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Using a systematic review to develop a cellulose nanocrystals production framework for use as a design baseline and optimization tool

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ABSTRACT

Various cellulose nanocrystals (CNC) production processes are not systematically reviewed. Therefore, there lacks a basis for future CNC process designs and optimizations. To solve this problem, the objective of this study was to perform a systematic review of selected CNC processes using the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidelines to review the process information from each selected literature item to identify the common process segments to create a segmented CNC production framework. The results revealed four major CNC production segments: feed pretreatment, chemical treatment, separation, and product purification. Statistical data analysis indicated that varying forms of mechanical pretreatment comprised 100% of the lignocellulosic feedstock pretreatment. However, the most common chemical treatment, separation, and product purification options are acid hydrolysis (60–75%), mechanical separation (40–60%), and washing (20–50%), respectively. The technology options explored within each segment created a design basis for CNC production improvements to assist the design of new CNC production plants and the optimization of existing ones. The model can also help improve the understanding of the minimum protocol content and improve the competency of process designers.

1. Introduction

The commercial viability of cellulose nanocrystals (CNC) is inhibited by the lack of up-scaling techniques from the laboratory to the commercial scale. CNC is a wonder material with various high-end applications in fields such as biomedical, pharmaceuticals, electronics, barrier films, nanocomposites, membranes, and supercapacitors (Trache et al., 2017). Many applications have been found, while others are still being developed. CNC is produced from cellulose- the most abundantly available biopolymer on earth (Pacheco-Torgal, 2016). Therefore, CNC production is sustainable. The CNC demand is steadily increasing globally. The nanocellulose market exhibits a compound annual growth rate of 19.9% (Market Research Report, n.d.).

The literature contains various patented and commercialized CNC production processes that have not been systematically reviewed and presented. These production processes are often very different concerning raw material pretreatments, reaction pathways, separation processes, and product purification. These process differences create a lack of basis for future designs and make it difficult to identify common optimization areas in existing CNC production processes. These two problems are currently inhibiting the widespread commercialization of CNC production processes. Examples of commercially piloted CNC production processes include the American Process Inc. and Forest Products Laboratory, while examples of patented processes include RISE Innventia AB and Nano Green Biorefineries. The development of a conceptual framework is required to guide and streamline the design of new CNC production processes from the laboratory to the commercial scale.

To overcome the current challenges, the aims of this article are threefold: to systematically review and present the recent developments in CNC production processes (commercialized and patented), to determine if any of the processes can conform to common process pathways, and to provide a conceptual CNC production framework that can be universally applied to design new processes and optimize existing ones. The systematic review was undertaken using the Preferential Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines to minimize any potential research biases. The objective of this study is to identify the main CNC production segments to create a

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segmented CNC production framework. This research is novel as it presents a comprehensive model that can be universally applied as a design baseline and optimization tool for new and existing CNC processes. While most research articles present variations within the CNC production segments, this research study groups the segment variations to create a unified design tool that can be further built upon over time. Furthermore, while other review articles present recent CNC production developments without substantial attempts to formulate a design framework or undertake statistical data analyses, this article attempts to fill these knowledge gaps.

It is argued that a universal conceptual framework based on the systematic review of the current CNC production processes can aid the design of new novel CNC production processes and the optimization of existing CNC production processes. Considering that the nanocellulose market value is forecasted to increase to 783 million US dollars in 2025 (Fernandez, 2021), optimizing CNC processes is vital to ensure their competition against new processes and a steady supply to meet the projected demands (Roopchund, 2021). Furthermore, optimizing existing processes enables improved quality and sustainability. The framework, comprised of process pathways or segments, provides a segmented perception of CNC production processes, implying that the process pathways can be optimized individually to make the overall process more efficient.

2. Literature review

2.1. Summary of CNC production processes

A summary of the major production processes currently used in global CNC production is shown in Table 1, along with the overall process yields. It is notable that the reported yields depend on the precursor material. If the precursor material is raw biomass, then lower yields are found. Conversely, if the raw material has already been refined- such as micro-crystalline cellulose, then higher yields are reported. A review of the processes follows the summary.

2.2. Part 1: review pilot plants in operation

2.2.1. American Process Inc

American Process Inc. (API) created the American Value Added Pulping (AVAP) process that can be applied to any lignocellulosic biomass to produce CNC (Nelson and Retsina, 2014). The AVAP technology is novel as it enables the final products' varied morphology and surface properties.

The AVAP pretreatment process mixes eucalyptus biomass with sulfur dioxide de-lignifying agent (to release cellulose and hemicellulose from lignin), ethanol solvent (to aid the penetration of sulfur dioxide into the biomass material), and water (Nelson and Retsina, 2014). Strong lignosulfonic acids are created to facilitate the hydrolysis phase, leading to CNC and cellulose nanofibers (CNF). This process is unique from other processes that require concentrated sulphuric acid for hydrolysis. The dissolved sugars in the residual liquor produce biofuels and biochemical products. The CNF and CNC products are washed to remove the dissolved lignin and sugars. Every output stream from the process can be refined to obtain valuable products instead of disposal. Such recycling is remarkable from an economic and environmental perspective. API has a CNC production capacity of 0.5 tons per day (Miller, 2016). The reported process is advantageous as it outputs low-cost and clean CNC while having the ability to produce CNC at a large scale (Glassner, 2013).

The process is simplistic as no mechanical separation units are required besides a fractionation column to separate the cellulose from the hemicellulose and lignin. The other process equipment is standard, thus positively impacting process implementation. Fig. 1 shows a simplified schematic.

2.2.2. Blue Goose Biorefineries Inc

Blue Goose holds a CNC production capacity of 100 kg daily (Miller, 2016). The pilot plant produces CNC for sale while generating process data for commercial-scale plant design. Although acetate-grade dissolving pulp is used for CNC production, other biomass types have been successfully converted ("Blue Goose Biorefineries Inc.," n.d.).

The production method is based on transition metal-catalyzed oxidation of lignocellulosic biomass. According to the company, the chemistry involves spontaneous reactivity of the biomass with the input

Table 1
Summary of CNC production technologies with corresponding process yields.

Process	Process steps Feedstock pretreatment	Chemical treatment	Separation	Purification	Yield (%)
Part A: Commercial Processes					
American Process Inc.	Fractionation with sulphuric acid, ethanol, and water	Bleaching	Unspecified mechanical separation	Unspecified mechanical treatment	26
Blue Goose	Catalytic oxidation (stage 1)	Catalytic oxidation (stage 2)	Washing	Washing and dewatering	30
Forest Products Laboratory	None (raw material is pulp, rather than biomass)	Acid hydrolysis	Gravity settling	Sodium hydroxide neutralization and ultrafiltration	50
ICAR-CIRCOT	Zinc chloride treatment, rinse, and high-pressure homogenization	Acid hydrolysis	Mechanical processing	Chemo-bio mechanical processing	> 95
Innotech Alberta	Not mentioned	Acid hydrolysis	Centrifugation	Ultrafiltration	< 30
Part B: Patented Processes					
Domtar Corporation (Patent number: US P,297,111 B1)	Not mentioned	Acid hydrolysis	Liquid-liquid extraction using a water-insoluble solvent	Dilution and neutralization	35 - 65
FPInnovations (Patent number: US 2010/0,286,387 A1)	Not mentioned	Acid hydrolysis	Gravity settling and decanting or centrifugation	Dilution	< 50
Hebrew University of Jerusalem WO 2012/U14213 A1	Homogenization of sludge	Successive acid hydrolysis	Centrifugation	Washing	< 40
RISE Innventia AB (Patent number: US 8911,591 B2)	Acceleration and disintegration of biomass	Not needed (pulp is the end product)	Not needed (pulp is the end product)	Not needed (pulp is the end product)	Not reported
Nano Green Biorefineries Inc. (International Publication Number: WO 2017/127,938 A1)	Mechanical size-reduction	Catalytic oxidation	Filtration	Washing and concentration	> 28

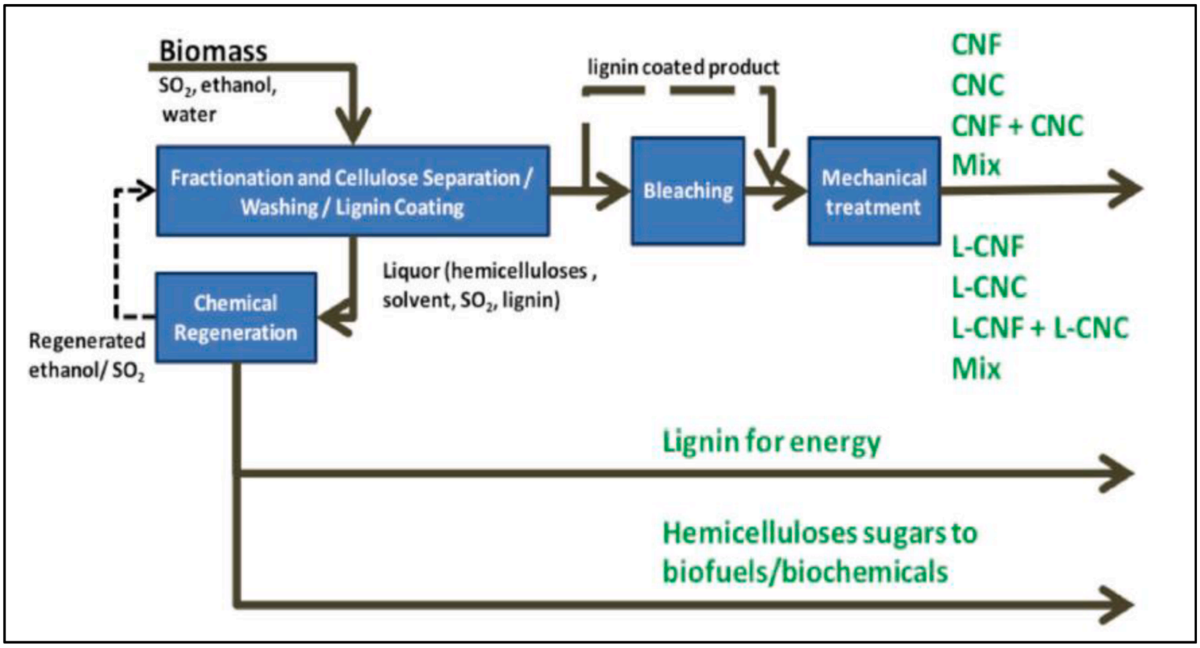

Fig. 1. Schematic of CNC production used by American Process Inc. (Nelson and Retsina, 2014)

reagents. The process comprises two oxidation stages in two separate reactors with intermediate alkaline extraction. The first oxidation reaction on fibrous biomass significantly reduces the fiber length. The reaction is complete when the suspension color changes from greyish to white ("Blue Goose Biorefineries Inc.," n.d.). The oxidation reaction generates carboxylic acids, which are soluble in the subsequent alkaline extraction step. In the extraction phase, sodium hydroxide is added to the suspension to increase the acid solubility, enabling separation from the biomass. This separation enables the acid to be washed from the CNC product ("Blue Goose Biorefineries Inc.," n.d.).

The second oxidation reaction enables the separation of the non-CNC biomass portion. The CNC product can then be washed, dewatered, and packaged ("Blue Goose Biorefineries Inc.," n.d.). Although no detailed design information was available at the time of review, the prerequisites for effective operation are proper mixing, temperature control, and maintaining the correct ratio of oxidant to biomass ("Blue Goose Biorefineries Inc.," n.d.). Although the Blue Goose process seems straightforward, more information outlining the process yield, techno-economics, and optimization techniques is required to understand the process.

2.2.3. *Forest products laboratory*

The Forest Products Laboratory's (FPL) initial laboratory-scale process entailed hydrolyzing 20 g of commercial viscose-grade dissolving pulp with 64% sulphuric acid for an hour (Reiner and Rudie, 2013). After hydrolysis, centrifugation separates the residual cellulose from the acid. Thereafter, dialysis and ion exchange remove the residual acid and salt. Due to increased CNC demands, FPL scaled its process to produce one kg of CNC. Consequently, the hydrolysis reaction is quenched by dilution, and the solution is neutralized (Reiner and Rudie, 2013). The CNC is then gravity-settled in a 900 L tank. The salt solution is decanted from the settling tank, the CNC is diluted, and the remaining salt is removed using membrane filtration (Reiner and Rudie, 2013). In addition, membrane filtration replaced the dialysis step. During the membrane filtration, CNC is circulated through a tubular ultra-filtration (UF) system, which passes the dilute salts and sugars and retains the CNC. Demineralized water dilutes the retained CNC to achieve 1 wt% concentration (Reiner and Rudie, 2013). Despite the energy intensity of membrane filtration, a trade-off must be realized between production capacity and separation time versus alternate technologies such as dialysis. Considering the increasing CNC demand, the trade-off seems to have been met.

The mentioned operation continued until funding was obtained for new pilot plant equipment to produce CNC at the 20 kg scale. The new pilot plant comprises five reactors to produce CNC and CNF (Reiner and Rudie, 2013). The CNC reaction uses a 400 L De Dietrich glass-lined hydrolysis reactor, a 6000 L initial quenching reactor, and a 4000 L neutralization and settling reactor (Reiner and Rudie, 2013). The plant also has a 400 L glass-lined reactor to dilute the sulphuric acid and a membrane filtration system to remove the residual sodium sulfate and glucose (Reiner and Rudie, 2013).

The process is initiated by cutting and packing 50 kg of machine-dried kraft rayon-grade dissolving wood pulp into the 400 L glass-lined reactor placed under a nitrogen atmosphere at 45 °C (Reiner and Rudie, 2013). The second 400 L glass-lined reactor heats 300 L of the 64-weight% sulphuric acid, which is then sprayed over the dried pulp strips (Reiner and Rudie, 2013). After adding 100 L of sulphuric acid, the dried strips are degraded and rotated as a tangled mass under the spray nozzles. After adding another 100 L of sulphuric acid, the strips are mixed (Reiner and Rudie, 2013). The total acid addition step requires 15 min, and the resulting slurry is stirred for 90 min. The pulp-to-acid mass ratio is 1:10 (Reiner and Rudie, 2013). The reaction is quenched by transferring the suspension into the 6000 L reactor containing 1200 L of water. The suspension is further diluted to 3000 L by adding 2 L of 4 wt% hypochlorite solution to de-color the suspension (Reiner and Rudie, 2013).

After that, the suspension is neutralized by adding 5–8 wt% sodium hydroxide (Reiner and Rudie, 2013). Subsequently, the suspension is split between the 6000 L and 4000 L reactors and diluted to a volume of 11,000 L (Reiner and Rudie, 2013). The CNC suspension is then settled, and the salt/sugar solution is decanted from the two reactors. The suspension is diluted a second time to reduce the sodium sulfate concentration to approximately 1 wt%, thus enabling the CNC to disperse into the solution (Reiner and Rudie, 2013). The CNC suspension is then circulated in a tubular UF system (Membrane Specialists, A19 modules), where the dilute salt/sugar solution passes through the membrane. At the same time, the CNC is retained (Reiner and Rudie, 2013). Deionized water maintains the CNC concentration at 1 wt% while the filtration is continued until the residual salt concentration corresponds to a conductivity of 40–50 μS/cm (Reiner and Rudie, 2013). This process requires a total dilution time of 24 h and 20,000 L of deionized water (Reiner and Rudie, 2013). Following the purification step, the CNC suspension is filtered using a 20-micron polypropylene cartridge-style filter and concentrated to 5-weight% solids via UF (Reiner and Rudie, 2013). The authors claim that the overall yield is 50%.

2.2.4. ICAR-CIRCOT

The Indian Council for Agricultural Research (ICAR) has a Central Institute for Research on Cotton Technology (CIRCOT), which primarily uses cotton, bacterial cellulose, and agricultural biomass as raw materials to produce nanocellulose (CNC and CNF). ICAR uses chemical, biological, and mechanical pretreatments to decrease the process energy requirements ("ICAR- Central Institute for Research on Cotton Technology," n.d.). The CIRCOT developed and patented three novel processes to produce nanocellulose from cotton fibers and linters. Furthermore, ICAR-CIRCOT established a novel 10 kg nanocellulose pilot plant within an eight-hour shift. The exact CNC and CNF proportions are unknown. The patented pretreatments reduce the energy requirements by 40% (via enzyme technology) and 35% (via chemical technology) ("ICAR- Central Institute for Research on Cotton Technology," n.d.).

Based on the ICAR website information, microcrystalline cellulose is prepared through traditional acid hydrolysis. The approach is novel as the material is treated with zinc chloride for two hours to initiate swelling. After that, the material is rinsed in water and homogenized at 40 000 psi. The produced nanocellulose has an average length and thickness of less than 500 and 50 nm, respectively. The zinc chloride pretreatment decreases the number of passes for complete conversion from 10 to 5. This remarkable 50% reduction in energy requirements corresponds to a yield exceeding 95%. The process sequence is shown in Fig. 2 ("ICAR- Central Institute for Research on Cotton Technology," n.d.).

2.2.5. InnoTech Alberta

InnoTech Alberta produces CNC from residual crops and wood fiber. The novel CNC pilot plant was commissioned in 2013 with a 100 kg per week production capacity (Ngo et al., 2018). InnoTech Alberta characterizes the produced CNC to understand the chemical and physical properties, which informs the development of specific applications. This integration is valuable for quality assurance. The CNC manufacturing cycle has four major phases: feedstock pretreatment, acid hydrolysis, purification by iterative centrifugation and ultrafiltration, and drying of the final product (Ngo et al., 2018). Characterization is performed at each stage.

The process is continuously optimized by re-processing unreacted cellulose, recovering the spent acid, and extracting the sugars from the spent acid (Ngo et al., 2018). Furthermore, constant tuning and troubleshooting, maintaining feedstock control, controlling reaction conditions, and developing standard characterization methods minimize technical challenges (Ngo et al., 2018).

Dissolving pulp, bleached softwood kraft pulp, and bleached hardwood kraft pulp can be used as raw materials (Ngo et al., 2018). The CNC yield depends on the feedstock purity and alpha-cellulose content (Ngo et al., 2018). The feedstock is hydrolyzed in a Pfaudler 190 L glass-lined jacketed reactor. Thereafter, 110–115 kg of 63.5–64 wt% sulphuric acid is pumped into the reactor (Ngo et al., 2018). The acid is stirred at 200 rpm and heated to 45 °C by the reactor jacket using low-pressure steam (Ngo et al., 2018). Thereafter, 10 – 13.5 kg feedstock is added and reacted for two hours at 200 rpm (Ngo et al., 2018). The reaction contents are quenched by pumping 50 kg of water into the reactor at a pulp-to-quench-water ratio of 1:12 (Ngo et al., 2018). The hydrolysate is then transferred into a 7500 L storage tank containing 1200 kg of demineralized water to complete the quenching (Ngo et al., 2018). Immediately after, the reaction contents are neutralized using sodium hydroxide (Ngo et al., 2018). The sodium hydroxide is likely added until neutralization. The CNC purification is initiated by centrifugation to separate the CNC from the waste. A GEA Westfalia SC-35 disk stack centrifuge with a bowl speed of 6500 rpm is used (Ngo et al., 2018).

The liquid-solid separation is performed at 90 L/min (Ngo et al., 2018). The CNC is collected as a paste-like cake from the centrifuge, while the centrate is discarded. The CNC cake is then transferred into a storage tank and diluted with 1500 L of water (Ngo et al., 2018). A uniform CNC suspension is formed, which is pumped back into the centrifuge and processed to remove traces of large particles, dirt, and unreacted materials (Ngo et al., 2018).

This process differs from others, such as the FPL, which uses gravity settling to separate the initial CNC instead of centrifugation. After centrifugation, the CNC suspends in the liquid and contains sodium sulfate salts, glucose, and oligomers. UF removes these impurities from the CNC and concentrates the product to 3 wt% consistency. GEA-Niro produces the UF system with installed 800-micron membranes produced by PALL Corporation (Ngo et al., 2018). The UF is configured with 11–13 modules in parallel, designed to process 1500 L over an eight-hour cycle (Ngo et al., 2018). The CNC suspension is circulated through the hollow fiber tube modules allowing the dilute, low-molecular-weight salt or sugar contaminates to pass through the membrane (Ngo et al., 2018). At the same time, the CNC is trapped

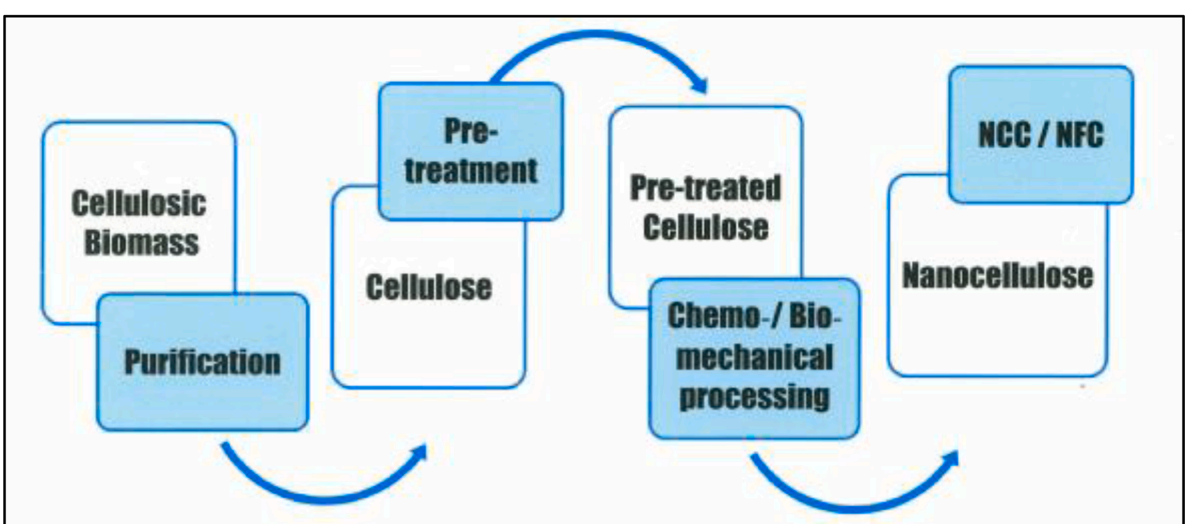

Fig. 2. Schematic of ICAR-CIRCOT CNC production process ("ICAR- Central Institute for Research on Cotton Technology," n.d.) .

within the tubes. The CNC concentration is maintained at 0.5 wt% by adding demineralized water (Ngo et al., 2018). The primary filtration stage is ended once the suspension conductivity reduces below 300 μS/cm (Ngo et al., 2018).

The UF membranes foul quickly due to the high CNC suspension viscosity. Hence, InnoTech Alberta developed a cleaning protocol to recover 80% of the membrane efficiency within two days (Ngo et al., 2018). The purified CNC suspension is then centrifuged to remove dirt, large particles, and unreacted materials (Ngo et al., 2018). The colloidal CNC suspension is filtered using a 20-micron cartridge-style filter to remove dirt and small unreacted cellulosic materials (Ngo et al., 2018). The clean CNC suspension is then transferred to the UF system for secondary purification. The purified CNC suspension is concentrated at 3 wt % and subsequently pumped to a 300 L transfer vessel (Ngo et al., 2018).

2.2.6. *Summary of pilot plants in operation*

API's process is novel due to its raw material flexibility, simplistic process design, and the beneficiation of dissolved sugars from the delignification stage into biofuels. This configuration offers technical and economic merit. The Blue Goose process is also beneficial as any biomass can be used as raw material. However, it requires a two-stage catalytic reaction and extensive separation procedures. Considering that the recyclability or beneficiation of the process reagents is not mentioned, the process is not as sustainable as the API process. The ICAR CIRCOT process uses multiple feedstock pretreatments, resulting in twice the process yield compared to the Forest Products Laboratory. While InnoTech Alberta follows a similar process route to the Forest Products Laboratory, characterization is undertaken at each production stage for quality control. Most process streams, such as the unreacted feedstock, spent acid, and sugars extracted from the spent acid, are recycled and beneficiated. Hence, InnoTech Alberta's process is more sustainable than Forest Products Laboratory's. The process is also more flexible concerning the raw material. However, it is not as simple as API's process.

Overall, the API process is most flexible regarding the raw materials and the most sustainable regarding materials recovery and beneficiation. Hence, it is the most effective and economical process in operation.

2.3. *Part 2: review of pilot plant patents*

2.3.1. *Domtar Corporation (Patent number: US P,297,111 B1)*

Domtar Corporation developed a novel CNC production process using a water-insoluble solvent to quench the acid hydrolysis reaction and recover unreacted acid, thereby separating the acid from the CNC (Marcoccia et al., 2016). The pulp fibers are hydrolyzed with sulphuric acid. After that, the sulphuric acid-specific water-insoluble solvent terminates the reaction and separates the first stream (comprised of 70% unreacted sulphuric acid in the water-insoluble solvent) from the second stream (comprised of CNC and the remaining unreacted sulphuric acid) (Marcoccia et al., 2016). It is likely that the sulphuric acid is the excess reagent to the lignocellulose feedstock. Considering that the excess sulphuric acid is subsequently recovered in the liquid-liquid extraction phase, it is not wasted. Therefore, it is reasonable that the sulphuric acid is used in excess at the start of the process. The outlined procedures are shown in Fig. 3.

The sulphuric acid is separated from the CNC by liquid-liquid extraction (LLE). The second stream is diluted in water or neutralized before solid-liquid separation (Marcoccia et al., 2016).

The bleached pulp feedstock is hydrolyzed with 40 to 60% sulphuric acid. The water-insoluble solvent migrates sulphuric acid from the aqueous phase (Marcoccia et al., 2016). Increasing the pH reduces downstream equipment capital costs due to less corrosion. Therefore, glass-lined equipment would not be required, eliminating the expense of handling and transporting acidic materials (Marcoccia et al., 2016). The stream containing the polysaccharides and water separated from the CNC is sent to a waste treatment facility to digest the polysaccharides (Marcoccia et al., 2016). The water-insoluble solvents were not specified.

2.3.2. *FPInnovations (Patent number: US 2010/0286387 A1)*

The patent registered by FPInnovations outlined a method for producing crystalline sulfated cellulose II materials from spent sulphuric acid. The crystalline sulfated cellulose I materials includes cellulose whiskers, microcrystallites and nanocrystals, crystalline nanocellulose, and stable colloidal cellulose suspension (Hashaikeh et al., 2010). The crystalline sulfated cellulose II materials are typically soluble in concentrated sulphuric acid solutions. Furthermore, the aqueous diluent includes (but is not limited to) 0 – 40% sulphuric acid (Hashaikeh et al., 2010). The method entails separating the spent acid from the cellulose I materials (cellulose derived from wood pulps) by diluting from 64% to 10–50% by adding up to 40% sulphuric acid (Hashaikeh et al., 2010). This step is followed by settling and decanting (or centrifuging), after which the diluted spent liquors are added to water or heated at 30–80 °C for no longer than 48 h (Hashaikeh et al., 2010). After that, the re-crystallized sulfated cellulose II materials are recovered by filtration and washing or by washing and freeze-drying. The method can produce

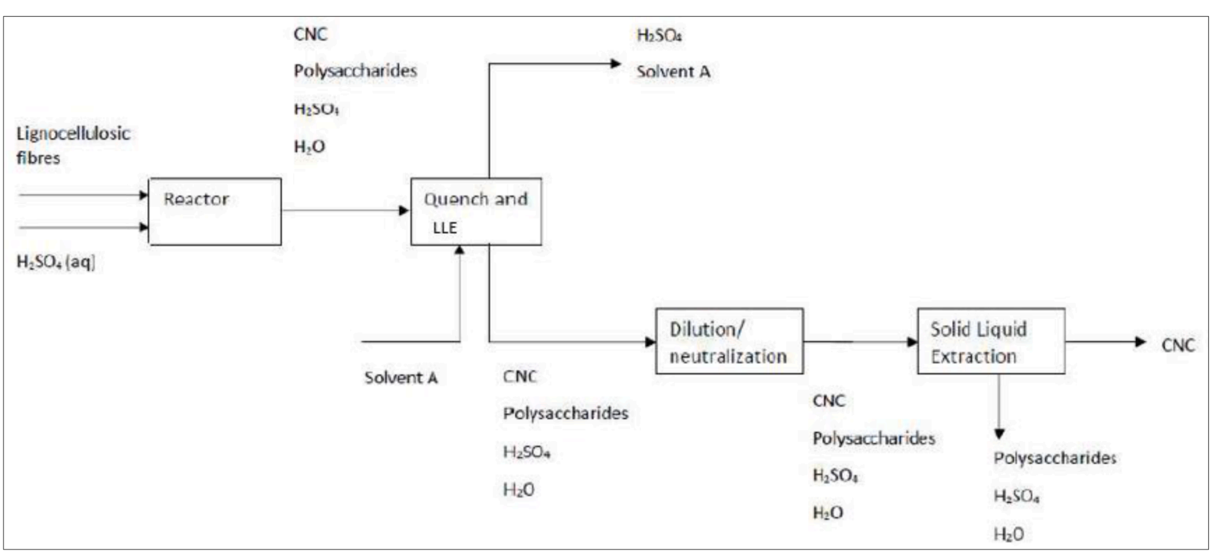

Fig. 3. Domtar Corporation CNC production schematic (Marcoccia et al., 2016).

both crystalline sulfated cellulose I and II materials (Hashaikeh et al., 2010). A process schematic is shown in Fig. 4.

The hydrolysis of cellulose is generally performed by mixing cellulose with concentrated sulphuric acid (approximately 64%) at 45–65 °C (Hashaikeh et al., 2010). The hydrolysis is performed for at least 20 min at 45 °C and 15 min at 65 °C (Hashaikeh et al., 2010). The spent liquor contains residual sulphuric acid and soluble cellulose degradation products. The acid-insoluble, sulfated cellulose (with a typical yield of less than 50%) is separated from the spent liquors by settling and decanting or centrifuging and repeated filtration and washing (Hashaikeh et al., 2010).

The sulfated cellulose II materials are recovered by diluting the spent liquors from concentrated (56–68%) sulphuric acid hydrolysis, separating the diluted spent liquors from the acid-insoluble sulfated cellulose, and adding the diluted spent liquors to water (Hashaikeh et al., 2010). These steps enable the recrystallization and isolation of the sulfated cellulose II material.

2.3.3. Hebrew University of Jerusalem (International publication number: WO 2012/U14213 A1)

This invention can produce CNC from solid waste from Pulp and Paper mills. Despite claims that the outlined CNC production process is cost and energy effective, no techno-economic study was available. The invention outlines a process to recover cellulose from sludge. This recovered cellulose is then used for CNC production (Shoseyov et al., 2012). Sludge could contain between 5 and 60% cellulose (Shoseyov et al., 2012). The authors conceded that the recovery process yields a cellulose purity of 90%, which is sufficient to allow its further processing.

Typically, the paper sludge contains high levels (40 to 60%) of dry solids comprised of wood bark, plastics, and metals (Shoseyov et al., 2012). Mechanical separation removes these solid contaminants. The sludge is homogenized and exposed to weak acidic treatment under agitation. Centrifugation then separates the liquid phase containing the soluble non-cellulosic material from the solid phase containing the cellulose. The separated soluble material is then washed to obtain pure cellulose-containing less than 5 to 10% impurities by mass (Shoseyov et al., 2012).

In the CNC production phase, the acid used to degrade the amorphous regions of the pure cellulose differs from the acid used to dissolve the impurities. Alternatively, the same acid can be used at a greater concentration (Shoseyov et al., 2012). The acid treatment must enable hydrolysis using a 20 – 60% concentration range (Shoseyov et al., 2012). The higher acid concentration also dissolves additional impurities in the liquid medium, thus separating the highly pure CNC fibers. In some embodiments, the acid may be recycled. Acid recycling is advantageous as it recovers valuable components found in paper waste.

Once the amorphous cellulose regions have been degraded, the CNC is washed (Shoseyov et al., 2012). The remaining cellulose is separated, dialyzed against water, and mechanically dispersed to produce CNC. The hydrolyzed sugars can be fermented to produce bioethanol. In addition, sulphuric acid causes gypsum formation, which can be recovered and used for construction or fertilizer (Shoseyov et al., 2012). This beneficiation is remarkable as alternate by-products provide an opportunity for more significant economic benefit.

2.3.4. RISE Innventia AB (Patent number: US 8,911,591 B2)

The feedstock in the reactor is heated until a suitable pressure is attained. In one embodiment, 1 – 4% of the raw material in water suspension is heated to 180 °C in a closed reactor (Lindstrom et al., 2014). The fibers are accelerated through an outlet at lower pressure, causing the raw material to disintegrate. The lower pressure may be ambient or lower, so a sufficient pressure difference is achieved. The pressure can be lowered in several steps, corresponding to several accelerations. The nano pulp exiting the reactor outlet is collected in a cyclone (Lindstrom et al., 2014). In a third embodiment, there is steam flow. Rapid steam production optimizes raw material disintegration. The steam flow containing the disintegrated raw material passes through a contracting nozzle, which causes a sudden expansion (Lindstrom et al., 2014). This method varies the nanocellulose homogeneity by adjusting the flow speed, elevated reactor pressure, pressure reduction speed, and geometry. The nanocellulose may comprise fibrils and other particles within the size range of 10 – 250 nm (Lindstrom et al., 2014). In the fourth embodiment, the pulp fibers are pretreated by milling, enzymatic degradation, the introduction of charges, carboxymethylation, acidic hydrolysis, alkaline hydrolysis, or any combination of these methods (Lindstrom et al., 2014). These procedures weaken the fibers, increasing the nano-pulp yield. In the fifth embodiment, the gas or liquid flow steam conforms to flow speed within 50 to 1000 m/s. The reactor pressure is held within 2 – 13 bars (Lindstrom et al., 2014).

2.3.5. Nano Green Biorefineries Inc. (International publication number: WO 2013/000074 A1)

Nano Green Biorefineries Inc. develops technology to produce CNC from various biomass sources. The technology patented by Olkowskl and Laarveld (2013) efficiently degrades biomass into cellulose, lignin, hemicellulose, and their respective degradation products. This production is achieved by a catalytic reaction to degrade complex lignocellulosic structures by reactive oxygen species generated from hydrogen peroxide within an acidic medium. In addition, fractionation and

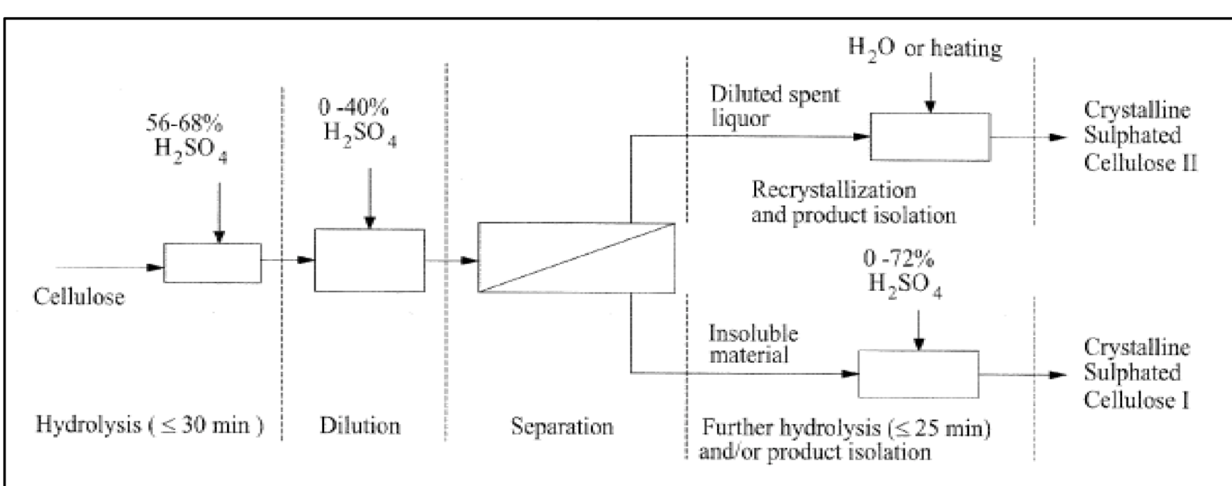

Fig. 4. CNC production schematic at FPInnovations (Hashaikeh et al., 2010).

de-polymerization techniques yield the end products (cellulose, hemicellulose, and lignin) and their corresponding degradation products (Olkowskl and Laarveld, 2013).

The catalytic process is regulated to produce platform chemicals with varying biomass degradation rates. The lignin and cellulose fractions are treated separately using different catalytic reactions (Olkowskl and Laarveld, 2013). Fig. 5 shows a process schematic.

Nano Green also patented the technology to produce crystalline cellulose (patent number: WO 127,938 A1). The production process entails reacting the cellulosic raw material in an aqueous slurry comprising a transition metal catalyst and hypothalite solution (having an initial pH greater than six and final pH less than 9) and recovering the crystalline cellulose fraction (McAlpine and Koneshny, 2017). The initial pH of the slurry exceeds 7 (preferably between 9 and 12) and has an oxidation-reduction potential exceeding 500 mV. As the hypochlorite is consumed, the pH gradually reduces below 9 (preferably less than 7). A buffer controls the pH during or upon reaction completion (McAlpine and Koneshny, 2017).

In some cases, the oxidation reaction completes due to a significant decrease in the Oxidation Reduction Potential (ORP). The oxidation reaction is repeated to produce crystalline cellulose. The CNC is preferably washed in an alkaline solution before oxidation. In another aspect, CNC is produced by reacting cellulose in an aqueous transition metal catalyst and hypothalite solution slurry and washing the cellulosic material in an alkaline solution. The reaction is repeated before recovering the CNC fraction (McAlpine and Koneshny, 2017). Fig. 6 shows a process schematic.

Interestingly, the standards for deciphering CNC quality based on several parameters are presented in this patent. No such standards were previously reported in other inventions. The assessment criteria are presented in Table 2 (McAlpine and Koneshny, 2017).

No evidence suggests that the process has been conducted on a pilot plant scale. However, exploring the CNC production process and recovery is still significant. In addition, the CNC quality criteria can be applied to other processes to ensure that CNC production is taking place optimally.

2.3.6. *Summary of patented pilot plant innovations*

Although Domtar Corporation uses traditional acid hydrolysis as the chemical treatment, it follows an innovative acid recovery procedure using a water-insoluble solvent. This acid recovery aids the process's sustainability. Similarly, FPInnovations recover soluble cellulosic compounds through crystallization. However, alternate recovery methods must be considered due to the energy intensity of the crystallization procedure. A trade-off can be found in feasibility studies. The Hebrew University's innovation enables cellulose recovery from Pulp and Paper mill sludge using weak acid treatment and mechanical separation. The process is sustainable, as hydrolyzed sugars can produce biofuels, and the acid can produce gypsum. The catalytic oxidation to produce CNC recommended by Nano Green is also used at American Process Inc. and Blue Goose. However, this patent is novel as it outlines the quality standards for CNC production. Each innovation is notable and can be implemented to improve the CNC process sustainability.

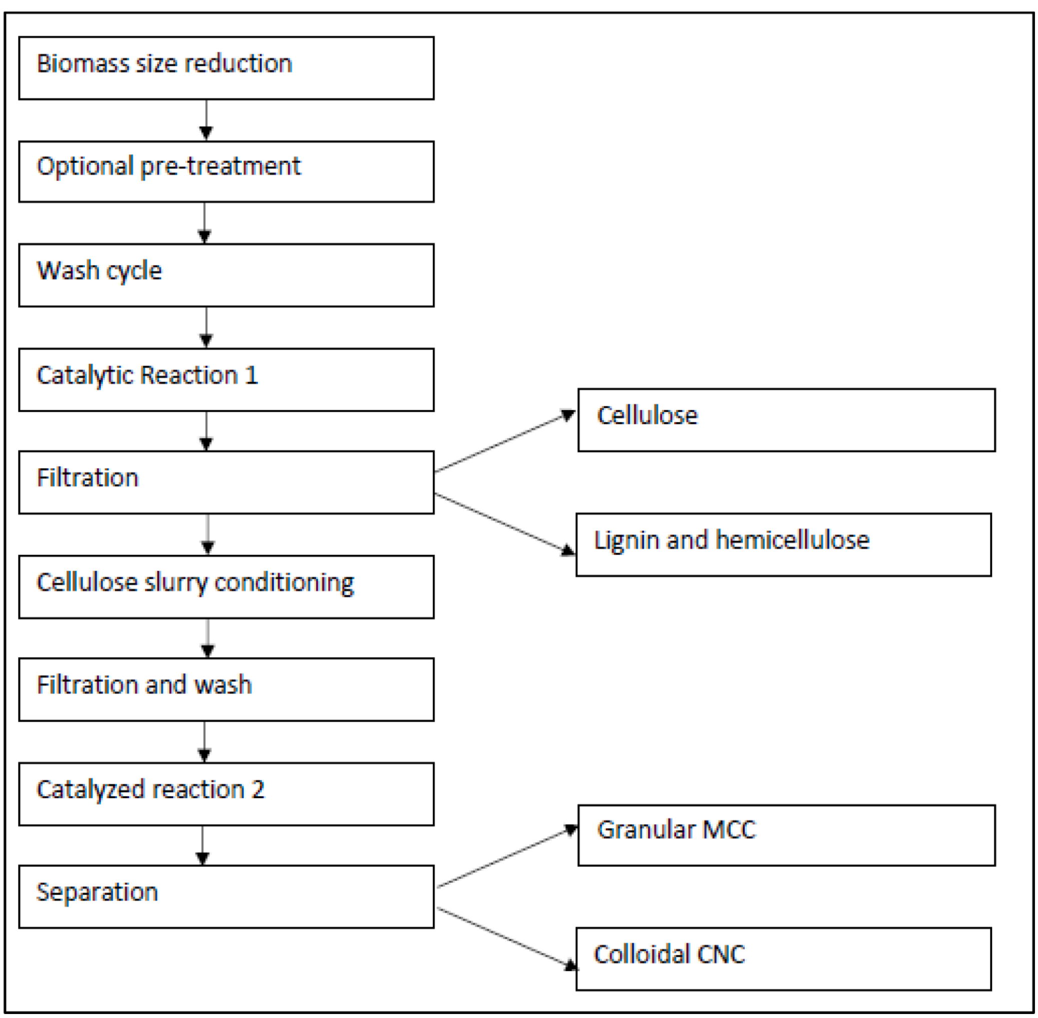

Fig. 5. Catalytic biomass conversion at Nano Green Biorefineries Inc. (McAlpine and Koneshny, 2017).

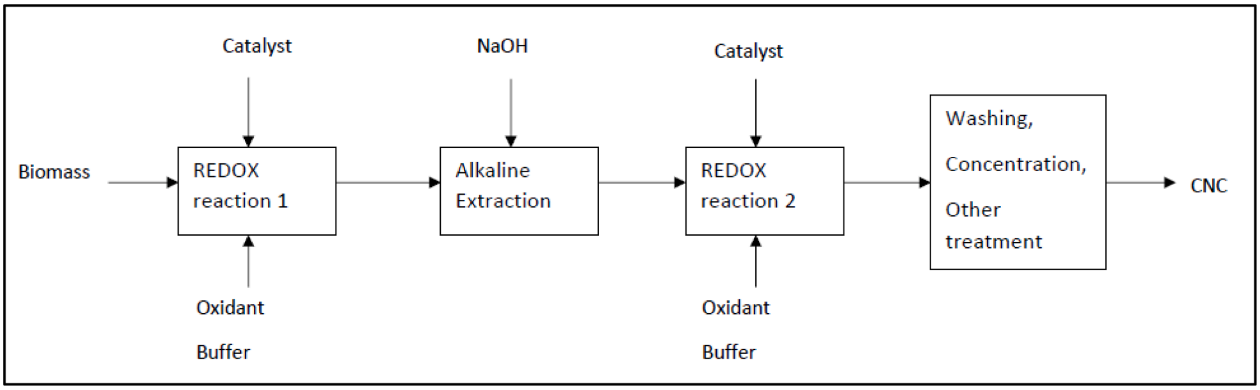

Fig. 6. CNC production schematic at Nano Green Biorefineries Inc. (McAlpine and Koneshny, 2017).

Table 2
Assessment criteria for CNC production at Nano Green Biorefineries Inc. (McAlpine and Koneshny, 2017).

Measurement	Good quality	Poor quality
Cake on filter paper	Rubbery or greasy texture	Soft or fibrous texture
Microscope image 10 X	Small visible particles with no particles after sonication	Visible fibers several microns in length
Visible appearance of gel or suspension	Relatively clear with evidence of Rayleigh scattering. Sample becomes clear with ultrasound.	Opaque gel, white or off-white and remains opaque after ultrasound treatment.
Size by Dynamic Light Scattering (DLS)	One size peak at around 100 nm	Two size peaks. One at 800 nm – 1500 nm
Zeta potential	Below −30 mV	Higher than −30 mV in association with settling particles

3. Methodology

The methodology recommended for this systematic review was adopted from Moher et al. (2015) and Heyn et al. (2019). The latter outlined the primary considerations when undertaking the systematic review based on the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P). How these considerations were addressed in this study is outlined in Table 3.

In addition, the literature was systematically searched, appraised, and synthesized into the article (Heyn et al., 2019). A comprehensive and unbiased search strategy was used for all research and review articles relating to the CNC production trends. The findings were tabulated (Table 1). Furthermore, the systematic review was organized with summaries and narratives (Heyn et al., 2019).

Conceding with the recommendations of Heyn et al. (2019), the systematic review aimed to collate all relevant evidence that fits pre-specified eligibility criteria to justify the argument (Moher et al., 2015) that the review findings can formulate a conceptual CNC production process framework and optimization tool. The systematic review is characterized by explicit, systematic methods to minimize bias in identifying, selecting, synthesizing, and summarizing studies to provide reliable findings from which conclusions can be drawn and decisions made (Moher et al., 2015). Accordingly, the critical characteristics of a systematic review are depicted in Fig. 7 (Moher et al., 2015).

The research methods outlined by Moher et al. (2015) and Heyn et al. (2019) were beneficial and appropriate as the literature was searched for the most relevant information regarding CNC. A systematic methodology was adhered to in keeping with the PRISMA-P 2015 checklist (Moher et al., 2015). A protocol outlined the objectives, planned methodology, and eligibility criteria. This method is considered a best practice for conducting a systematic review (University of Texas Libraries). The elements of the protocol were integrated into the body of the article. This protocol ensures that the systematic review is carefully planned for consistency, accountability, research integrity, and transparency (University of Texas Libraries).

4. Results and discussion

Based on the summary of the CNC production processes in Table 1, the CNC process conforms to four major segments, as shown in Fig. 8.

4.1. Step one (feedstock pretreatment)

Essentially, various pretreatment methodologies were proposed based on the characteristics of the lignocellulosic feedstock material. The feedstock pretreatment is step one in the overall CNC production process scheme. The primary feedstock pretreatments are fractionation (Nelson and Retsina, 2014), oxidation ("Blue Goose Biorefineries Inc.," n.d.), homogenization, and disintegration ("ICAR- Central Institute for Research on Cotton Technology," n.d.; Shoseyov et al., 2012) and mechanical reduction (Olkowskl and Laarveld, 2013; Lindstrom et al., 2014). These findings align to those of Kumar et al. (2009), who reported five broad pretreatment categories for the treatment of biomass. These methods include physical (mechanical comminution and pyrolysis), physico-chemical (steam explosion, ammonia fiber explosion, and carbon dioxide explosion), chemical (ozonolysis, acid hydrolysis, alkaline hydrolysis, oxidative delignification, and the organosolv process), biological and pulsed electric field treatments. The choice of the pretreatment for a particular biomass depends on its composition and the byproducts produced as a result of pretreatment. These factors significantly affect the costs associated with a pretreatment method (Kumar et al., 2009).

4.2. Step two (chemical treatment)

In the second step of the model, chemical treatments are applied to break down the pretreated cellulosic feedstock into its morphological constituents: amorphous and crystalline. The primary chemical treatments observed in the review are bleaching (Retsina, 2016), catalytic oxidation ("Blue Goose Biorefineries Inc.," n.d.; Olkowskl and Laarveld, 2013), and acid hydrolysis ("ICAR- Central Institute for Research on Cotton Technology," n.d; Ngo et al., 2018; Marcoccia et al., 2016; Hashaikeh et al., 2010; Shoseyov et al., 2012).

4.3. Step three (separation)

The third step involves a technique to separate the morphological constituents. This separation enables the untreated CNC to be separated from its amorphous components. However, the untreated CNC often contains residual chemicals from the chemical treatment process and

Table 3
Primary considerations for systematic reviews.

PRISMA-P (Moher et al., 2015)	Applications in this study
Eligibility Criteria	Research articles, patents, review articles, and commercial websites related to cellulose nanocrystals production. No years, language, or publication statuses were excluded.
Types of studies	Pilot, upscaling, and commercial studies. Reviews and optimization studies.
Types of participants	Researchers, engineers, and plant technicians.
Types of interventions	Any new development relating to unit operation replacements or variations in CNC production processes or waste management
Context	Any relevant information regarding new developments in the field of CNC production. Any information about laboratory-scale innovations, pilot upscaling, or commercial CNC production processes. Maintenance and operational information.
Types of outcome measures	Relevant information, process flow diagrams, and automation strategies.
Information sources	Journal articles, conference papers, website articles, and information about commercial CNC production processes. Mainly electronic databases with all coverage dates.
Search strategy	Searches with the following keywords were performed: "cellulose nanocrystals", "production processes", "optimizations", "process design", "patents", and "process flow diagrams".
Study records	
Data management	Mendeley software will be used to manage data and records throughout the review.
Selection process	Sources matching the keywords listed in the search strategy will be selected. After that, two independent reviewers will be used to select the studies incorporated in the review (the author and co-author).
Data collection process	The selected sources are added to the Mendeley folder designated explicitly for the CNC review search.
Data items	Research articles, review articles, conference proceedings, patents, and website information. There are no pre-planned data assumptions and simplifications.
Outcomes and prioritization	Once the sources are obtained, they are prioritized in the following order: research articles, patents, review articles, and website information. This prioritization is based on novelty.
Risk of bias in individual studies	The literature sources must be selected if they satisfy the search criteria at the outcome and study level. This practice eliminates the possibility of bias risk.
Data	Information and diagrams relating to CNC production processes must be qualitatively reviewed.
Synthesis	The data were qualitatively synthesized in a systematic review as per PRISMA guidelines.
Meta biases	No assessment is planned, as the expected bias risk is minimized by following the search criteria and the pre-defined selection process.
Confidence in cumulative evidence	If the CNC production process unit operations can be categorically ordered, it indicates confidence in the cumulative evidence.

often has a low pH if acid hydrolysis was used in step two. The main separation techniques are gravity settling (Hashaikeh et al., 2010), centrifugation (Ngo et al., 2018; Shoseyov et al., 2012), filtration (Olkowskl and Laarveld, 2013), and liquid-liquid extraction (Marcoccia et al., 2016). Considering that centrifugation and filtration are mechanical in nature, mechanical separation dominated the separation segment.

4.4. Step four (product purification)

Step four is required to complete the CNC production model by purifying the untreated CNC into its final product specifications. Often, the product purification step is not singular. The main purification techniques include washing and dewatering ("Blue Goose Biorefineries Inc.," n.d.; Shoseyov et al., 2012; Olkowskl and Laarveld, 2013), neutralization (Reiner and Rudie, 2013), ultrafiltration (Ngo et al., 2018) and (successive) dilution (Marcoccia et al., 2016).

4.5. Statistical data analysis

Based on the reviewed operational pilot plants and patented innovations reported in Table 1, the primary technology options for each process segment were quantified and shown in Table 4.

The statistical data analysis in Table 4 shows that three main feedstock pretreatments were equally used in operating pilot plants. For the chemical treatment, separation and purification segments, acid hydrolysis, mechanical separations, ultrafiltration, and chemical/mechanical treatments were the major segment options. For the patented innovations, mechanical processing was the largest pretreatment. At the same time, acid hydrolysis was the primary chemical treatment, centrifugation was the main separation, and dilution and washing comprised the main purification segment. From a process engineering perspective, mechanical treatment is easier to implement on a commercial scale. However, it is easier to implement varied pretreatments on a pilot scale. Hence, 100% of the patented processes employ mechanical pretreatment, while mechanical pretreatment is not well considered on the pilot scale.

The statistical analysis showed three major feedstock pretreatments, indicating a lack of uniformity within this process segment. This finding was attributed to the diverse lignocellulosic feedstocks used in CNC production. All the patented pretreatments comprised mechanical processing due to the patents focusing on recovering and beneficiating wastes from the CNC production process. Acid hydrolysis dominated the chemical treatment segment for both operational and patented pilot plants. This finding aligns to the study of Thompson et al. (2019), in which it was found that acid hydrolysis was a major CNC production route, followed by other hydrolysis treatments, such as enzymatic and sub-critical water hydrolysis. Hence, innovations to recover and recycle spent acid are vital.

Similarly, mechanical separation dominated the separation segment for both operational and patented pilot plants. Considering the power requirements for mechanical separations, such as centrifugation, alternate separations, such as gravity, are preferred for improved sustainability. Regarding the purification segment, washing and dewatering are typical for operational and patented pilot plants. Considering the scarcity of water as a utility, it must be collected, treated, and recycled for improved sustainability.

4.6. Overall perspectives

Considering that the results were based on the cumulative literature findings, the framework presents a theoretical confirmation of the literature. Hence, there are no contradictory findings.

The four main CNC production segments highlight the potential process pathways that can be followed to produce CNC from any source material. The choice of pretreatment technology depends on the composition of the lignocellulosic feedstock and the resulting byproducts (Kumar et al., 2009). The overall CNC production process yield (Table 1) depends on the precursor material. If refined precursors, such as micro-crystalline cellulose are used, greater yields are obtained compared to the use of raw biomass. The reason for the higher yields is that much time and energy have been expended to treat the raw biomass to produce purer cellulose forms which are more easily converted to CNC. Hence, the choice of precursor material is an important process design consideration.

Compared to the diverse feedstock pretreatment segment, the chemical treatment segment is more uniform, with only two major chemical treatments found in the patented processes (Table 4). The separation segment is an important consideration for the plant layout as gravity settling (the most economical separation technique) will require

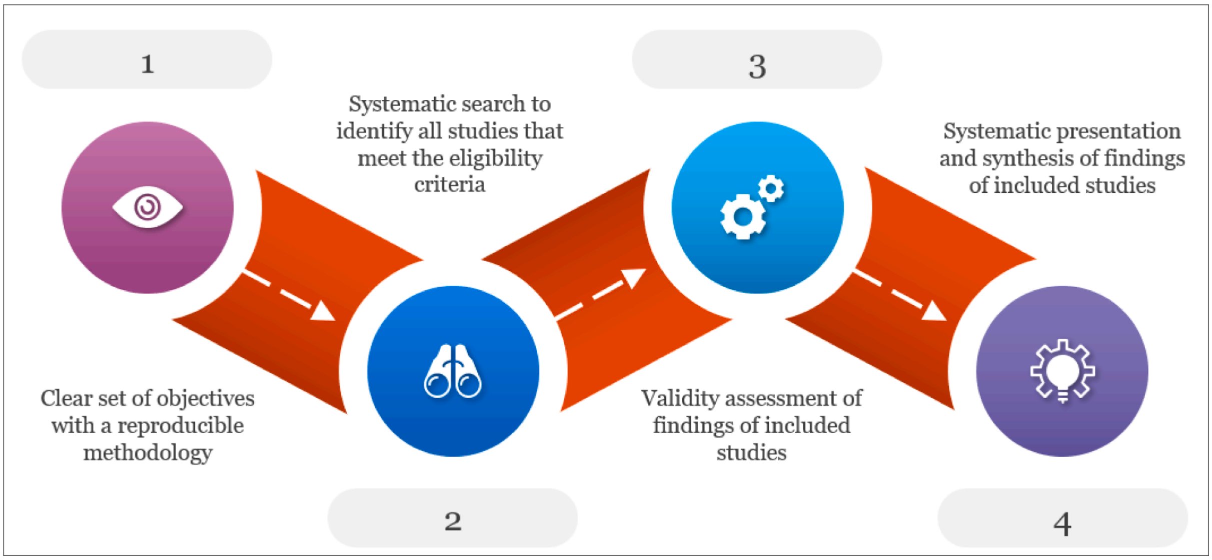

Fig. 7. The key characteristics of a systematic review (Moher et al., 2015) .

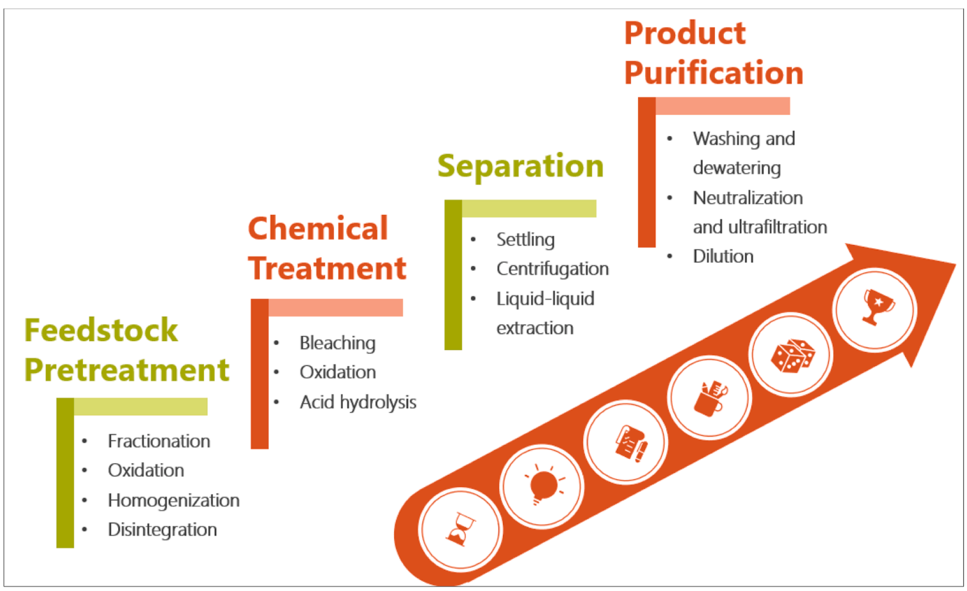

Fig. 8. The four main segments of CNC production.

height elevations.

The CNC purification stage solely depends on the required CNC purity. From a quality control perspective, samples from each CNC batch must be characterized to ensure that the required CNC purity and quality are being achieved (Table 2). In commercial-scale operations, it is recommended that samples from each process segment undergo characterization. The characterization results must be compared against the expected specification benchmarks to ensure that the process is operating optimally. Automatic sampling and analyzing strategies can be implemented within the control and instrumentation design. If the required CNC specifications are not met, then the respective production phase can be repeated until the specifications conform to the expected limits. If such measures are implemented in each production segment, the final CNC product purification phase is optimized. As new technologies are made available, the four production segments (Fig. 8) can be updated.

4.7. Impact on existing knowledge

The summary of CNC production processes across the relevant operational pilot plants and patented innovations (Table 1) overviews the current state of the CNC production industry regarding the globally applied technologies. The segmented CNC production model (Fig. 8) can be universally applied by academics and engineers to design new and improved CNC production processes using any available lignocellulosic feedstocks or to improve existing CNC production plants. The statistical data analysis (Table 4) indicates each process segment's major technologies, enabling recommendations for potential improvements. For existing CNC plants, an improvement of one or more production segments will improve the entire process. Hence, the argument is supported. The model is therefore recommended as a design and optimization tool for academics and engineers dealing with CNC production processes.

Table 4
Statistical data analysis for operational pilot plants and patented innovations.

Process segment	A. Operational pilot plants Description	%	B. Patented innovations Description	%
Feedstock pretreatment	Fractionation	33	Mechanical treatment	100
	Catalytic oxidation	33		
	Zinc chloride treatment	33		
Chemical treatment	Bleaching	20	Catalytic oxidation	25
	Catalytic oxidation	20	Acid hydrolysis	75
	Acid hydrolysis	60		
Separation	Mechanical separation	60	Liquid-liquid extraction	20
	Gravity settling	20	Centrifugation	40
	Washing	20	Gravity settling	20
			Filtration	20
CNC purification	Washing	20	Dilution and neutralization	50
	Ultrafiltration	40	Washing	50
	Chemical/mechanical treatment	40		

5. Conclusions

The main statistical results showed several pretreatment options to accommodate various lignocellulosic feedstocks for CNC production. Considering that acid hydrolysis is the main chemical treatment, its recovery and recycling are vital to offset the use of this corrosive and toxic reagent. Mechanical separations are the most common separation option and can be replaced with gravity settling to reduce energy requirements. Furthermore, the water used for washing and dewatering (product purification) must be treated and recycled. These recommendations can improve the overall economic and environmental sustainability of CNC production processes and can therefore be viewed as potential areas of improvement.

Regarding future considerations, the patented innovations reported in this study must be implemented within the recommended design framework in Fig. 9. Considering that these innovations focus on the recovery, recycling, and beneficiation of process reagents and wastes, they can be implemented to substantially improve the economic and environmental sustainability of new and existing CNC production processes. More advanced sustainability metrics relating to production efficiency, process economics, and the environment can also be used to identify additional ways to improve process sustainability.

Based on the ability to segment the major process phases in CNC production, this study found that a logical iterative framework (Fig. 9) can be applied to design and optimize new manufacturing processes and existing processes.

The primary operations required are identified and categorized in chronological order when applied to new process designs. After that, the potential variations (options) in each process category can be identified. The most efficient variation in each process category is then identified based on economic, technical, and environmental considerations. This logic is repeated for all the process categories, after which the process is deemed to be theoretically optimized.

The primary process operations are identified and categorized in chronological order when applied to existing processes. The potential variations in each process category are then identified. At this stage, the most efficient variation in each process category can be identified based on economic, technical, and environmental considerations. The potential replacement is noted if an existing operation can be replaced with a more efficient one. This logic is successively applied to all the process categories. After that, the process is deemed to be theoretically optimized. The final step involves integrating the replacements into the existing process. Once the final step is undertaken, the process is practically optimized.

The iterative framework is relevant to academics and engineers in the process design and optimization domain. Applying the model can help improve plant design proposals' quality, completeness, and consistency. Furthermore, if the model is implemented as a standardized protocol within an organization, it can improve the peer review efficiency of the proposed designs. The model also enables easy comparison of different process configurations and can inform decision-making for policymakers relating to safety, health, environmental, and quality considerations between potential configurations. The model can train process design students at the tertiary education level when working on design projects.

The empirical implication is that the iterative framework offers new design and optimization strategies for processes with multiple reaction pathways and products that can be produced from a wide range of feedstocks. Furthermore, process optimization is an iterative function that requires systematic reviews to investigate and consider the vast range of technologies and protocols currently being used. Once an overview database is created, it can inform the design pathways for future and novel processes.

The scientific contributions are threefold: providing an overview of the current trends and developments in CNC production, the proposed conceptual framework for CNC production, and finally, the cyclic process development and optimization guideline.

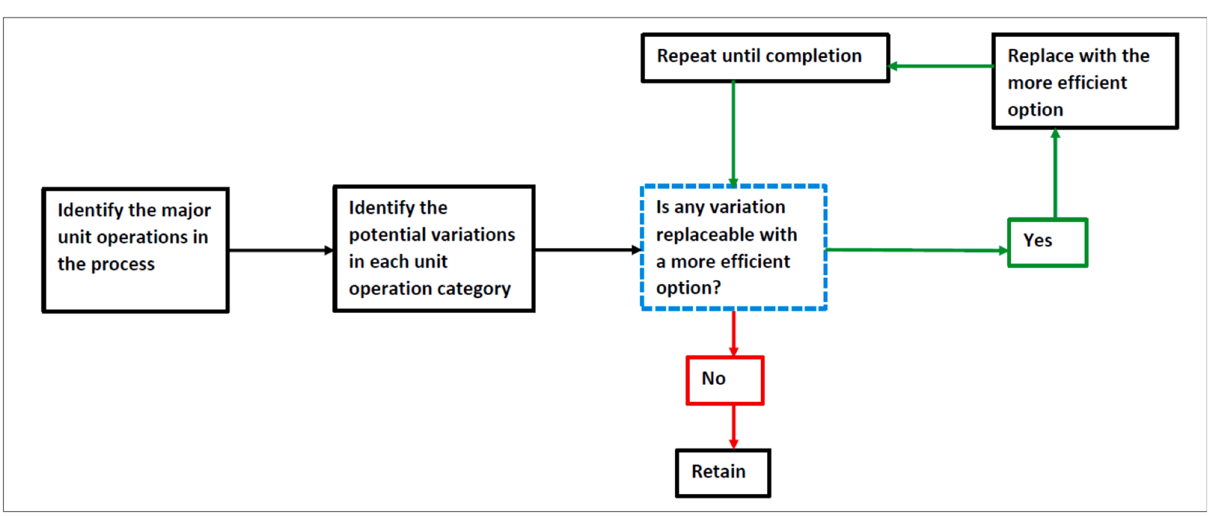

Fig. 9. Iterative process design and optimization model.

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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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