NANOCELLULOSE RECYCLED FROM THE AGRO WASTES AND ITS APPLICATIONS IN PHARMA AND OTHER INDUSTRIES

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Abstract

Nanoocellulose, predominantly, is a chain of glucose residue and one of the renewable natural polymer in expanding field of sustainable materials easily obtained from nature. In recent times, nanocellulose is one of the rapidly evolving fields focused mainly on polymer and particle engineering and science. The particle engineering applications offer merits in terms of excellent physical properties, such as acceptable specific strength, low density, high toughness and good thermal properties. Additionally, some of the biological properties such as biocompatibility, biodegradability and low cytotoxicity, are salient features of nanocellulose. The nano size dimensions of the structural elements in cellulose backbone result in a high surface area and hence, will result in powerful interaction of these molecules with surrounding species, such as water, organic, polymeric compounds, nanoparticles and living cells. This review encompasses isolation techniques and method of manufacture of nanocellulose from various lignocellulosic natural wastes. This article emphasizes widespread applications of particle engineered nanocellulose in pharmaceutical, packaging, tissue engineering, cosmetic and medical devices. Various extraction and characterization techniques pertinent to nanocellulose are also discussed in this review.

Key Words

Nanocellulose, Renewable natural polymer, Lignocellulose, Tissue engineering, Drug delivery, Nano composites

Introduction

Organic wastes produced from crops, which are otherwise a challenge, can be an ideal substitute for alternative production of value added products benefitting both rural communities as well as environment. Utilizing renewable natural resources through value addition, can support transition from petroleum based distressed economy to bio-based rich eco-nomy. One of such organic waste is cellulose, generally obtained from wood and non-wood plants. However cellulose from non-wood plants is gaining more attraction as source as its lignin content is less, which in-turn makes the process of delignification, purification and fibrillation easier, less harmful and energy efficient.

While cellulose can be produced from diverse materials that include wood, sesame husk, cotton, rice husk, oil palm, iigroundnut shells, potato peel, jute, spruce bark, mango seed, sugarcane bagasse, corn, bamboo, straws, soy hulls, olive stones, miscanthus giganteus, kapok,flax fibers, pineapple leaf and coir, banana, sisal, tomato peels, calotropis procera fibers, onion waste, citrus waste and coconut [1].

Corn is of particular interest as it is the third most important food crop in India after rice and wheat. And corn husk derived from it is one of the most commonly found agro waste which poses problem of disposal. Hence, using it to develop any products would mean value addition leading to income generation [2].

Corn husk (CH), which contains 39-42 % cellulose, 20-32 % hemicellulose and 8-13 % lignin, is most often disposed by open burning. Hence developing suitable scientific & economic method of recycling corn husk will help aligning as well as catering the needs from perspective of green energy. Global production of maize in the year 2016-2017 is as shown in **Fig. 1,** of which India produces ~2%.

In volume, production of corn in India has grown to 26 million metric tons in 2016-17 [3]. If 26 million metric tons of corn is produced in India annually, it could generate approximately 5 million metric tons of husks which could in turn lead to production of about 0.5 million metric tons of cellulose fiber [4].

Known for its strong renewability, low density, biodegradability, low thermal expansion, biocompatibility, high surface areas, excellent property and high chemical reactivity [5-9] cellulose has attracted various researchers across the globe [10-16].

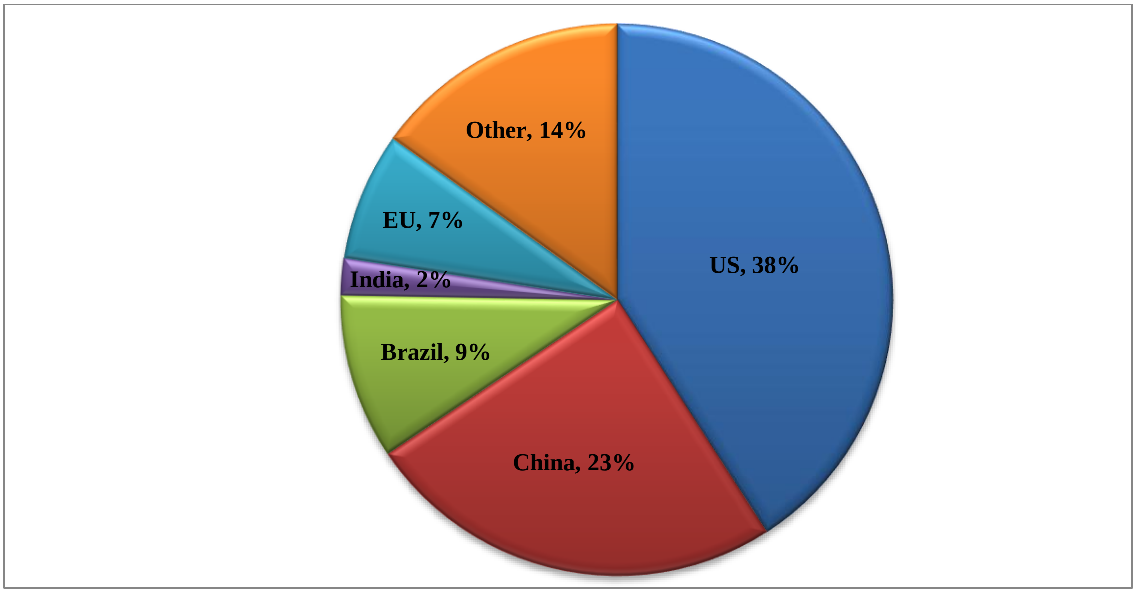

FIG. 1: GLOBAL MAIZE PRODUCTION IN LEADING NATIONS OF WORLD IN THE YEAR 2016-2017

However there is limited work reported around extraction and application of nano cellulose (NC) from agro-waste in pharmaceutical field. Hence current review focuses on worldwide production, properties and method of extraction of NC from agro waste and also explores the application of NC as a novel versatile excipient for the formulation of pharmaceutical dosage forms.

1. Structure and chemistry of cellulose

Primary structural component responsible for mechanical strength of harvested sources such as wood, annual plants or agricultural residues is known as cellulose. Each cell consists of cell wall layers, which differ from each other with regard to their structure and chemical composition, having a total thickness of 1–5 µm [17] and also representing a fiber with width of 10–50 µm (depending on the source).

Multiple layers that constitute the cell wall include – the primary wall (P), the middle lamella (ML), outer (S1), middle (S2) and inner (S3) layers of secondary wall and the warty layer (W) as shown in **Fig. 2**. Given high volume of lignin content in middle lamella, it binds the neighboring cells. The three main components that constitute primary and secondary walls are: cellulose, hemi-cellulose and a matrix (typically composed of pectin in primary and lignin in secondary walls). Thickness of primary cell wall ranges between 30-1000 nm and consists of cellulose microfibrils (MF) positioned crosswise. Secondary cell wall on the other hand is made of three layers (S1, S2 and S3) each of which differs in microfibrils angle with reference to the fiber axis. Microfibrils in these layers are densely packed in a flat helix and parallel aligned.

While thickness of secondary wall varies from 100 nm (cotton) to 300 nm (spruce wood) most of its cellulose (C) mass is contained in the fiber. Also warty layer, located in the inner surface of the cell wall, is a thin layer and mainly composed of lignin (L) and hemicellulose (H) [18,19]. As explained earlier, cellulose is present in fibers in form of the microfibrils and that both cellulose microfibrils as well as elementary fibrils are referred to as cellulose nanofibrils. However, it's desirable to obtain individual elementary fibrils with regular diameter than in bundles. As per fringe micelle theory cellulose is a semi-crystalline polymer which consists of crystalline (Cr) (ordered) and amorphous (Am) (disordered) regions within the microfibrils, where the individual cellulose molecule is considered to pass through several crystalline and amorphous parts [20].

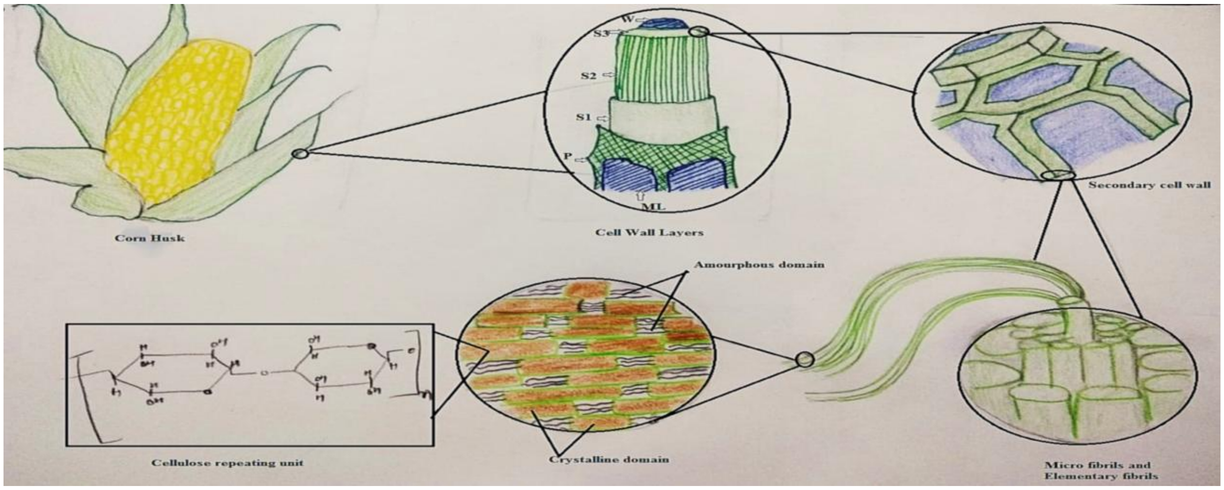

FIG. 2: HIERARCHICAL STRUCTURE OF CORN HUSK

Native degree of crystallinity usually ranges from 40-70%, depending on the origin of cellulose and isolation method. D-glucopyranose (glucose) molecules, building blocks of cellulose polymer chain, when linked by β-1, 4-glucosidic bonds turn into anhydroglucose units - two of which make one anhydrocellobiose which basically is the repeating unit of cellulose polymer. However, cellulose degree of polymerization (DP) is generally expressed as number of anhydro glucose units. While each anhydroglucose unit has six carbon atoms with three hydroxyl (viz., alcohol) groups (at C2, C3 and C6 atoms), giving high degree of functionality to cellulose molecule, there are three types of anhydroglucose units: (i) a reducing end with free hemicetal or aldehyde group at C1 atom, (ii) a non-reducing end with free alcohol group at C4 atom and (iii) internal rings [21, 22].

2. Microcrystalline cellulose as pharmaceutical excipient

Controlled hydrolysis using dilute mineral acid solutions of α-cellulose, obtained as pulp from fibrous plants, microcrystalline cellulose can be synthesized. It can be further purified by filtration and aqueous slurry is spray-dried to form dry, odorless, tasteless, white porous particles of a broad size distribution. It is widely used in pharmaceuticals as a binder, diluent, lubricant and disintegrant in oral tablet and capsule formulations. It is also used in cosmetics and food products [23-30]. Below Table 1, captures the work done by different researchers for extracting MCC from different sources using varied methods.

TABLE 1: DIFFERENT PROCESSING CONDITIONS USED FOR THE PRODUCTION OF MCC

Process	**Source**	**Treatment Condition**
Acid Hydrolysis	*Lageriana siceraria* (water gourd) [31]	• Grinding • Hydrolysis with 2% w/v sodium hydroxide for 5 h at 800 °C followed by 2.5N hydrochloric acid at 105 °C for 15 min • Bleaching with sodium hypochlorite for 15 min at 800 °C • Filtration, washing, drying at 60 °C for 60 min in hot air oven.
	Corn Husk [32]	• Treatment with boiling water for 3 hr and colloid mill grinding • 500 ml of a 2 N Sodium Hydroxide at 80°C for 2 hr. • Treatment of each batch of corn husk with 500 ml of 1 N Sulphuric acid, Hydrochloric acid and Nitric acid at 90°C for 45 min. • Filtration, washing and bleaching with a 1L of 3.5% w/v sodium hypochlorite at 55 °C for 30 min. • Washing, drying at 60°C for 6 hr.
	Sawdust [33]	• Drying, milling • 17.5% w/v sodium hydroxide 100 °C for 12 hr • 3.5% w/v sodium hypochlorite solution 80 °C for 8 hr • 20% hydrogen peroxide at 40 °C for 2 hr • 2.5M hydrochloride acid at 105 °C for 15 min • Filtration, drying in an oven at 60 °C for 1 hr
	Corn cobs [34]	• 3.5% nitric acid and 0.01% sodium sulphite at 90°C for 2 hr • 2% sodium hydroxide, 2% sodium sulphite at 50°C for 1 hr • 17.5% sodium hydroxide at 80°C for 0.5 hr • 3.2% sodium hypochlorite at 40°C for 1.5 hr • 2 N hydrochloric acid hydrolysis at 37 °C for 15 min • Washing, drying
	Groundnut husk [35]	• Washing, milling , drying at 60°C for 24 hr • Toluene-ethanol (2:1 v/v) extraction in a Soxhlet extractor for 6 hr • 3.5% nitric acid for 2 hr at 90°C • Sodium sulphite at 50°C for 1 hr • 3.5% w/v sodium hypochlorite at 100 °C for 10 min • 17.5% w/v sodium hydroxide at 80°C for 0.5 hr • 3.5% w/v sodium hypochlorite for 5 min at 100°C • 2.5 N hydrochloric acid at boiling temperature for 15 min • Washing, filtration, drying at 60°C in fluidized bed dryer

	Indian Bamboo (*Bambusa vulgaris*) [36]	• Washing, pulverizing • 2.5N hydrochloric acid at 100ºC for 30 min • Bleaching with 0.1% w/v solution of sodium hypochlorite • Drying at 60°C for 24 hr
	Banana plant wastes [37]	• 1 M sodium hydroxide at 80 ºC for 4 hr • Bleaching with 5% sodium hypochlorite at 30 ºC for 3 hr • Hydrolysis with 76, 70 or 64 wt.% of sulphuric acid • Washing, freeze drying

3. Nanocellulose as pharmaceutical excipient

Cellulose processed to have nano scale dimensions in width, length or both, is called nanocellulose. Broadly, it can be classified in four major categories listed below depending on the production conditions. CNC and CNF are produced by disintegration of cellulose fibers into nanoscale particles (top–down process),whereas BC and ECNF are generated by a buildup of nanofibers (bottom–up process) from low molecular weight sugars by bacteria or from dissolved cellulose using electro spinning, respectively.

3.1 Cellulose nanocrystals (CNC) or cellulose whiskers

Acid hydrolysis of cellulose degrades its amorphous regions while preserving crystalline ones. Thus producing CNC commonly with diameter of 3–35 nm and a length of 200–500 nm. By such treatment, rod-like rigid CNC are produced with about 90% crystallinity. Their morphology generally depends on the source of cellulose [38].

3.2 Cellulose nanofibrils (CNF) or Nanofibrillated cellulose (NFC) or Microfibrillated cellulose (MFC) or Cellulose nanofibers

Generally prepared by mechanically destructuring cellulose involving milling/grinding or high-pressure homogenization, CNF can also be prepared by chemical or enzymatic treatment or combination of all three. CNF does not have the same high crystallinity as CNC. CNF dimension, depending on cellulose source and pretreatment, can vary from 10-100 nm [38,39].

3.3 Bacterial cellulose (BC)

Production of BC is a bottom up process wherein high-purity cellulose void of any lignin or hemicellulose residue is generated by bacteria in aqueous culture media containing a sugar source, time for which ranges from few days up to two weeks. While BC has the same chemical composition as plant cellulose, it is free of functional groups other than alcohol. BC is produced in the form of twisting ribbons with cross-sections of 3–4 nm × 70–140 nm and a length of more than 2 µm. It has a 3000–9000 of degree of polymerization and a distinct crystallinity of 80–90% [38].

3.4 Electrospun cellulose nanofibers (ECNF)

Post dissolving cellulose in an appropriate solvent, high voltage is applied to a droplet of cellulose solution to overcome the surface tension and form a jet of the solution. Which when passed through air, solvent evaporates, forming a filament collected on an electrically grounded target [40, 41]. Generally, ECNF produced start from few hundreds of nanometers to few hundreds of nanometer to few microns in diameter often referred as nanofibers [42].

4. Extraction process of nanocellulose

4.1 Acid hydrolysis

This method involves an acid-induced destructuring process during the course of which the heterogeneous acid hydrolysis involves the diffusion of acid molecules into cellulose microfibrils resulting in the cleavage of glycosidic bonds within cellulose molecular chains in the amorphous domains along the cellulose fibrils, thus leading to the breaking of the hierarchical structure of the fibril bundles into NC [43,44]. The employed acids release hydronium ions that tend to penetrate the cellulosic material in the amorphous domains, react with the oxygen elements on the glycosidic bonds between two anhydroglucose moieties initiating protonation of oxygen elements and thus hydrolytic cleavage of glycosidic bonds of amorphous regions [45]. As a result of acid hydrolysis there is rapid decrease in the degree of polymerization of nano cellulose. Towards the end of the process, the mixture undergoes a series of separation and washing/rinsing steps followed by dialysis against deionized water to eliminate residual acid and neutralized salts. Sonication treatment is generally applied to get the better and homogeneous dispersion of NC in aqueous media [46-51]. Properties of the resulting nanocellulose depends on temperature and time of hydrolysis procedure as well as nature and concentration of acid used [52,53].

4.2 Mechanical treatment

There are multiple mechanical methods for the production of nanocellulose such as, microfluidization, ultra-sonication, high pressure homogenization, high energy bead milling [54, 55]. Generally, these procedures produce cellulose nanofibers characterized with a diameter in nanometers or tens of nanometers and a length of up to several microns [56].

4.2.1 High-Pressure Homogenization

In this technique suspension is forced through a very narrow channel or orifice under high pressure of 50-2000 MPa and depending on the viscosity of the suspension as well as the applied pressure the width of homogenization pressure varies from 5 to 20 μm. The gas bubbles formed, due to the increased dynamic pressure and a reduction in the static pressure below the vapor pressure of the aqueous phase (both of which are due to resultant high suspension streaming velocity), collapse immediately as the liquid leaves the homogenization gap, being again under a normal air pressure of 100 kPa. As a result the fribrillar structure of cellulose is disrupted due to formation of shockwaves and cavitation induced by gas bubble formation and implosion phenomenon [57].Through a large pressure drop, high shear forces, turbulent flow, and interparticle collisions cellulose fiber size can be reduced, the extent of which depends on a) the number of homogenization cycles and b) the applied pressure(higher the pressure, the higher the efficiency of the disruption per pass through the machine [58].

4.2.2 Grinding

In grinding, fibrillation process happens due to shear stress generated when cellulose slurry is passed between static and rotating grindstones revolving at approx. 1500 rpm, degrading the cell wall structure and individualizing the nanoscale fibrils. Distance between the disks, morphology of disk channels and number of passes through the grinder determine the extent of fibrillation. [58]

4.2.3 Microfluidization

It operates at constant shear rate. The pulp slurry upon passing through specially designed fixed geometry micro channels positioned in a z-shaped chamber accelerates to high velocities and reaches high shear force, the pressure of which can reach levels up to 40,000 psi. Upon leaving the interaction chamber, using a heat exchanger the product may be recirculated through the arrangement for further processing, or advanced externally to the next step in the process. To improve the degree of fibrillation, its essential the procedure is repeated multiple times using differently sized chambers [59-63].

4.2.4 High-Intensity Ultrasonication

In high-intensity ultrasonication, as water molecules absorb ultrasonic energy cavitation are generated which in turn form, expand and implode in form of microscopic gas bubbles disrupting the cell wall in aqueous medium, leading to defibrillation of the cellulose fibers [64].

4.3 Oxidation method

Oxidation is one of the recent novel methods to introduce charge carboxylate groups into cellulosic materials which help in disintegrating into nanofibrils with smaller widths, consuming quite lesser energy as compared to the traditional pure mechanical treatment [65] in which never-dried native celluloses are oxidized using 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) radical and subsequently homogenized by the mechanical treatment.

TEMPO-mediated oxidation of cellulose, one of the regioselective chemical alteration of primary hydroxyl groups, is well explained elsewhere [66]. The reaction takes place on the surface of cellulose fibers and in amorphous domains. Cellulose starts to disperse in aqueous solution as the carboxyl content is increased to a specific amount, however the crystalline regions remain intact and which therefore can be released [67].

Researchers have reported usage of direct ultrasonic-assisted TEMPO–NaBr–NaClO system to produce carboxylic cellulose nanocrystals from cotton linter pulp [68, 69] where some of the amorphous domains of cellulose were found to be gradually hydrolyzed during oxidation process, subsequently providing a stable as well as well dispersed aqueous suspension in one step. Microscopic observations confirmed the presence of cellulose nanocrystals 5–10 nm in width and 200–400 nm in length [70].

However there are some serious drawbacks to TEMPO-mediated oxidation method such as toxic TEMPO reagents (leading to environmental issues), oxidation time and limited oxidation at C6 primary hydroxyl groups in NC. Another oxidation method reported uses periodate chlorite, wherein periodate oxidizes the C2 and C3 hydroxyl groups using chlorite, which is a two-step process requiring expensive and toxic periodate as well as high on energy consumption [71-74]. Additionally the glycosidic rings will be successively split after the oxidation reaction reducing the molecular chain lengths/rigidity of the NC.

4.4 Enzymatic hydrolysis

Enzymatic hydrolysis is one of the less expensive alternative for preparation of NC. Usage of enzymes that selectively digest the amorphous domain of cellulose fibers but do not degrade the crystalline areas considerably, yield NC that preserve a hydroxyl group surface chemistry thus allowing easier chemical manipulation and an expanded commercial potential. One such class of enzymes is, the mixture of endoglucanases, exoglucanases, and cellobiohydrolases. While endoglucanases randomly attacks and hydrolyzes the amorphous domains, exoglucanases reacts with the cellulosic chain from either non-reducing or reducing ends and cellobiohydrolases hydrolyze cellulose from either C_1 or the C_4 ends employing a protein in each case, into cellobiose sub-units. Thus cellulose gets into amorphous part of cellulose fibers and also affects the crystalline regions as the function of cellobiohydrolases. Nonetheless, cellobiose formed during the reaction process can absorb on the activity center of cellobiohydrolases, avoiding thorough enzymolysis. Given this favorable effect, it's advantageous for controlled enzymolysis production of NC [75]. Enzymatic routes for production of NC have economical (i.e., high cost of cellulose enzyme) and technical (rate limiting step of cellulose degradation with a long processing period) limitations to it. Among the numerous factors the structural features resulting from pretreatment & enzyme mechanism are found to affect the slow rate of enzymatic hydrolysis [76].

4.5 Ionic liquid treatment

Given the recyclable, highly stable, low melting point and low vapor pressure reagent characteristics of Ionic Liquids it has gained increased attention from the scientific community for enabling innovative and sustainable solutions. Known for their unique solvating properties they are emerging as eco-friendly solvents for the pretreatment and processing of lignocellulosic materials. Few of the most interesting and highly investigated IL solvents for cellulose are 1-butyl-3-methylimidazolium chloride ([BMIM]Cl), 1-ethyl-3-methylimidazolium diethyl-phosphonate ([EMIM]DEP), 1-butyl-3-methylimidazolium acetate ([BMIM]OAc)[77] and 1-butyl-3-methylimidazolium hydrogen sulfate ([BMIM]HSO_4)[78,79]. Usage of [BMIM]HSO_4 has been successfully emphasized for isolation of rod-like NC from microcrystalline cellulose, both in dry and aqueous medium, wherein preferential dissolution of amorphous domains lead to increase in crystallinity during the treatment, while the native conformation of cellulose type I was conserved[80]. Quite recently, researches leveraged the solvent system tetrabutylammonium acetate/dimethylacetamide in conjunction with acetic acid, in which both the dissolution of amorphous cellulose and the acetylation of hydroxyl groups takes place[81].The resultant NC were hydrophobic with rod-like morphology, good thermal stability and high crystallinity index.

4.6 Subcritical water hydrolysis

Evident from the hydrothermal process of hemicellulose elimination, ability of water to hydrolyze polysaccharides is quite well-known. Presence of water molecules and availability of H_30^+ ions influence the hydrolysis rate. Given lower K_w values of sub and super critical water, concentration of ionized species is higher which can be efficiently utilized for hydrolysis reactions. The green characteristics as well as its low and cleaner effluent, low corrosion and low cost characteristics renders utilization of water as reagent quite promising one. Using high temperature and pressure of water hydrolyzes the lignocellulosic materials contained in the commercial MCC thus producing NC [82,83].

4.7 Combined processes

Apart from the above listed processes, one of the most effective ways to enhance NC properties and yield is by developing combination of two or more of the aforementioned methods but its equally essential to factor the limitations such as the environment pollution, equipment corrosion and difficulty in controlling the hydrolysis degree of cellulose [84]. Combination of processes affect crystallinity, thermal stability of NC. Below **Table 2**, captures the work done by different researchers for extracting NC from different sources using varied methods listed above.

TABLE 2: DIFFERENT PROCESSING CONDITIONS USED FOR THE PRODUCTION OF NC

Process	Source	Treatment condition
Acid hydrolysis	Cocos nucifera var aurantiaca peduncle[85]	• Grinding • 0.7 % w/v of sodium chlorite, drying at 120°C in an oven for 120 min • 17.5% w/v of sodium hydroxide at 30°C for 35 min • 80% acetic acid and 70% w/v nitric acid at 120°C for 15 min • Drying at 102°C
	Empty fruit bunch[86]	• Grinding • Boil in water for 80°C for 1 hr • 5% w/v sodium hydroxide for 1 hr at 80°C • Washing, bleaching with 5% w/v sodium chlorite at 80°C for 1 hr • Drying in an oven at 80°C
	Apple Pomace[87]	• Grinding and washing • 6- 12% sodium hydroxide for 30- 240 min at 30 - 90°C.
	Acacia bark[88]	• Grinding • 5% w/v sodium hydroxide for 30min, • 80% v/v acetic acid • 70% v/v nitric acid at 120°C for 15 min • 64% sulfuric acid treatment for 70 min • Sodium hypochlorite, glacial acetic acid at 75 °C • Washing, centrifugation

	Old newspapers and recycled newsprints[89]	• Milling • 60% w/v H2SO4 at 45 ºC • 5% w/v sodium hydroxide for 2 hr at 125 ºC • 2% w/v sodium hypochlorite for 2 hr at 125 ºC • Overnight drying at 105 ºC ,
	Rice husk[90]	• 4M sodium hydroxide at 80 ºC for 12 hr • 15 % sodium hypochlorite at 60 ºC for 60 minutes • 4M sulphuric acid at 60 ºC for 60 minutes
	Cassava Bagasse[91]	• 0.7 % w/v sodium chlorite solution and 17.5 % w/v sodium hydroxide for 5 hr • 5% w/v sodium sulfite solution for 5 hr • Dimethylsulfoxide at 80 °C for 3 hr • 62.4% w/w sulfuric acid at 45 °C for 120 min • Washing, filtration, drying at 40 °C for 12 hr
	Sugarcane bagasse fibers and pith[92]	• Grinding • Organosolv pulping using ethanol/water at 190◦C for 2 hr • 24% hydrogen peroxide • 4% sodium hydroxide • 65 % sulfuric acid for 40 min • Washing • Centrifugations performed at a speed of 10,000 rpm and temperature of 15°C
	Wood pulp[93]	• 55–65 % w/v sulfuric acid at 45-65°C for 30-180 min
	Oil palm frond waste[94]	• 10% v/v sodium chlorite and acetic acid • 64% v/v sulphuric acid hydrolysis for 1 h.
	Posidonia oceanica[51]	• Sodium hydroxide, acetic acid, sulfuric acid, sodium chlorite treatments at 55 °C • Centrifugation, dialysis
	Recycled newspaper[95]	• Grinding • Sodium hydroxide, sodium chlorite treatments at 125 °C, • 65% sulfuric acid at 45 °C • Centrifugation, dialysis
	Hardwood pulp[96]	• Phosphotungstic acid hydrolysis • Extraction with diethyl ether • Decantation • Ethanol precipitation

		• Washing, centrifugation
	Banana plants[97]	• Soxhlet extraction • 64 % sulfuric acid hydrolysis at 50 °C • Sodium hypochlorite at 55 °C • Centrifugation, dialysis
	White coir[98]	• Organosolv process • alkaline-peroxide bleaching • 30% sulfuric acid at 60 °C hydrolysis • Centrifugation, dialysis, ultrasonication
	Pineapple leaf[99]	• Grinding • 64% sulfuric acid at 45 °C • Centrifugation, dialysis, ultrasonication
	Whatman filter paper[52]	• Blending • 4 N hydrochloric acid at 100 °C for 120 min • 85% phosphoric acid at 60 °C hydrolysis • Ultrasonication, lyophilization, Centrifugation, dialysis
	Raw cotton linter[100]	• 60% w/w sulfuric acid at 45 °C for 60 min • Centrifugation for 15 min at 13,000 rpm
	Sugarcane bagasse [101]	• 17.5% w/v sodium hydroxide solution for 5 hr • Dimethylsulfoxide in an 80 °C water bath for 3 hr • 60% w/v sulfuric acid hydrolysis for 5 hr at 50 °C • Washing, filtration, drying
	Pineapple leaf fibers[102]	• Ball milling • 2% sodium hydroxide for 4 hours at 100°C • 1.7 wt% sodium chlorite • Lime juice hydrolysis • Drying
	Hardwood[103]	• Bleaching • Acid hydrolysis • Filtration and centrifugation
	Eucalyptus pulp[104]	• Bleaching • Acid hydrolysis • Filtration and centrifugation
	Sisal fibers[105]	• Grinding • 60% Sulfuric acid hydrolysis at 55 °C • Bleaching • Centrifugation

	Eucalyptus pulp[106]	• Formic acid hydrolysis at 95 °C • Bleaching • Centrifugation and dialysis
	MCC[107]	• Hydrochloric acid hydrolysis • Washing, Bleaching • Tray drying
Mechanical treatment	Eucalyptus pulp[108]	• 1% w/w 1-Butyl-3-methylimidazolium chloride at 150 °C • High pressure homogenization from 40 to 120 MPa and for up to 50 cycles • Centrifugation at 12,000 rpm, vacuum freeze drying
	Wood[109]	• Ethanol solvo thermal treatment • Alkaline hydrogen peroxide treatment, • Ultrasonication, washing, drying
	Microcrystalline cellulose[53]	• Dispersion in water, ultrasonication for 50 minutes at an output of 500 W, frequency of 20 kHz • High-energy bead milling • Decantation, freeze drying
	Microcrystalline cellulose[107]	• High pressure homogenization,Drying
	Needle Grass [110]	• Carboxylation, centrifugation, lyophilization
Oxidation method	Bleached kraft hardwood pulp[72]	• Lithium chloride-assisted sodium metaperiodate oxidation at 75 °C • Washing
	Jute fibers[69]	• Grinding • Sodium hydroxide and dimethylsulfoxide treatments • Treatment with TEMPO/NaClO/NaBr system • Centrifugation, sonication, drying
Enzymatic hydrolysis	Bleached kraft pulp[111]	• Pre-soaking in water, grinding, centrifugation • Treatment with commercial enzymes or termite cellulose and incubated at intervals from 6–72 hr at 35 °C • Washing, lyophilization
	Flax and hemp fibers[112]	• Washing • Treatment in acetate buffer supplemented with endoglucanases and incubated in a shaker at 50 °C, • Centrifugation, rinsing, ultrafiltration, freeze drying
	Cotton fibers[75]	• Dimethyl sulfoxide and sodium hydroxide treatment with buffer solution at 45 °C

		• Centrifugation • Drying
	Cotton fibers[113]	• 4 N Hydrochloric acid hydrolysis • Fermentation, Centrifugation • Ultrafiltration, Freeze drying
Ionic liquid treatment	Hardwood pulp board[81]	• Treatment with solvent system tetrabutylammonium acetate/dimethylacetamide in conjunction with acetic acid at 65 °C • Washing, centrifugation, drying
	Pure cotton[114]	• Swelling in 1-butyl-3-methylimidazolium chloride and 1-(4-sulfobutyl)-3-methylimidazolium hydrogen sulfate followed by quenching by adding cold water • Washing/centrifugation cycles, freeze drying
	Angelim vermelho wood[77]	• Grinding • Treatment with 1-ethyl-3-methylimidazolium acetate at 60 °C, • Centrifugation • Washing • Dimethyl slphoxide treatment, dissolving, drying
	Bleached wood kraft pulp[78]	• Swelling in pure 1-butyl-3- methylimidazoliumhydrogen sulfate at room temperature followed by the incorporation of deionized water • Centrifugation, dialysis, freeze drying
	Commercial microcrystalline cellulose[115,116]	• Water hydrolysis at 120 °C and pressure of 20.3 MPa • Filtration • Dialysis, ultrasonication
	Cotton cellulose fibers[117]	• Drying at 105 °C during 24 hr • Treatment with 1-butyl-3-methylimidazolium chloride in presence sulfuric acid at 80 °C • Washing, centrifugation, freeze drying
Combined processes	Oil palm empty fruit bunch microcrystalline cellulose[118]	• Sono-assisted TEMPO-oxidation followed by sonication (mechanical treatment) • Washing, centrifugation, drying
	Commercial microcrystalline cellulose[119]	• Dispersion in water, ultrasonication combined with tungstophosphoric acid • Extraction with diethyl ether, drying

	Old corrugated container material[120]	• Soaking in water • Sodium hydroxide pretreatment • Phosphoric acid hydrolysis • Washing, enzymatic hydrolysis • Ultrasonication, centrifugation, dialysis, freeze drying
	Corncob[121]	• 3% w/w sodium hydroxide treatment for 3 hr at 100 °C • Sodium hypochlorite at 80 °C for 2 hr • 64 wt% sulfuric acid hydrolysis at 45 °C for 30 min • TEMPO-mediated oxidation
	Corn stalk[122]	• Sodium chlorite/acetic acid pulping • 5 % sodium hydroxide for 2 hr at70–80°C • TEMPO-mediated oxidation at pH 10, using Sodium chlorite as oxidizing agent and TEMPO as a catalyst • Filtration, washing,
	Cotton stalk[123]	• 64% sulfuric acid at 45°C for 50 min • Sodium bromide + TEMPO (75 mg) was stirred continuously for 10 min • 13% sodium hypochlorite solution, ethanol was added to quench the reaction and the pulp fibers were dispersed in deionized water and sonicated.
	Filter paper[124]	• Cut into pieces • Treatment with sulfuric acid solution assisted by simultaneously ultrasonic wave and microwave • Dilution, centrifugation, drying

5. Properties of nano cellulose

5.1 Biodegradability

Of the multiple properties of nanocellulose, one is biodegradability which enables its usage in coating and packaging purposes. Multiple reports have documented the improvised thermal & mechanical strength of materials when aided by nanocomposite, for instance biodegradable films in particular reflected improved tensile strength, elongation potential, thermal and structural stability and oxygen barrier, forming a resistant yet durable film when enhanced with nanocellulose [125-132].

5.2 Mechanical properties

Young’s modulus, measure of the force required to stretch or compress a material, in case of NC is reported up to 150 GPa. It is higher than steel and similar to Kevlar, however it may be influenced to certain extent depending on the source of cellulose and the type of treatment [133]. Further, multiple studies have confirmed significant increase in tensile strength when utilizing nanocrystals as compared to the original fiber state [134]. Such inherent property of NC when used as reinforcing agents, renders it useful to beat the mechanical limitations of biodegradable films.

5.3 Thermal resistance

Natural cellulose is highly crystalline in its structure. Acid hydrolysis treatment, which tends to eliminate amorphous components such as residual lignin, hemicellulose, extracts, pectin and imperfect cellulose crystals, leads to a more resistant and stable structure, affecting several properties in NC such as their thermal stability [135].

5.4 Morphology

Initial material used for NC production are influenced by the source of raw material. Such specific properties followed by different production methods in turn yield NC having similar morphologies but different characteristics with respect to its dimensions (diameter and length). While having an accurate comparison of fiber dimensions is difficult given different raw materials, but in general it can be seen that in cases where pre-treatment step is included, it yields more narrow size distribution and can also produce fibers with diameter as low as 3-5 nm [136,137]. Such low values can also be attributed to centrifugation step post fibrillation process, as it eliminates the larger NC fibers. Depending on the source, the extracted NC fibers have higher or lower dimensions while on one hand studies conducted on the effect of lignin content on fiber dimensions have reported larger diameter of NC fibers produced from lignin-containing pulp irrespective of the origin of pulp used [138,139] on the other hand it has been confirmed that hemicellulose content correlates with smaller nanofibers dimensions i.e. it limits the association between cellulose nanofibers [140-143]. Implying, both lignin as well as hemicellulose residues influence the fiber morphology. Given each material source is specific and production methods also differ from one study to another, its difficult to accurate picture about the effect of all factors on fiber dimensions.

5.5 Degree of polymerization and tensile strength

Strong correlation between degrees of polymerization (DP) for cellulose with aspect ratios of the nanofibers have been reported; higher the DP longer are the fibril. DP may decline by 30-50%, as number of mechanical treatment cycles are increased during NC isolation [144]. Also there is direct correlation between DP to the NC tensile strength i.e. higher the DP, higher is the tensile strength [145], however exact values of tensile strength are yet to be determined precisely. Still based on the results of kraft pulp containing 70-80% of NFC fibrils distributed in a parallel direction, the strength of NC fibrils has been estimated to be at least 2 GPa [146]. Furthermore, given the high elastic modulus of cellulose, approx. 130 GPa – 250 GPa for a perfect crystal of native cellulose, NC has high toughness index.

5.6 Rheological properties

Shear thinning is a phenomenon referred to the pseudo plastic gel behavior of highly entangled aqueous NC suspensions, showing large decrease in viscosity with an increasing shear rate [131, 132]. As the number of passes through homogenization equipment increases, viscosity of NC also increases. The rheological properties render the usage of NC as thickener or stabilizer in suspensions or emulsions across varied sectors as food, paint, cosmetic & pharmaceutical [147], [148].

5.7 Crystallinity

The three hydroxyl groups present in the molecular structure of nanocrystalline cellulose have the potential to build extensive inter-or-intra-molecular hydrogen bonds in cellulose chains while oxygen atoms of adjacent molecules promote parallel chains rendering a highly compact crystal system - theoretically 100% crystallinity [136]. In case of insufficient removal of amorphous regions the normal crystallinity ranges from 55-90% basis different sources and reaction conditions [137]. Highly ordered crystalline regions of nanocrystalline cellulose lower the accessibility of organic solvents and water uptake which in-turn reduces the binding water molecules at equilibrium of the composite rendering it difficult for gas and water penetration [138]. Implying usage of NC with tightly-packed crystalline structure as excellent reinforcement in bio-polymer composition materials.

6. Applications of nanocellulose

NC finds its application in various sectors which are discussed briefly below, however its usage in pharmaceutical industry is of particular interest given the scope of this review and hence its usage as pharmaceutical excipient is discussed in detail.

6.1 As pharmaceutical excipient

Nanocellulose is not only a good biocompatible and biodegradable material but also has relatively low toxicity levels making it an ideal choice for medical applications especially dosage forms and pharmaceutical drug delivery systems. As mentioned above, current thesis is focused on exploring usage of NC as pharmaceutical excipient, the existing work on NC by other researchers was reviewed in detail. Below **Table 3**, lists the different formulations derived using NC extracted from different sources.

TABLE 3: FORMULATIONS DERIVED USING NC

Source of NC	**Formulation**	**Preparation method adopted by researcher**
MCC[139]	Composite	Solution casting method: NC suspension, glycerol and agar mixed vigorously, stirred on a hot plate at 95°C, cast it in a petri dish and dried at 45°C in an oven
Rice husk[140]	Hydrogels	Chemical crosslinking method: Gelatin, CNC suspension, and glutaraldehyde stirred on a hot plate at 55 °C for 1 hour, cast in a petri dish and dried at 45 °C in an oven
kraft pulp[141]	Composite	Casting process PVA and NFC suspension stirred at 120°C for 2 h followed by sonication for 2 min and dried at room temperature for 7 days.

Corn Husk[142], [143]	Tablet	Direct compression method by applying I-optimal design individually for comparison of pre and post compression parameters between MCC PH200 as well as AH-NC.
	Pellets	Extruder spheronization by applying box behnken design. Ethanolic solution of PVP K30 is adding to the powder blend to produce wet mass. The dough is then extruded, air dried and then filled in capsule.
	Liquisolid compact	Propylene glycol as the nonvolatile liquid vehicle. AH-NC and/or Avicel PH 200 using as the carrier and Aerosil 200 as coating material.
Pinecone biomass [144]	Films	Cellulose suspension filter using polyethersulfone membrane, peel the wet mass and pressed at less than 50 PSI for 15 min, dried for 24 h at room temperature, and then oven-dried overnight at 40°C

6.2 Construction – cement; pre-stressed and pre-cast concrete

Usage of cellulose nanomaterial and micro-cellulose fibrils in certain proportion has been reported to increase the toughness of otherwise brittle material like concrete [145]. With slight change in processing procedure the addition of ~3% micro- and nanofibrils in combination can increase the fracture energy by >50% as compared to the unreinforced material.

6.3 Packaging – filler

Given cellulose nanomaterial tend to increase the fiber bond strength, it results in strong reinforcement effect on paper materials with lesser usage of cellulose pulp through the thickness. As a result packaging weight is lighter which in turn reduces fuel cost and consumption during transportation [146].

6.4 Packaging – film

Cellulose nanomaterial, given their mechanical and optical properties, had improved the performance of reinforced plastics such as thermosetting resins, soy protein, starch-based matrices, poly(lactide) etc. [147].

6.5 Paper – filler

Given clay, the filler content in paper, is typically much cheaper as compared to wood pulp, paper manufacturers intend to increase its usage. When fibrillated cellulose nanomaterial are added in the production process, it allows to add more filler given its superior structural strength which reduces the consumption of wood pulp, thus reducing production costs. Also the energy required to dry the paper is considerably less given cellulose needed through the thickness is quite less. The resultant paper has better print quality, less porous and less translucent. Material inputs as well as energy required during production stage drop considerably with this application and alternative it also supports the light weighing thus improving overall energy efficiency in transportation [148].

6.6 Personal care - hygiene and absorbent products

Cellulose nanomaterial are ideal biodegradable water retention filler in incontinence pads and diapers as its water absorbency capacity is quite high. It can also be used as hydrating agent and composite coating agents, in cosmetics (e.g., for eyelashes, hair, eye-brows, nails etc.) [148].

6.7 Paint

Viscosity of paints and coatings can be altered using nanocellulose. It has been reported that usage of cellulose nanomaterials as additive in water based polyurethane varnishes and paints, improves the durability of a coat of paint, protects from erosion due to UV radiation thus extending the life and reducing environmental burden [149].

6.8 Sensors – medical, environmental, and industrial

While CNC films absorb water, individual crystals do not dissolve or swell water. Implying its potential usage in humidity sensors or real-time contaminant detection. Elevated stress on structures like bridges can be monitored using cellulose nanomaterials. Altering cellulose nanomaterials using double-walled carbon nano-tubes and graphite carbon plus nano-powder expands its usage for sensor applications [150].

7. Market study of nanocellulose

Nanocellulose market has been witnessed to have a significant growth in the recent years. It is predicted to reach a value of $250 million by 2019, signifying an increase of 19% CAGR between 2014 and 2019 [151]. Overall, the demand of nanocellulose shows a stable circumstance and the market will witness an increasing trend in the near future. Several applicant segments still supply an enormous potential market for NC. **Table 4**, illustrates the worldwide production of NC and its production capacity [152].

TABLE 4: WORLDWIDE PRODUCTION OF NC AND ITS PRODUCTION CAPACITY

Company	Country	Capacity	Production	Type
Alberta Innovates	Canada	100 Kg/week	Pilot	NCC
Asahi Kasei	Japan	40,000 tons/ year	Pilot	NCC and NFC
BASF/Zelfo	Germany	N.A	Pilot	NFC
Bio Vision Technologies	Canada	4 tons/year	Pilot	NFC
Borregaard/SCA	Norway	150 tons/year	Pilot	NFC
Celluforce, Inc./Domtar	Canada	1 ton/day	Commercial	NCC
Daicel	Japan	N.A	Commercial	NFC
EMPA	Switzerland	15kg/day	Lab scale	NFC
Innventia	Sweden	100 Kg/day	Pilot	NFC
J.Rettenmaier&Sohne	Germany	N.A	Commercial	NFC
Nippon Paper	Japan	30 tons/year	Pilot	NFC
Oji Paper	Japan	40 tons/year	Commercial	NFC
Stora Enso	Finland	15 kg/day	Pilot	NFC and MFC

UPM-Kymmene	Finland	25 kg/day	Pilot	NFC
US Forest Service	USA	35-50 Kg/day	Pilot	NCC and NFC
University of Maine	USA	500 Kg/day	Pilot	NFC
VTT	Finland	15kg/day	Lab scale	NFC

8. Conclusions

Environmental friendly bio-renewable materials form different natural resources has resulted in a great interesting in exploring new materials for advanced applications. Among different renewable materials, cellulose is the most important and common polymer available on the mother earth. Cellulose can be processed into different forms such as fibers; micro and nanocellulose. Very recently the nanocellulose are being explored for a number of advanced applications especially because of their crystalline structure and the properties resulting from the crystalline structure. However, in spite of the huge advantages of the nanocellulose, the energy consumption and production costs have limited their wide spread applications. Hence, the first part of this review article has focused on the different sources of cellulose and later has focused on the production methods for NC. In addition structural organization of cellulose of cellulose and production of corn husk as an agro waste has also been discussed for beginners in this field. We believe that the studies presented in this article will increase the interest of researchers on agro waste cellulose based nanomaterials as well as the utilization of it in drug delivery system.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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