Preparation of Cellulose Nanocrystals and Compliance as Pharmaceutical Excipient: a review

Margaretha Efa Putri¹, Anis Y. Chaerunisaa¹, Marline Abdassah¹, Iman Rahayu²

¹Department of Pharmaceutics, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang 45363, Indonesia
²Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Padjadjaran, Sumedang 45363, Indonesia

Received: 21 Feb 2020/Revised: 23 Feb 2020/Accepted: 2 Maret 2020/Published: 23 June 2020

ABSTRACT

Cellulose nanocrystals is a cellulose derivates which has been widely researched and observed as an chemical agent. Different with cellulose that has been widely used as pharmaceutical excipient especially in solid dosage form, cellulose in nanocrystals form is not available in pharmaceutical grade. Cellulose nanocrystals have different characteristics and quality which are depend on its preparation including sourcing, isolation procedure, and hydrolysis reaction involved. This difference is very important to deeply observed its impact in pharmaceutical dosage form with different active ingredients. In addition, cellulose nanocrystals should meet FDA requirement as pharmaceutical excipient. This review describe cellulose nanocrystals preparation and its characteristics, its application to active pharmaceutical ingredients, and its properties in order to meet FDA requirement.

Keywords: Cellulose, nanocrystals, pharmaceutical excipient

1. Introduction

Cellulose is widely used as a pharmaceutical excipient, such as powdered cellulose, microcrystalline cellulose, carboxymethyl cellulose salt, cellulose acetate, cellulose acetate phthalate, methyl-, ethyl-cellulose, hydroxymethyl-, hydroxyethyl methyl-, hydroxypropyl-, hydroxypropyl methyl-(hypermellose), modified hypermellose. These cellulose derivatives are commonly applied in every pharmaceutical dosage form as polymeric agents (1). These derivate have many weaknesses that lead researchers to explore new excipient. A new type of cellulose-derived excipient that has been developed is cellulose nanocrystal. This cellulose nanocrystals was first developed by Ranby in 1951. He hydrolyzed wood cellulose fibers with sulfuric acid and found that the amorphous part disintegrated leaving highly crystallinity nanoparticles (2). Cellulose nanocrystal is cellulose crystals with high crystallinity degree which are produced by hydrolysis of cellulose polymer from plant, some animals, or other resources (3). Cellulose is a polymer that is composed of d-glucose unit which is linked at carbon atom number 1 and number 4, or 1→4, d-glucose monomer (4). Cellulose polymer in nature usually in 500 of polymerization degree with 243.000 molecular weight (1). Cellulose is the main compound of the stem system in plant (4) that supports the plant body. Powder cellulose, microcrystalline cellulose, and modified cellulose have been used widely in pharmaceutical as excipient not only in solid dosage form but also in semisolid dosage forms (1). Although cellulose nanocrystal has not been used yet, many researches were conducted to
describe cellulose nanocrystal and character as a pharmaceutical excipient.

**Cellulose sources**

In the starting phase in plant growth, cellulose is synthesised by merenkim cell and is transferred from the cytoplasm into the plant cell wall. The synthesis is catalyzed by cellulose sintase enzyme to form the main microfibril in plant cell wall besides matrix phase. Beside that noncrystalline matrix phase contains pectin, lignin, and hemicellulose (5). Cellulose is continuously produced into the cell walls, and increasing its polymerization degree and is found to more elongated and thickened. Then, the thickened cellulose squeezing organelles, likes cell nuclei, mitochondria until cell death (6). This means, the higher the body of plant, the longer the cellulose in the form of fiber. Then, cellulose often calls with plant fiber.

Based on the sources, cellulose is divided into natural and synthesis cellulose (7). Natural cellulose usually get from woody plant or herbs, not only from the stem but also can be found in fruit (coconut fiber), seed (cotton), and (sisal). Moreover, the first synthesis cellulose has been conduct without a biosynthetic pathway, using glycosyl fluoride substrate in the cellulase enzyme (8).

Cellulose also can be found in animal especially in their fur, like hemp, llama, and camel, moreover in bacteria, algae, and marine biota. Waste from wood, agriculture, oil, sugar, fruit and nut, textile, and conservation waste also contain cellulose (3).

**Cellulose isolation**

The main production of world cellulose mostly use wood form high plant include cellulose production for pharmaceutical ingredient (1). In nature form, cellulose fiber in woods (2-3 mm in diameter) composed of 3 levels of fiber. First, a thin fiber is in 50-100 µm, main fiber (10-20 µm) which is composed of 70-75% cellulose, 15-20% hemicellulose, 3% pectin, and 3% lignin, and the smallest part is microfibril in 4-10 nm or 6000-9000 degree of polymerization (6). To obtain high purity cellulose, its necessary to remove lignin, pectin, and hemicellulose.

Lignin in the unit phenylpropane from precursor p-coumaryl alcohol (H), coniferyl alcohol (G), dan sinapyl alcohol (S). Lignin has alcohol, carbonyl, carboxylate, methoxyl, and sulfonic acid. Lignin structure is usually different based on sources, for example, lignin in grass that contains nitrogen element (9). Lignin soluble in water (in form lignosulfonate), soluble in ethanol, methanol, and dioxane (solvent lignin), insoluble in water and organic solvent (kraft lignin dan hydrolyzed lignin) with glass temperature around 127-227°C (9). The main methods of the extraction of lignin and cellulose from different sources historically explored are hydrothermal, acidic, alkaline, wet oxidation, ammonia fiber explosion, organosolvent, and, most recently, ionic liquid pretreatment methods (10).

Pectin can be completely removed when the alkaline boiling process is integrated into fiber bast. However, acid scouring does not help to remove pectin molecular chains so that more residual pectin is evident in the sample after acid scouring (11).

Hemicelluloses chemically are a class of polymers of sugars, including the six-carbon sugars mannose, galactose, glucose, and 4-O-methyl-D-glucuronic acid and the five-carbon sugars xylose and arabinose. The number average DP is about 100-200 sugar units for each hemicellulose molecule. Hemicelluloses are much more soluble and labile, that is, susceptible to chemical degradation, than is cellulose. They are soluble in 18.5% NaOH. The low molecular weight hemicelluloses become soluble in dilute alkali at elevated temperatures, such as in kraft cooking (12).

In synthesis cellulose process, pectin, lignin, and hemicellulose is removed from fiber and cellulose trough acid treatment, alkali boiling treatment, and bleaching (13,14), an alkaline process solubilizes most of pectins and hemicelluloses. A standard procedure would be the treatment of the pulp free of extractives in 2-5 wt.% NaOH or KOH with a solid to liquid ratio of 1:20, stirring the solution at 80°C for 2 hours. After washing until neutral pH, several bleaching cycles are performed to remove lignin. Bleaching agents break down phenolic molecules present in the lignin and remove the by-products of this reaction, thus bleaching the material, usually use
chlorine agent, hydrogen peroxide, acetic acid, or sulphuric acid. After several washing and cleaning steps, the pulp is ready to hydrolyze (13,15).

**Chemical properties of cellulose**

Cellulose consists of D-glucopyranose ring units in the 4C1-chair configuration, which exhibits the lowest energy conformation. Such units are linked by β-1,4-glycosidic bonds that result in an alternate turning of the cellulose chain axis by 180°. Cellobiose with a length of 1.3 nm can be considered the repeating unit of cellulose (4).

![Figure 1. Structure of cellulose](image)

Changes in the molecular structure originate from reactions leading to hydrolysis or oxidation of the cellulose chain. Such reactions mainly occur on the surface of the fibrils or in amorphous regions. The DP of native cellulose of various origins is in the range of 1,000–30,000, which corresponds to chain lengths of 500–15,000 nm. The cellulose samples that are obtained by isolation methods possess DP values ranging between 800 and 3,000 (4).

From this cellulose, cellulose nanocrystals can be prepared through a hydrolysis reaction which can then be used as a pharmaceutical excipient. This review is describing the preparation of nanocrystals cellulose and how important its role in the pharmaceutical dosage forms.

### 2. Methodology

This article review uses 9 articles about isolation and preparation of nanocrystals cellulose (CNC), 10 research international articles from 2019-2020 about the application of CNC in pharmaceutical and drug delivery, and 3 more from 2015-2019 about the toxicology of CNC. However, for support argument, this articles use more either research and review article about cellulose sourcing, isolation, and other cellulose properties.

<table>
<thead>
<tr>
<th>Cellulose sources</th>
<th>CNC method preparation</th>
<th>Research outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotton (Whatman filter paper)</td>
<td>63% sulfuric acid at 50°C for 30 min</td>
<td>Cholesterol was successfully covalently anchored to cellulose nanocrystals (CNCs) surfaces. Modified cellulose nanocrystals with cholesterol exhibit potential as drug release excipients and nano-reinforcing agents within hydrophobic polymer matrices.</td>
<td>(17)</td>
</tr>
<tr>
<td>Purchased Cellulose nanocrystals</td>
<td>CNC rod shape; degree of polymerization 137; half sulfate ester 254 mmol/kg, diameter 4-5 nm, length 300-400 nm</td>
<td>Using of 0.6% (w/v) CNCs improved significantly the Anti-stx2B-Ab immobilization and the level of signal detection of <em>Escherichia coli</em> O157:H7. The formulation could be used for the preparation of antibody immobilization support for pathogens detection</td>
<td>(18)</td>
</tr>
<tr>
<td>roots of <em>Dorema koptedaghens</em></td>
<td>Sulfuric acid</td>
<td>Cellulose I with the crystallinity index of 83.20% and size of 4.95 nm. The cytotoxicity of CNCs against A549 cell line has not exhibited any cytotoxic effects. The analysis of labeling efficiency in regards to $^{99m}$Tc-CNCs has been observed to be above 98%, while the biodistribution of radioactivity has displayed a</td>
<td>(19)</td>
</tr>
<tr>
<td>Material</td>
<td>Methodology</td>
<td>Performance Description</td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Cotton filter paper</td>
<td>64% Sulphuric acid 45°C for 60 min.</td>
<td>Cetyltrimethylammonium bromide (CTAB) modified nanocrystalline cellulose has the best performance in terms of loading and release of paclitaxel at pH 5.8 and 7.4. Sodium dodecyl sulfate (SDS) modified nanocrystalline cellulose has the lowest loading of paclitaxel which is 43.61 mg/g, with the highest cumulative release of 95% at pH 7.4 and 65% at pH 5.8 for 16h. Tween 20 modified nanocrystalline cellulose can sustain the release until 19 h for around 80% at pH 5.8 and 7.4.</td>
<td></td>
</tr>
<tr>
<td>Kenaf bast fiber</td>
<td>Pretreatment: NaOH 4% at 80°C for 3 hours, bleaching with NaClO in acetate buffer at 80°C for 4 hours. Treatment: 64% H2SO4 at 45°C for 40 min</td>
<td>Yield nanocrystalline cellulose is 41% with 8.03 nm diameter, 107.68 nm length, and aspect ratio 13.4. The surface modification of NCC with the cationic surfactant of the CTAB increased the thermal degradation of the nanoparticle. The prepared CTAB– NCC nanoparticles were able to bind significant quantities of hydrophobic curcumin with a range of 80% to 96%. The FTIR and elemental analysis shows that the optimum modification of NCC was at 4 mM of CTAB with DS value of 0.12, as well as the highest binding efficiency with 96% up to 100 µg curcumin added.</td>
<td></td>
</tr>
<tr>
<td>Not available</td>
<td>Sulphuric acid</td>
<td>The chalcone hydrosolubilization was achieved through these β-CD/CNCs/chalcone complexes. Loading ratio was around 20% for the two complexes. Then, β-CD/CNCs/chalcone complexes demonstrated in vitro antiproliferative effect against colorectal and prostatic cancer cell lines. As β-CD/CNCs alone were shown to have no effect on cell proliferation, the antiproliferative activity.</td>
<td></td>
</tr>
<tr>
<td>Banana fiber</td>
<td>Oxalic acid</td>
<td>The nanoparticles of rifampisin loaded alginate-CNC exhibited pH dependent swelling and in vitro drug release properties. Only 15% of the RIF was released in 2h, showing that the nanoparticles could effectively protect the drug from gastric conditions.</td>
<td></td>
</tr>
<tr>
<td>Wood</td>
<td>Not available</td>
<td>The CNC is used in astaxanthin nanoemulsion inhibit cell poliferation thus it induces apoptosis and was effective ROS against cancer cells.</td>
<td></td>
</tr>
<tr>
<td>Cotton lint</td>
<td>Sulphuric acid and nitric acid</td>
<td>This research has evaluated CNC influence on in situ gelation behavior and in vitro release of pilocarpine hydrochloride from nanocomposites formulation for ophthalmic drug delivery. The CNC was found increasing gel strength and the drug release kinetics of the sustained release of</td>
<td></td>
</tr>
</tbody>
</table>
This study bacterial nanocrystal cellulose (BCN) was used in Pickering emulsion with alginate and hydrophobic drug which is alfacalcidol. The BCN has good colloidal property formed by external gelation achieving the loading and sustained release of alfacalcidol. The alginate composite beads with BCN exhibited low cytotoxicity and good capabilities for osteoblast differentiation.

3. Discussion

Natural cellulose can be transformed into micro- and nanoscale materials by applying specific top-down approaches, yielding defined products such as microcrystalline cellulose, microfibrillar cellulose, and whiskers. The micro- and nanoscale materials mainly differ in DP and crystallinity according to the disintegration technique used and, consequently, differ in shape (4).

The three main types of nanocellulose are cellulose nanofibers (CNF), cellulose nanocrystals (CNC), and bacterial cellulose (BC), that differ in their dimensions, functions, and preparation methods. Cellulose nanofiber has 5-60 nm diameter and several micrometers in length, which is produced by chemical, mechanical, or enzymatic treatment. The preparation of cellulose nanofiber uses high-pressure homogenization, microfluidization, refining, grinding, electrospinning, ultrasonication, cryo crushing, and steam explosion. Cellulose nanocrystals or nanocrystalline cellulose have 5-70 nm in diameter and 100-250 nm (plant source) or 100 nm–several micrometer (tunicates and algae) in length, moreover it is can be obtained by hydrolyzing cellulose with some acid catalyst. The bacterial cellulose have 20-100 nm in diameter and is produced through bacterial culture (28).

3.1 Nanocrystalline cellulose

Typically, to produce CNC, cellulose has to be previously isolated to be directly attacked. Therefore, new tendencies of CNC production are focused on the isolation of CNC without a previous cellulose purification. However, when CNC is desired to be obtained from biomass, including wood and agricultural residues, not only cellulose is present but also different extractives, hemicelluloses, lignin, or inorganic particles. In these cases, different pretreatments might be applied before the acid hydrolysis (28).

A standard recipe for the acid hydrolysis of a pulp starts with the milling of the dry sample. Then, a solution of 60-66 wt.% H₂SO₄ at an acid to pulp ratio between 8 and 20 mL/g (28). oxalic acid at the concentrations between 50 and 70 wt.% (28).

<table>
<thead>
<tr>
<th>Source</th>
<th>Treatment</th>
<th>Pretreatment</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eucalyptus wood</td>
<td>Sulfuric acid (56-64%, 45 or 60C) for 10-120 minute</td>
<td>Toluen/ethanol extraction, acidified NaClO₂, KOH</td>
<td>Max. Yield 66.7%. CNC-I in spindel-shape, CNC-II twisted strip.</td>
<td>(29)</td>
</tr>
<tr>
<td>Cotton (Whatman filter paper)</td>
<td>63% sulfuric acid at 50C for 30 min</td>
<td>Not available</td>
<td>good dispersion in water, Rod-like particles, negative surface charge of ζ = −52.5 ± 0.5mV at 0.1g/mL</td>
<td>(17)</td>
</tr>
<tr>
<td>Brown, red, and greed seaweeds</td>
<td>51% sulfuric acid at 45C for 30 min.</td>
<td>De-polymerization: 0.2 M HCl at 30c for 2 h and 4% NaOH at 75C for 3 hours. Bleaching: 5% KOH</td>
<td>Amorphous ron were effectively removed, Rodshape particles with 21-248 nm length and 4.8-41 nm width. Aspect ratio 2.5-1.5. Cellulose I with crystalline index</td>
<td>(30)</td>
</tr>
</tbody>
</table>
for 3 hours, 6-10% NaClO. Then 30% H2O2 at 80°C for 70 min

<table>
<thead>
<tr>
<th>Material</th>
<th>Treatment</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bamboo</td>
<td>Sulfuric acid 6.5 M, phosphoric acid 6.5 M, hydrochloric acid 6.5 M, and acetic acid 99% : nitric acid 68% (10:1) at 60°C for 2 hours</td>
<td>Not available</td>
<td>(31)</td>
</tr>
<tr>
<td></td>
<td>HCl and acetic acid more be able to broke the hydrogen bonding in crystalline region by swelling with low crystallinity. Sulfuric acid: rod shape in 4-9 nm diameter and 6-200 length. Phosphoric acid: 20-85 nm with particle size distribution narrower than sulphuric acid. Acetic acid/nitric acid: 6,5 -20 nm length. HCl: nanocrystal particle can aggregate due to no particle charge. Crystallinity: sulfuric acid &gt; phosphoric acid &gt; acetic acid/nitric acid &gt; hydrochloric acid. Thermal stability HCl&gt; sulphuric acid and phosphoric acid.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton</td>
<td>Hydrochloric acid at 4N concentration and 100°C temperature for 120 minute and 64% sulfuric acid at 50°C for 45 minute. Phosphoric acid in room temperature at concentration 6,2; 7,8; 9; or 10,7 M then was increased the temperature to 100°C.</td>
<td>Not available</td>
<td>(32)</td>
</tr>
<tr>
<td></td>
<td>At 50°C the cellulose still in pulp form. At 7,8 M concentration of phosphoric acid, the hydrolysis reaction was not homogenous and completely done. Cellulose nanocrystal that was prepared by phosphoric acid has very low charge density, however very easily dispersed in polar solvent. Additionally, the thermal stability of nanocrystalline cellulose with phosphoric acid is higher than sulfuric acid. The optimal condition is 90 minute at 100°C with 10,7 M phosphoric acid. The particle size has 31 nm width and 316 nm length, and aspec ratio 11, compared than H-CNC 20 nm and S-CNC 22 nm, and aspec ratio respectively 10 and 9. The crystallinity respectively was 81, 81, 85, dan 79 %.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton</td>
<td>62 % sulfuric acid at 47C</td>
<td>Enzyme or chemical pretreatment</td>
<td>(33)</td>
</tr>
<tr>
<td></td>
<td>Particle size 183 – 209 nm, DP: 173-210, PDI 0,17 – 0,20. NCC dengan enzyme pretreatment can resulting yield to 82% or 12% higher than chemical degumming.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cotton Microcrystals cellulose</td>
<td>6M HCl was autoclaved 110°C for 3 jam, and</td>
<td>Not available</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td>The highest yield rendemen tertinggi was obtained at 2 hours of reaction time in acid/cellulose ratio</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The application of sulfuric acid in nanocrystals isolation can produce sulfate ester on the hydroxyl group of cellulose, acetic acid can produce acetyl, and hypochlorite can produce carboxylic acid groups (36).

The drying of CNC can be done with air drying, freeze-drying, supercritical drying, and spray drying. The supercritical drying can obtain good thermal stability and low crystallinity. Spray drying may obtain the most stable with high crystallinity, however, the yield obtained is low. The drying process with dry air increases the proportion of cellulose II crystalline compared to the other methods. Therefore, freeze-drying is the most suitable drying process with a high yield and better thermal stability and crystallinity (37).

### 3.2 Nanocrystalline cellulose as excipient

Microcrystalline cellulose with molecule \((\text{C}_6\text{H}_{10}\text{O}_5)^n/2\) \((n=220)\), is usually used as absorbent, anti-adherent, capsule or tablet filler, binder, and disintegrant. Microcrystalline cellulose slightly soluble in 5% NaOH, practically insoluble in water, acids, and organic solvents. Besides, it is stable despite being hygroscopic (1). The disintegration mechanism of microcrystalline cellulose is due to the hydrophilic and hygroscopic nature of the molecule, resulting in a high water uptake rate. This property triggers the breaking of the hydrogen bonds between cellulose particles, swelling, then expanding the volume of the solid material. The combination of these mechanism can trigger the penetration of solvents into solid drug particles and dissolved them (38,39).

Nanocellulose can increase the amorphization of derivates and nifedipine (biopharmaceutical system class II drugs) thereby increasing their solubility and bioavailability by testing the drug release both in-vitro and in-vivo in mice (40,41). Cellulose nanofiber can improve the intrinsic dissolution of indomethacin (42).

Disintegration time and dissolution of CNC continually resulting in fast disintegration and dissolution and effective in low concentration of CNC (43). CNC has mucoadhesive properties in the gastrointestinal tract based on CNC interaction with mucin molecule and changes the mucin-CNC complex surface charge (44). Moreover, CNC may interact with intestine membrane cell
phospholipids and disrupt the membrane cell integrity (45), thus increase drug permeability (46).

3.3 Cellulose nanocrystals to meet pharmaceutical excipient requirement

Based on IPEC-European safety test guidelines (De Jong, 1999), an oral excipient should meet the requirements for fulfilling some various tests. The zero phase is ADME (absorption, distribution, metabolism, and excretion). The first phase must require the basic data including the oral acute toxicity, sensitization skin, chromosomal damage, AMES test, micronucleus, and 28-days toxicity (2 species) intended route. Additional data for short of medium repetition intake (multidose): 90-days toxicity (most appropriate species), teratology (rat and rabbit), genotoxicity assays. As for IPEC-America acute dermal toxicity, eye irritation, and first-generation reproduction testing for chronic use.

![Table 3. Cellulose nanocrystals testing to fullfill IPEC requirement](image)

<table>
<thead>
<tr>
<th>Cellulose sources</th>
<th>CNC preparation method</th>
<th>Research outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheat bran</td>
<td>Sulfuric acid</td>
<td>Zeta potential values of the CNC suspensions ranged from $-36.5$ to $-39.8$ mV, high crystallinity (70.32%). The thermal stability of CNC shifted to lower temperature with increasing hydrolysis time. In addition, the obtained CNC exhibited interesting physicochemical properties (the water/oil retention capacities and the adsorption capacities to heavy metals) and good biocompatibility. CNC showed no obvious cytotoxicity to Caco-2 cells at $1000$ g/mL.</td>
<td>(47)</td>
</tr>
<tr>
<td>Microcrystals cellulose</td>
<td>Sulphuric acid</td>
<td>Nanocrystals cellulose was not able to induce micronuclei in BEAS 2B cells in 2.5-100 g/mL for 48 hours treatment and not induce interleukin $1\beta$ (IL-$1\beta$) and pro-inflammatory cytokines tumor necrosis factor-$\alpha$ (TNF-$\alpha$). Thus, CNC is not genotoxic and immunotoxic</td>
<td>(48)</td>
</tr>
<tr>
<td>Wood</td>
<td>Not available</td>
<td>Nano cellulose induced cytotoxicity to HaCaT cells (&gt;156 g/mL) and HDF-$\alpha$ cells (&gt;313 g/mL) but did not induce the skin and eye irritation on 3D models.</td>
<td>(49)</td>
</tr>
</tbody>
</table>

4. Conclusion

CNC has been widely used as a pharmaceutical excipient in the research world. However, CNC has not provided yet in the pharmaceutical industry, especially in a pharmaceutical grade. This review has explained how important CNC in solid dosage form not only for improving drug oral bioavailability but also in the drug delivery system. CNC also has meet some of IPEC requirement and has high potential as new as pharmaceutical ingredients. Thus, the research about the CNC oral acute and chronic toxicity has not well evaluated which is important to prepare the CNC in pharmaceutical grade. Besides, the research about CNC function an effect in solid dosage form has not widely observed in various drugs. Also, more research about the effect of catalyst residue of CNC not only in its compatibility with drugs but also in chronic toxicology testing.

References

2. Rånby BG. Fibrous macromolecular systems. Cellulose and muscle. The
colloidal properties of cellulose micelles. Discuss Faraday Soc [Internet]. 1951;11(0):158–64. Available from: http://dx.doi.org/10.1039/DF9511100158


1;122(43):9973–81. Available from: https://doi.org/10.1021/acs.jpcb.8b07765


