressing and scaffolds. Fluorescent labeling of cellulosic nanofibers with various fluorophores is also of potential interest in bio-imaging, targeting and sensing uses.

In summary, cellulosic nanofibers-based materials are now recognized as unique materials that can be employed to produce exceptional films, composites and gels that show interesting features as an alternative to petroleum-based materials with environmentally friendly and renewable characteristics. It is revealed that various nanocellulose-based materials and composites hold great promise in several biomedical applications. Even though various cellulose nanofibers have been

demonstrated as nongenotoxic and noncytotoxic, further studies are required to completely address such issue. Chemical modification of the cellulosic structure to improve interactions with living tissues could enlarge the utilization of nanocelluloses in biomedical devices tremendously. However, the assessment of the potential risks attributed to this chemical modification is also needed, since each modification could result in drastic behavioral changes in cell–material interactions. Clearly, despite the significant developments concerning biomedical cellulose nanofibers-based materials, this area is still promising and intensive investigations necessitate to be performed. As materials science continues to rapidly develop in biomedical field, cellulose nanofibers may provide a promising solution in the future to overcome some of the insurmountable challenges of biomedical materials.

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Conflict of interest

The author declares that there are no conflicts of interest regarding the publication of this paper.

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