AN OVERVIEW OF NANO-CRYSTALLINE CELLULOSE NANOFIBERS AND THEIR APPLICATIONS IN DRUG DELIVERY

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ABSTRACT

Made from a variety of natural sources, nanocrystalline cellulose (NCC) is a unique renewable nanomaterial with a wide range of applications due to its high stiffness and strength, low weight, biodegradability, and environmental benefits. Because of its special inherent qualities, NCC is one of the most renewable materials to be addressed by nanomaterials. The origins, manufacture, characteristics, and applications of nanomaterials, including NCC and nanofibers, have been extensively studied by a large number of researchers throughout the years. Strong chemical reactivity, crystallinity, strength and stiffness, biocompatibility, biodegradability, shape, and nanoscale dimensions are just a few of the remarkable properties that these nanomaterials have been shown to possess in countless investigations. These characteristics enable the application of these nanoparticles in a number of fields, including medicine. Among the most traditional and popular techniques. Electrospinning is one of the earliest and most popular techniques for producing nanofibers. This method works well and can be modified to produce continuous nanofibers. NCC-based nanofibers are novel materials in the biomaterials industry. Recent studies demonstrated that electrospun nanofibers could be efficiently loaded with a wide range of drugs, such as proteins, chemotherapeutic agents, antibiotics, and analgesics with anti-inflammatory qualities. One application of NCC and nanofibers in the medical field is drug delivery. This review highlights a number of issues related to NCC nanofibers and their use in drug delivery applications, beginning with discussing the various natural polymer types used in drug delivery applications,

the physicochemical and biological properties of NCC, its various applications, its significance, and its preparation techniques.

Keywords: Nanofibers, Nanocrystalline cellulose, Drug delivery applications,Electrospinning process.

INTRODUCTION

A great deal of research interest has been placed on the application of nanocrystalline cellulose-based materials in medical procedures like dressing of wound, drug delivery, medical implants as well as framework for tissue engineering and vascular grafts in recent years [1]. The rising environmental awareness in recent years has further sparked a high request for materials that are environment-friendly with terms like 'biodegradable', 'renewable', 'recyclable', 'biodegradable', 'sustainable', etc., to achieve the desired design and structural requirements [2]. The most essential structural element found in the cell wall of plants is cellulose and in general, the mechanical characteristics of naturally occurring fibers depend on it [3]. Natural fibers give materials that contain them certain advantages over conventional engineering fibers like carbon and glass fibers as well as mineral fibers, including low density which is approximately 1.4 g cc^{-1} when compared to the density of E-glass which is approximately 2.5 g cc^{-1}, parallel specific moduli and strength to the glass fibers, as well as high flexibility property [4]. Natural fibers have their pros and cons; notwithstanding, greater natural fibers loading in materials that bear them is possible compared to the traditional inorganic fillers because of the softer, nonabrasive nature of natural fibers [5]. Molecular chains of cellulose are generally arranged in an organized manner to create a consolidated microfibrils that are made stable by intramolecular and intermolecular hydrogen bonds [6]. Cellulose molecular chains are bio-synthesized and auto-assembled to form micro fibrils with amorphous regions alternating with crystalline regions [7]. In terms of size, cellulose micro fibrils range from 10–30 nm in diameter and they consist of thirty to one hundred molecules of cellulose in long chains conformation and gives the fiber strength mechanically [8]. The three alcoholic hydroxyl groups account for the hydrophobic nature of cellulose macromolecules [9].

As a result, an unbounded -OH group which is present mainly in the noncrystalline or amorphous area of cellulose performs a key function in their pattern of reaction in the course of hydrolysis, the cellulose crystalline part however remains integral. Since one of the properties of medical biocomposites is biocompatibility or the ability to properly function in the body of human beings

to give expected medical outcomes without causing side effects, cellulose Nanocrystals as biomaterials can be promising biomaterials [10].

Search Criteria:

Based on specified keywords, a systematic literature search for all relevant studies up to 2024 in Google Scholar (https:// scholar.google.com), Pub Med (https://pubmed.ncbi.nlm.nih.gov), ResearchGate (https://www.researchgate.net) and Web of Science(http://www.webofknowledge.com).Text words and phrase words were utilized. Nanofibers was one of the major keywords used, nanocrystalline cellulose, electrospinning process, and finally nanofibers in different drug delivery applications.

NATURAL POLYMERS IN DRUG DELIVERY

Increased research interest has been devoted toward advanced drug delivery technologies in recent decades, owing to their superior attributes in comparison to conventional drug delivery systems [11]. These advantages encompass controlled drug release, the ability to sustain therapeutic drug concentrations throughout the treatment duration, targeted drug delivery, enhanced pharmacokinetics, reduced side effects, improved patient adherence, prolonged drug half-lives, and various other benefits [11].

Among these advanced drug delivery technologies, micro and nanocarriers, liposomes have gained immense interest, particularly polymeric based advanced Drug Delivery Systems (DDS)[12, 13]. Synthetic and natural polymers have garnered high interest due to their bio-adhesive properties, biodegradability, biocompatibility controlled release properties, and low toxicity [14].

Chitosan

Chitosan is a widely used polymer derived from the shells of marine organisms such including lobsters and crab shells, as well as insects, fungi, and yeast [15]. The process of N-deacetylation of chitin produces chitosan, a polysaccharide characterized by the presence of 2-deoxy-2-(acetylamino) glucose units connected through 1,4-glycosidic linkages [16, 17].

Chitosan have elicited considerable interest due to its biocompatibility, biodegradability, non-toxicity, nan-carcinogenicity, antibacterial properties, unique behavior due to its positive charge,

high encapsulation properties, good mechanical strength, high cellular uptake, absorption enhancing and mucoadhesive properties [18]. In addition, chitosan's structure resembles the biologically occurring glycosaminoglycans, degraded by biological enzymes, and supports haemostasis [19].

Chitosan has been employed in the drug delivery in various contexts such as micro and nanocarriers as well as in the formulation of coating materials [20, 21]. Recent investigations have revealed diverse innovations and uses of chitosan in the domain of drug delivery. Chitosan has been employed in bio-printing in tissue engineering and drug delivery applications as chitosan-based inks for 3D/four-dimensional (4D) (bio)printing [22]. In addition, Chitosan has been employed in nucleic acid delivery owing to its capacity to form complexes with nucleotides through electrostatic interactions with the phosphoric groups of DNA/RNA [23]. Crossing the blood brain barrier is considered one of the major challenges in delivering drugs to the brain. Clonazepam was carried in chitosan-coated niosomes (chitosomes) [24], vinpocetine carried in chitosan containing nanoparticles [25], and protein loaded chitosan nanoparticles were fabricated [26] for nose to brain delivery of the drugs. Chitosan has been immensely used for oral colon-specific delivery of several medications including irinotecan and quercetin [27], paclitaxel [28], and 5-fluorouracil [29].

Alginate

Alginates comprise a category of unbranched, water-soluble polysaccharide anionic polymers, derived from brown seaweeds, algae, and soil bacteria [30]. The structure of alginates includes a linear biopolymer of two uronic acids namely, αguluronic acid (G) and 1,4-linked-β-D-mannuronic acid (M) [31]. The chemical characteristics of alginate, including its solubility and hydrophobicity, render it an appropriate polymer for chemical functionalization [32].

Alginate's derivatives have gained increased interest in drug delivery as well due to their high mechanical strength, permeability, low toxicity, biocompatibility, high affinity with drugs, among others [33]. In addition, alginates have unique properties of gel forming which aids in its use in targeted drug delivery [34], suitable for sustained drug release, and have the ability to stabilize formulations [35].

In-vivo pharmacokinetics of alginate nanoparticles were investigated for the delivery of anti-tuberculosis drugs [36, 37]. Alginate-based formulations designed for pulmonary delivery were scrutinized for the delivery of d-cycloserine [38], paclitaxel [39], rofulmilast [40], ropinirole [41], and budesonide [42]. Alginate nanoparticles were examined for the delivery of antifungal drugs delivery [43].

Albumin

Albumin, a water-soluble globular protein, comprises three primary domains and two binding sites [44]. Almost 50% of the total plasma mass of the body is comprised of albumin which holds maintains the blood pH and holds fatty acids in the blood [45]. The blood compatibility of albumin attracted interest towards employing albumin in advanced drug delivery systems. Albumin is available in three forms including bovine serum albumin (BSA), ovalbumin (OVA), and human serum albumin (HAS)[46].

Albumin has attracted increased research interest because it is non-toxic, economical, stabilizes formulations, sensitive to pH or temperature changes, provides sustained drug release, biodegradable, has several reactive functional groups, and improves circulation profiles [47, 48].

Nanoparticles containing paclitaxel bound to albumin were examined for the treatment of metastatic breast cancer, showing reduced cytotoxicity [49, 50]. Albumin nanocarriers were investigated as a carrier of curcumin to increase its solubility [51]. Furthermore, albumin nanocarriers were examined for the delivery of many drugs including berberine [52], docetaxel [53], palmitic acid [54], colistin [55], and arsenite [56].

Hyaluronic Acid

Hyaluronic acid, conjointly termed as Hyaluronan, is a mucopolysaccharide composed of linearly repeated units of disaccharides of D-glucuronic acid and N-acetyl-D glucosamine linked by β-1,3 or β-1,4-glycosidic bonds [57]. Hyaluronic acid has carboxyl and hydroxyl functional groups in addition to its negative surface charge that help in its modification with hydrophobic macromolecules [58]. Hyaluronic acid is extracted from synovial fluids in the skin and vertebrate tissues of the body [59].

Hyaluronic acid has garnered heightened attention in research as it has high viscoelasticity, biodegradability, biocompatibility, mucoadhesion, ease of chemical modification, and ability to combine with several receptor ligands [60].

Hyaluronic acid can enhance the dermal transport of diverse molecules, particularly those with a high molecular weight that can be readily encapsulated in the pores. These systems aid in the regulated release of molecules, consequently mitigating dose-dependent toxicity and enhancing bioavailability [61]. Hyaluronic acid has been fabricated in advanced dermal drug delivery systems for the delivery of biomacromolecules [62], human growth hormones [63], sodium ascorbyl sulphates [64], and diclofenac [61]. Furthermore, the low viscosity of the ophthalmic preparations of hyaluronic acid and due to its bioadhesive properties, research has investigated the fabrication of hyaluronic based ophthalmic preparations [65, 66].Moreover, Hyaluronic acid has been utilized as a means for the nasal delivery of small molecular drugs to enhance their bioavailability and bioadhesion [67, 68].

Gelatin

Gelatin is a blend of protein and peptide materials found in two types, type A is obtained by acidic treatment whereas type B is obtained by alkaline treatment of collagen extracted from the skin, bones, and connective tissues. Gelatin is characterized by the abundance of amino acids proline, glycine, and alanine which are responsible of the triple helical structure [69].

Gelatin was regarded as a compelling material for formulations in drug delivery due to its availability, non-toxicity, biocompatibility, biodegradability, inexpensiveness, low antigenicity, ease of chemical alteration, ability to bind to drugs, and lack of pyrogens [70, 71, 72].

Gelatin nanoparticles have been examined for the delivery of antibiotics, anti-inflammatory agents, antivirals, antifungals, among others [73]. pH sensitive gelatin-based hydrogels were fabricated and examined for the delivery of riboflavin which showed non-cytotoxic and sustained release of the drug [74]. Moreover, the viscoelastic stress relaxation in colloidal hydrogels composed of gelatin nanoparticles were examined and demonstrated rapid stress relaxation within physiologically relevant strains of 10-50%, linked to cellular activity, potentially promoting the migration and proliferation of cells in colloidal hydrogels [75].

Pectin

Pectin is linear polysaccharide consists of α-1,4-linked D-galacturonic acid residues with 1,2-linked L-rhamnose residues. Its abundant of neutral sugars including galactose, rhamnose, arabinose, glucose, and xylose [76, 77, 78]. The pectin composition varies depending on the source, pectin can be obtained from apples and citrus fruits via acid hydrolysis of the inner portion of their peels [76].

Pectin has sparked growing research attention as a hydrophilic polymeric material due to its biocompatibility, biodegradability, availability, non-toxicity, and the fact that pectin itself has beneficial health benefits such as lipid and cholesterol lowering activity, protecting against gastric ulcers, and apoptogenic effects in the malignant tumor cells [79].

Pectin has been extensively explored as a carrier for targeted delivery to the colon, liver, and topical and transdermal drug delivery [80, 81].

Carrageenan

Carrageenan is an anionic sulphated polysaccharide composed of alternate units of 3,6-anhydrogalactose and D-galactose joined by β-1,4 and α-1,3 glycosidic linkages [82]. “Carrageenan” is derived from the Irish word “carrageen” which means “little rock” as it’s obtained from red seaweed of Rhodophyceae family [83].

Carrageenan has seen a surge in interest as drug carrier due to its interesting characteristics including thickening, gelling, stabilizing, and emulsifying properties. In addition, it possesses a variety of therapeutic properties such as anticoagulant, antihyperlipidemic, anticancer, and immunomodulatory properties [84].

Biomedically, carrageenan has been employed in tissue engineering [85], wound healing, and drug delivery [86].

Cellulose and cellulose derivatives

Cellulose stands out as one of the most significant natural biopolymers due to their widespread occurrence in nature. Cellulose consists of repeating glucose units linked together via β-1,4 glycosidic linkages in an unbranched natural polymer structure [87]. Cellulose can be derived from

various sources such as wood, plants, bacteria, algae, and tunicates, with wood and plants being the most commonly utilized [88].

Cellulose derivatives have been derived from cellulose via chemical functionalization and treatment, the purpose was to enhance the expanding flexibility of cellulose [89, 90]. Properties of cellulose derivatives depend on several factors including the type and degree of substitution and the pattern of functionalization along the polymer chain [91].

Methyl cellulose is the simplest cellulose ethers synthesized by the addition of methylating agent in alkaline medium. Methyl cellulose can be used in gels formation, the characteristics of the gel depends on several factors including molecular weight, the degree of cellulose substitution, and the concentrations of additives. In pharmaceutical formulations, methyl cellulose has been used as an emulsifying agent as well as its employment in drug delivery systems [92].

Carboxymethylcellulose (CMC) has gained increased interest in pharmaceutical industries due to its hydrophilicity, stability, non-toxicity, biodegradability, and biocompatibility [93]. CMC has been utilized in pharmaceutical formulations as thickening agent, stabilizer, binder, film former, and in advanced drug delivery systems [94, 95].

The chemical composition of ethyl cellulose involves the conversion of certain hydroxyl groups on the repeating glucose units into ethyl ether groups [96]. Ethyl cellulose has gained interest in its use in drug delivery systems due to its biodegradability, non-toxicity, barrier-forming characteristics, and water resistance properties [97, 98].

Reacting ethylene oxide with alkali cellulose results in the synthesis of hydroxyethyl cellulose, which can be further modified to its reactive hydroxyl groups [99]. Hydroxyethyl cellulose has several interesting properties such as its solubility in water and many organic solvents, non-toxicity, compatibility, and drug encapsulation properties. These characteristics have increased the interest towards employing hydroxyethyl cellulose in drug delivery [100, 101].

Partial or complete substitution of the free hydroxyls in cellulose to hydroxypropyl groups via the reaction with 1,2-propylene oxide results in the formation of hydroxypropyl cellulose [102]. Hydroxypropyl cellulose has been used in pharmaceutical formulations as tablets binder, viscosity enhancer, film coating, and in modified release formulations [103, 104].

Cellulose acetate, a biodegradable polymer, is created through the esterification of cellulose [105]. Its exploration in various biomedical applications, such as tissue engineering [106], wound healing [107], and drug delivery systems [108], is attributed to its resource availability, cost-effectiveness, and straightforward isolation techniques.

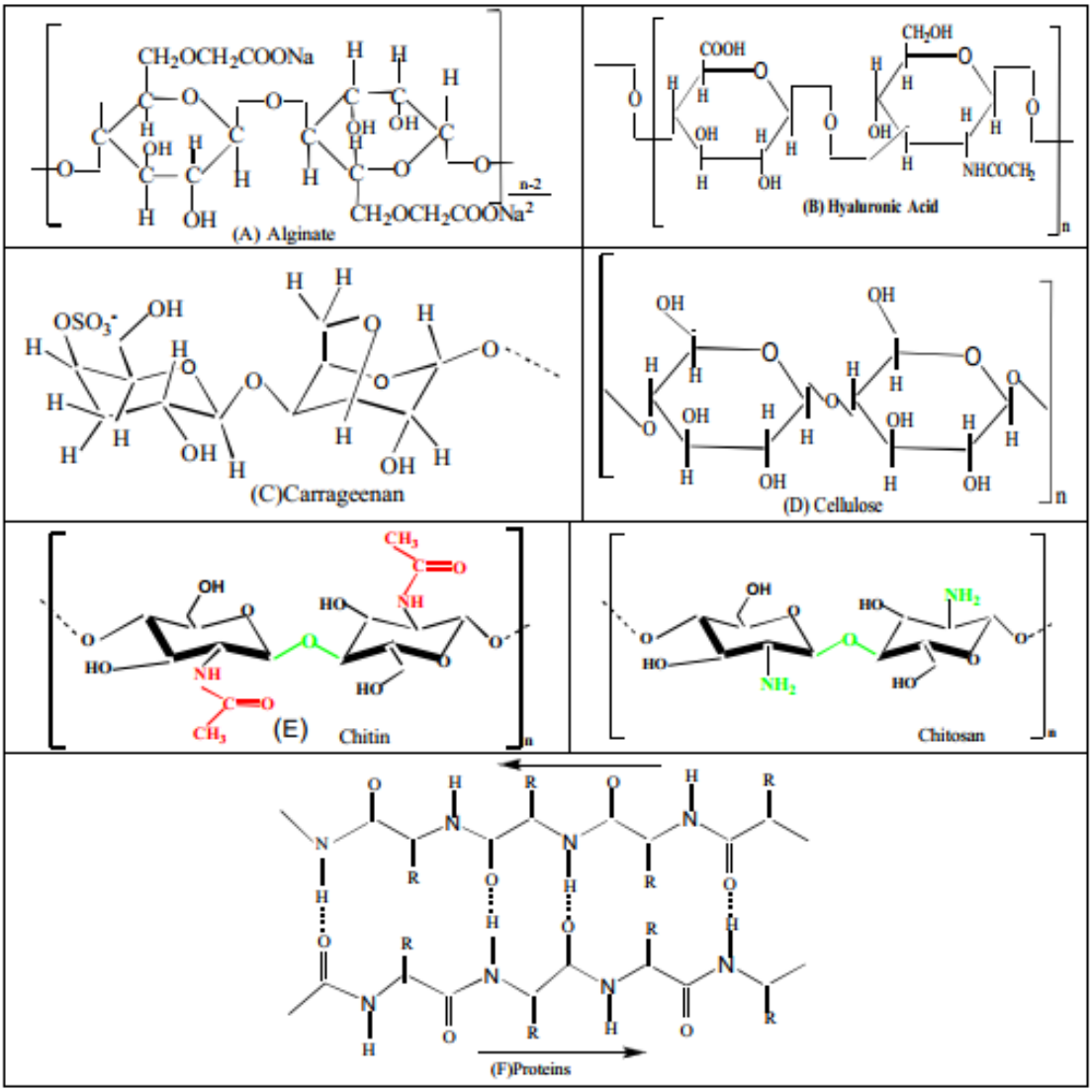

Fig. 1: Chemical structures of some natural polymers of potential to electrospinning: (**A**) Alginate, (**B**) Hyaluronic acid, (**C**) Carrageenan, (**D**) Cellulose, (**E**) Chitin & Chitosan, (**F**) Proteins. [109]

PHYSICOCHEMICAL PROPERTIES OF NANOCRYSTALLINE CELLULOSE

Nanocrystalline cellulose (NCC) is a nanometer-sized rod-like particle with high crystallinity, obtained in the form of a stable aqueous colloidal suspension [110]. NCC has received increased

interest as biomedical nano-carrier [111]. Its renewability, biocompatibility, biodegradability, abundance of active functional groups, and stability are the factors contributing to this interest [112]. Furthermore, NCChas interesting properties including liquid crystallinity, colloidal behavior, self-assembling properties [113].

NCC stands out as the stiffest and strongest among natural materials [114], showcasing a range of notable properties such as high hardness, elevated tensile strength [114, 115], extensive surface area, high aspect ratio, and low density [115, 116], optical transparency, gas barrier properties [117], among other characteristics.

Thermally, NCC degrades or its mechanical properties decline at high temperatures which limit its use, however, this property can be taken in advantage in some industries [118, 119].

NCC are characterized by their tensile properties, high crystallinity index, large surface area [120]. Moreover, NCC are characterized by their biocompatibility, biodegradibility, dispersion and water retention ability [121].

On the other hand, NCC possesses a range of remarkable optical, chemical, and electrical attributes attributed to its needle-like structure, expansive surface area, elevated aspect ratio (length-to-diameter ratio), exceptional crystallinity, nanoscale dimensions, impressive strength and rigidity, low density, and a pronounced negative charge. These distinctive qualities result in NCC exhibiting unique behaviors in solution.

Additionally, the high chemical reactivity of its surface renders NCC highly adaptable for diverse applications, complemented by its capacity to withstand high temperatures. Furthermore, NCC features abundant surface hydroxyl (OH) groups that serve as active sites for hydrogen bonding, facilitating interactions with polar matrices.

These elongated or whisker-shaped particles, measuring between 3 to 20 nanometers in width and 50 to 2000 nanometers in length, exhibit an extraordinary combination of attributes. They possess high axial stiffness, estimated at approximately 150 Giga Pascal (GPa), along with a remarkable tensile strength, believed to be around 7.5 GPa. Furthermore, they have a low coefficient of thermal expansion, approximately 1 part per million per degree Kelvin (ppm/K), and can maintain thermal stability up to approximately 300°C.

With an impressive aspect ratio ranging from 10 to 100, these particles are characterized by low density, about 1.6 grams per cubic centimeter (g/cm^3), display lyotropic liquid crystalline behavior, and exhibit shear-thinning rheology in cellulose nanocrystal (CNC) suspensions. Their exposed

hydroxyl (–OH) groups on the CNC surfaces are easily modifiable, enabling the achievement of various surface properties. This adaptability has been harnessed to influence CNC self-assembly and dispersion across a broad spectrum of suspensions and matrix polymers. Additionally, it allows for the control of interfacial properties within composites, such as CNC-CNC and CNC-matrix interactions.

However, it's crucial to note that the dimensions and degree of crystallinity of these particles vary depending on the source of the cellulose and the specific extraction conditions. This variability has been documented in studies by researchers such as Habibi *et al.* (2010), Abdul-khadil *et al*. (2014), and Abitol *et al*. (2016) [122, 123, 124]

BIOLOGICAL PROPERTIES OF NANO-CRYSTALLINE CELLULOSE

Nano-crystalline cellulose exhibits several biological properties. This is because nanocrystalline cellulose are derived from biological materials such as plants, bacteria, tunicate, etc. Some of the most notable biological properties of nanocrystalline cellulose include the following fields:

Antibacterial Properties: In a study by Eyley and Thielemans (2014), nanocrystalline cellulose was shown to have inherent antibacterial properties, suggesting its potential in the development of antibacterial materials for medical applications.

Biocompatibility: Nanocrystalline cellulose has been recognized for its excellent biocompatibility, making it appropriate for a wide array of biomedical applications. A study by Chen *et al*. (2018), revealed that nanocrystalline cellulose is not cytotoxic and is well tolerated by different types of cells, making it a promising material for application in drug delivery systems [125]

Wound Healing Applications: The ability of nanocrystalline cellulose to boost wound healing has been extensively explored. The researchers, cited by Klemm *et a*l. (2011) investigated the use of nanocrystalline cellulose-based materials in wound dressings, attributing their success to the material's hemostatic properties and its ability to support cell adhesion [126].

Immunomodulatory Effects: Recent research, as highlighted by Zhang *et al*. (2022), suggested that nanocrystalline cellulose may possess immunomodulatory effects, positively influencing the immune response. This opens up new possibilities for its use in immunotherapy and related fields [50].

Drug Delivery Systems: The high surface area ofnanocrystalline cellulose and its gel-forming ability have given rise to its exploration in drug delivery systems. In a review by Habibi *et al*. (2010), the authors discuss the prospective of nanocrystalline cellulose-based nanocomposites in controlled drug release applications [122].

USES OF NANOCRYSTALLINE CELLULOSE

The potential uses of nanocrystalline cellulose can be broadly categorized according to distinctive combinations of their characteristics, and a selection of these categories is presented below.

Rheology modifiers

The incorporation of nanocrystalline cellulose can modify the rheological properties of diverse substances, including liquids, polymer melts, and particle mixtures, which are employed in a wide array of industrial sectors. These sectors encompass paints, coatings, adhesives, lacquers, as well as the production of food, cosmetics, pharmaceuticals, and cement [127].

Reinforcement for Polymer Materials

Incorporating nanocrystalline cellulose into different polymer matrices brings about changes in the mechanical characteristics of the resulting composites. This alteration can be harnessed for creating resilient, pliable, long-lasting, lightweight, transparent, and dimensionally stable films, suitable for applications in packaging or structural composite materials.

Barrier Films

Composites based on nanocrystalline cellulose, where nanocrystalline cellulose surface chemistry and the spacing between nanocrystalline cellulose are carefully customized, have generated attention as barrier films. These films show promise in applications like selective filtration, batteries, and packaging, as indicated by Hubbe *et al*., in 2008 [128].

Optical Films or Coatings

The liquid crystalline properties of nanocrystalline cellulose suspensions, combined with the birefringent characteristics of the particles, give rise to fascinating optical effects that can be harnessed to create distinctive pearlescent and iridescent optical patterns on surfaces.

Nano-crystalline Cellulose-Hybrid Composites

nanocrystalline cellulose composites that incorporate inorganic nanoparticles or chemical compounds onto nanocrystalline cellulose surfaces and/or within nanocrystalline cellulose networks gain additional chemical functionalities. These functionalities have potential applications

in biosensors, catalysis, photovoltaics, drug delivery, filtration, and antimicrobial technologies, as mentioned in Lin *et al*., 2012 [129].

Nanocrystalline cellulose Foams

nanocrystalline cellulose foams, such as aerogels, exhibit a high degree of porosity with densities ranging from 0.01 to 0.4 g/cm3 and surface areas spanning from 30 to 600 m^2/g, as documented previously [130]. These materials hold promise for utilization in lightweight packaging, core-skin structures for lightweight applications, and as insulation materials for thermal or vibration control.

Nanocrystalline cellulose Continuous Fibers

Continuous CNC-composite fibers, have been successfully manufactured using customary fiber spinning methods, such as electrospinning, dry and wet spinning, as referenced in Peresin *et al*., study in 2010 [131]. These fibers offer potential applications in textile innovation and as reinforcements in both long and short fiber-reinforcement applications.

IMPORTANCE OF NANOFIBERS

The production of nanofibers is noteworthy due to their significant attributes, such as a substantial aspect ratio, heightened porosity, and the potential to integrate active elements on a nanoscale. These qualities render them versatile for a broad spectrum of industries, encompassing semiconductors, protective materials like chemical-resistant cosmetics and sound absorption, water purification, and applications in clean energy, enzyme immobilization, and biosensor immunoassay. Among these applications, the biomedical sector stands out as particularly promising, embracing functions such as drug delivery carriers, dressing of wounds and tissue engineering. In tissue engineering, nanofiber scaffolds are intertwined with seeded cells. The porous structure, crucial for wound healing, facilitates the efficient diffusion of drug particles out of the matrix. The modulation of the rate of release of the drug can be achieved by regulating the thickness of the nanofibrous mat synthesized [132, 133].

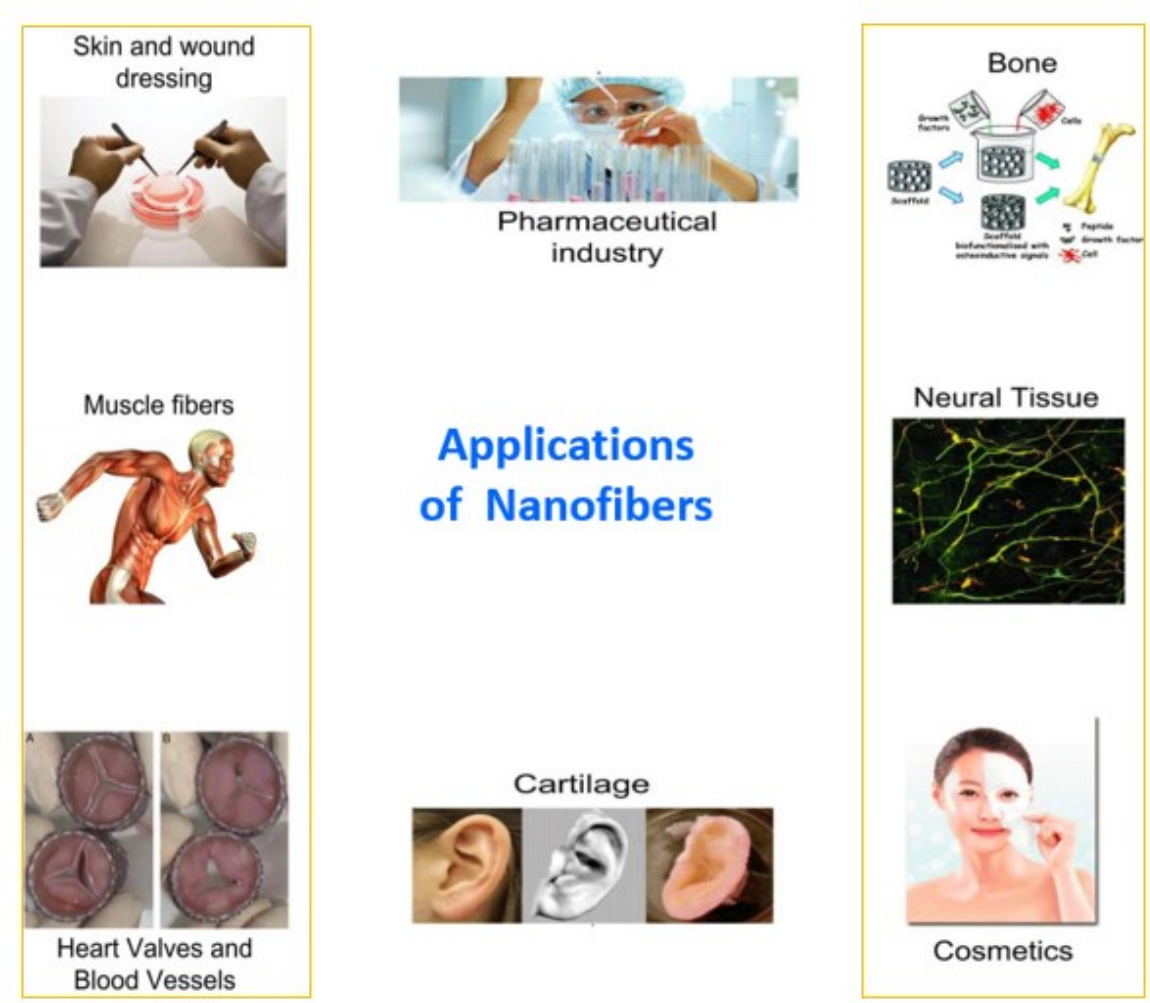

Fig. 2: Applications of nanofibers

Production of nanofibers

Cellulose nanofibers can simply be obtained by pretreating the breaking down of the cellulose fibers followed by mechanical delimination. Cellulose nanofiber was first isolated by Turbak *et al*. in 1983 through the use of bleached softwood fibers through high pressure homogenization [134]. Cellulose nanofibers have also been obtained from cassava peel [135], banana [136], oil palm tree [137], "*Helicteres isora* plant" [138], seeds of "*Citrullus colocynthis"*[139], as well as, pear and apple [140]. There was little scientific and industrial interest because of the high energy requirement of the preparation procedure. As a result, successful pre-treatments have been researched over the years. These include partial carboxymethylation [141], enzymatic hydrolysis

[142] and TEMPO catalytic oxidation [143].Ul-Islam *et al*. (2015) reported that the advantages of TEMPO-mediated oxidation include mophological stability, high crystalinity maintenance and product yield, simple and eco-friendly operations, selectivity of primary alcohol, and profitability [144]. After pretreatment, the fibres are then passed through a process of mechanical decomposition at "high pressure, micro fluidization, friction grinding, extrusion, cryopressure, and high-intensity ultrasonication" [145]. Further research on work of has led to cellulose nanofibers being extracted from fibres from curauá and sugarcane pulp [146], lignocellulosic biomassof lemon grass [142].

Electrospinning for nanofibers preparation

Electrospinning is a largely adopted procedure for the preparing cellulose-based composite nanofibers [148]. This technique involves the use of a high-voltage power source to create a liquid jet. Solid fibers are formed as this electrified jet consists of a high-viscosity polymer blend and is endlessly stretched due to the electrostatic repulsion resulting from surface charges and evaporation of solvent.

Nanofibers are generated by introducing a liquid polymer blend to form high electric field with the use of a capillary or tubesyringe needle. When the electrostatic forces surpass the surface tension of the liquid, a Taylor cone is formed, propelling the thin jet rapidly towards various collecting plates. Instabilities in the jet cause a whipping motion that elongates and narrows the jet, allowing for the evaporation of some solvent or cooling of the melt, resulting in the deposition of nanofibers on the collecting plates. Consequently, this process yields random non-woven films, electrospun nanofibers, and uniaxially aligned sheets [149].

Nanofibers produced through electrospinning find a wide array of use in the medical industry. By integrating nanoparticles, antimicrobial agents, and drug molecules into nanofibrous dressings, the risk of infection can be reduced, making them a promising solution for inflammation control and antibacterial properties [150, 151].

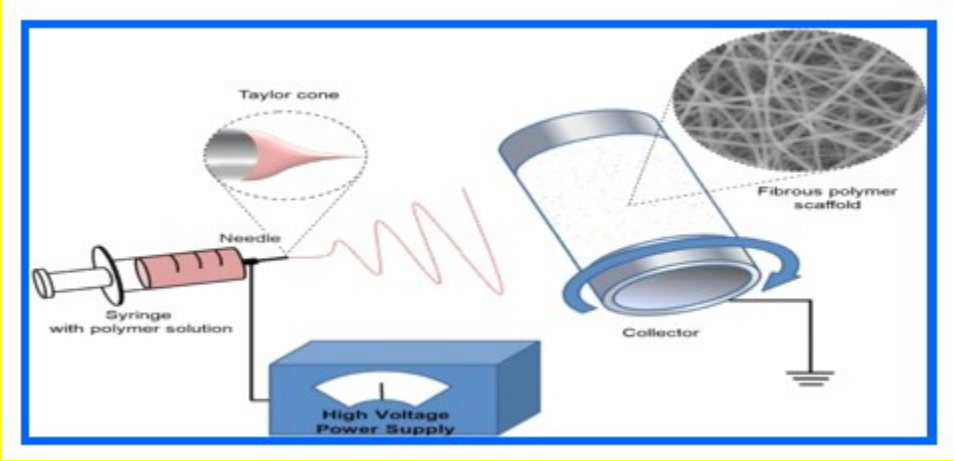

Fig. 3. Preparation of nanofibers by electrospinning.

Preparation of nanocrystalline cellulose nanofibers

Nanocrystalline cellulose is one of the most studied type of nanocellulose. The colloidal sulphuric acid-crystalysed breakdown of cellulose fibers was first reported by Ranby in 1951 [152]. An array of nanocrystiline cellulose preparations were made from various sources including wood [153], olive tree [154, 155], cotton [156], tunicate [157], sisal [158], bacterial [159], microcrystalline cellulose [160], and from waste material and biomass. Nanocrystalline cellulose obtained from acid hydrolysis of native cellulose has different morphological properties depending on its origin as well as the hydrolysis conditions [161]. According to Elazzouzi-Hafraoui et al. (2008), the separation of nanocrystalline cellulose from cellulose is founded on controlled hydrolysis of sulfuric acid, leading to a suspension that is moderately stable [162]. The weakest amorphous regions of local cellulose are hydrolyzed by acid treatment, and the resulting material changes its crystalline form. Besides sulfuric acid, high temperature hydrochloric, phosphoric and hydrobromic acids were also used to create aqueous structures at elevated temperatures [163, 164].

The common acid hydrolysis method for the preparation of individual cellulose entails the use of acid acids to treat cellulose at elevated temperatures under uninterrupted stirring. Dilution with water followed by centrifugation and then washing with water to get rid of too much acid can bring the reaction to end. Dong *et al*. (1998) gave a detail technique for hydrolysis of cellulose by sulfuric acid application [165]. In 2011, a preparation of surface carboxylated NCC (c-NCC) by oxidation of cotton linter pulp using “2, 2, 6, 6-Tetramethylpiperidine-1-oxyl (TEMPO)-NaBr-NaClO”

method with ultrasonic treatment, was done [166]. In like-manner, Leung *et al*. (2011) prepared c-NCC, oxidation through the application of ammonium per-sulfate at 60 °C [167].

NANOCRYSTALLINE CELLULOSE NANOFIBERS FOR DRUG DELIVERY APPLICATIONS

Oral drug delivery:

According to Jackson *et a*l. (2011), a great deal of research has been carried out on the oral application of various kinds of nanocellulose [168]. Burt *et al.* (2014) used nanocrystalline cellulose as a booster for some anticancer medications like paclitaxel, docetaxel and etoposide. The modification of the nanocrystalline cellulose surface was done by binding CTAB, a cationic surfactant, leading to a rise in the zeta potential of nanocrystalline cellulose in manner that was dependent on concentration [169]. The outcomes indicated a guided release of drugs for many days. Emaraa and colleagues (2016) conducted an investigation into the impact of NCC (nanocellulose crystals) and "microcrystalline cellulose (MCC)" transporters on the solubility of a low water-soluble drug. Their findings revealed that an elevation in the NCC loading led to an augmentation in drug solubility. As a result, this research substantiates the suitability of NCC as a carrier for drugs with low water solubility [170].

Cellulose nanofiber (CNF) is a captivating material, owing to its distinct physicochemical attributes across various interfaces. CNF offers a substantial specific surface area that fosters favorable interactions with drugs, enhancing their efficacy. Additionally, cellulose nanofiber exhibits mechanical properties that bolster the structural integrity of pharmaceutical dosage forms. Furthermore, as a result of the robust nanofiber-nanofiber interactions and high crystallinity, cellulose nanofiber films display exceptional oxygen barrier capabilities, particularly under low humidity conditions [171]. This improvement in oxygen barrier properties enhances the oxidative stability of drugs that are oxygen-sensitive during storage, making cellulose nanofiber an effective choice as a pharmaceutical excipient. Cellulose nanofiber has also been applied for instant release of drugs in paricles [172], "tablets" [173], and "capsules" as well as in form of film for regulated release of drugs [174].

In various research studies, cellulose nanofiber (CNF) combined with non-edible surfactants has been effectively employed through the Pickering method to enclose air bubbles, forming stable air

bubble structures. This innovative approach has been documented by several authors, including Kolakovic *et al*. (2012), Cervin, *et al*. (2016) [172, 175]. These three-dimensional closed-cell structures have demonstrated their utility as promising systems for the controlled and continuous release of drugs in medical applications. Notably, these aerogels can rapidly fill with liquid if their pockets are interlinked, leading to an enhanced medication release as a result of their larger surface area, as highlighted by Häbel *et al*. (2016) [176].

Guo *et al*. (2017) developed two types of beads for metformin hydrochloride release: CNF/alginate and MCC/alginate. CNF enhanced both mechanical properties and swelling, while alginate acted as the carrier for drug delivery. Notably, the aggregate release from the CNF/alginate beads surpassed that of MCC/alginate by 10%. Furthermore, the CNF/alginate beads exhibited a sustained release profile lasting up to 240 minutes [177].

A controlled release scheme for dimethyl phthalate was introduce by Patil *et al*. (2018), utilizing nanocomposites composed of urea-formaldehyde and gelatinized corn starch with the addition of cellulose nanofiber. While the first release of "dimethyl phthalate" was notably inhibited by CNF, it effectively facilitated the regulated release of the drug. The researchers concluded that the presence of a network within the starch matrix created an indirect pathway, resulting in a prolonged release, with approximately eighty to ninety-five percent of the drug being released over the course of a week [178]. In a related study, Supramaniam *et al*. (2018) developed nanocellulose alginate magnetic hydrogel beads, denoted as m-NCC, designed for the controlled and extended release of ibuprofen over a period of 30 to 330 minutes. These m-NCC beads not only held promise for targeted drug delivery and detection, particularly in cancerous tissue using MRI, but they also contributed to enhancing the release characteristics and mechanical strength of the drug [179]. Another noteworthy development in this field was reported by Thomas and colleagues, who prepared a nano-sized alginate-nanocrystalline hybrid polymer formulation with high "encapsulation efficiency" (EE). This formulation was designed for guided oral medication of rifampicin, showing potential for improved outcomes in treating "Mycobacterium tuberculosis" [180].

Hivechi *et al*. (2019) described the synthesis of nanofibers made from polycaprolactone (PCL) reinforced with nanocrystalline cellulose (NCC). Their research primarily examined the guided

release of tetracycline hydrochloride (TCH). Notably, they found that augmenting the concentration of NCC in the PCL nanofibers led to a reduction in the rate of drug release [181].

Transdermal drug delivery

Transdermal drug delivery systems (TDDS) are designed to administer drugs through the skin, allowing for systemic absorption to accomplish therapeutic concentrations. This method bypasses the digestive tract and liver metabolism, resulting in a therapeutic effect with lower doses of the drug. As a significant benefit, TDDS reduces the likelihood of hepatic and gastrointestinal side effects [182]. Nevertheless, it's important to note that TDDS has limitations, as it is not suitable for delivering larger drugs. Its application is primarily restricted to small drugs that can effectively enter the skin [183].

Cellulose nanofibers (CNF) hold significant potential for transdermal drug delivery systems (TDDS). Sarkar *et al*. (2017) for instance,developed a CNF/chitosan transcutaneous film for the delivery of ketorolac tromethamine, with cellulose nanofiber serving as a supportive component, making it a promising candidate for controlled TDDS [16]. In a separate study, Kolković *et al*. (2012) investigated the use of cellulose nanofiber as a base material in the production of sustained-release transdermal devices incorporating drugs such as indomethacin, beclomethasone and itraconazole. Using filtration techniques, they loaded the drug into the membrane matrix system at concentrations ranging from 20% to 40%. Their observations showed that drug release was sustained over a period of three months. This emphasizes the appeal of CNF as a material to control the release of drugs with low water solubility.

Various formulations based on nanocellulose, like the NFC/hydroxypropyl methylcellulose nanocomposite (Orasugh *et al*., 2018) and the nanogold-nanocellulose composite (GNPNC) (Anirudhan and Nair, 2017), have exhibited potential in regulating drug release within transdermal drug delivery systems (TDDS). Furthermore, Bhandari et al. (2017) devised drug-loaded CNF aerogels, deliberately engineered to encapsulate water-soluble drugs via physical adsorption. During in vitro assessments, both DCNF and CNF aerogels demonstrated their efficacy in facilitating drug delivery through the skin, showcasing the adaptability of CNF in this particular domain.

Local drug delivery

Local drug applications systems aim to administer drugs precisely at or in proximity to the target site, thereby improving treatment efficacy while reducing the necessary dosage. This strategy confines drug exposure to the specific area, decreasing the likelihood of systemic exposure and potential toxicity to healthy tissues [163].

In a research conducted by Laurén *et al*. (2014), cellulose nanofibers hydrogels emerged as a potentially potent matrix for controlled release or localized delivery of large molecules like peptide and proteins drugs [115]. Additionally, Laurén *et al*. (2018) developed adhesive films for drug delivery using biodegradable and atoxic polymers. These membranes use a combination of binder components, incorporating cellulose nanofibers and anionic CNF (ACNF) as the film forming material [117]. Functional bioadhesion activators such as mucin, pectin and chitosan were used for controlled application of metronidazole. The findings indicated a swift drug release, which proved advantageous in treating oral conditions like periodontitis. This rapid release ensured the patch became inactive upon detachment, making it well-suited for localized drug administration where a quick and potent local dose is often preferred. Furthermore, a recent study by Bertsch *et al*. (2019) highlighted the synthesis of hydrogels derived from cellulose nanocrystals (CNCs) via a salt-induced charge screening method. These hydrogels demonstrated sustained release patterns for proteins "(such as bovine serum albumin or BSA)", low water-soluble tetracycline, and moderately soluble doxorubicin. In the case of tetracycline, the initial release was within 2 days, while BSA and doxorubicin demonstrated sustained release over a period of up to two weeks.

CONCLUSION

This review has attempted to provide general information on the many characteristics and functions of nanocrystalline cellulose (NCC) and nanofibers. They are produced from various cellulose sources using mechanical and chemical methods. The commonest method is acid hydrolysis (chemical method). This is a selective method, because acid only hydrolyzes amorphous regions and crystalline regions are left. It has been established that nanocrystalline cellulose and nanofibers obtained by synthetic methods (mechanical and chemical) have more excellent dimensions and greater heat resistance. Due to the properties of nanocrystalline and nanofiber cellulose such as size, lack of immune response in the body, biodegradability, low cytotoxicity and hydrophilic properties caused by hydroxyl groups, increasing the potential of

these materials at the nanoscale as drug delivery excipients. Hydroxyl groups make the surface of nanocrystalline and nanofiber cellulose very flexible for adding different chemical groups, leading to effective drug release in the body. This also makes nanocrystalline and nanofiber cellulose very useful in targeted drug delivery to certain cells and increases the breakdown of drugs conjugated to nanocrystalline and fiber cellulose. Nanocrystalline and nanofiber cellulose can be affected by a variety of modifications in the biomedical field, including drug carriers, diagnostics and bio sensing, vascular graft replacement, tissue engineering, antibacterial and antiviral applications, regenerative medicine, printing applications and optical applications. Hydroxyl group makes the surface of nanocrystalline and nanofiber cellulose very flexible to add different chemical groups, leading to effective drug release in the body. This also makes nanocrystalline and nanofiber cellulose very useful in targeted drug delivery to certain cells and increases the destruction of drugs conjugated to nanocrystalline and fiber cellulose.

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