Perspective

Bacterial nano cellulose as non-active pharmaceutical ingredient. Advances and perspectives

Abstract

Nano Cellulose is commonly produced by the top-down enzymatic, mechanical and/or chemical treatments. In contrast, Bacterial Nano Cellulose (BNC) can be obtained by a bottom-up approach, where is biosynthesized from glucose using the direct action of specific bacterial strains. BNC impart attractive combinations of biologic and physicochemical characteristics such as biocompatibility, biodegradability, light weight, sustainability, and improved mechanical properties. The trend towards environmental sustainability and development of renewable resources has significantly increased interest. A critical aspect in BNC production is to identify a low-cost culture medium that can improve the yield of BNC and can be used as an economically viable solution for application in a range of fields. There is an immense perspective of BNC in health care as well as drug applications. Potential uses include barrier films, antimicrobial films, pharmaceuticals and drug delivery systems. Even though BNC has been demonstrated as nongenotoxic and noncytotoxic, further studies are required to completely address such issue. Key aspects for future development include the design of BNC for specific user requirements, the reduction of production costs, and the customization/functionalization using post production steps and different types of compounding/processing.

Keywords: bacterial nano cellulose, pharmaceutical biotechnology, pharmaceutics

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Introduction

Cellulose is a linear polysaccharide consisting of a chain of β (1-4) linked D-glucose units.[1] Cellulose is the major component of wood and most natural fibers from vegetal kingdom. This natural polymer represents about a third of the plant tissues and can regenerate through photosynthesis.[2] Although vegetable origin cellulose is widely applied at industrial level, the productive scale generates serious problems on ecosystems where the pulp mills mega industries known as “pasteras” are located.[3] In emerging countries such as Argentina and Uruguay, the location of these “pasteras”, generates great concern. A report presented by Uruguay Republic University (UDELAR) on 2006, summarizes the available scientific evidence about environmental impacts of the installation of pulp mills and the associated forestry model.[4] The report presents an analysis and studies of the effects of the forest crop on the ecosystem, benefits provided by the natural pastures, and the effects generated by the liquid effluents of the pasteras at hierarchical levels (molecular, individual, population, community and ecosystem).[4] Traditionally the Kraft method is used to obtain vegetable cellulose.[5] The numerous processes that make up the method, where each one contributes its share in the consumption of energy, chemical compounds and pollution, result in a clear disadvantage when it comes to thinking about sustainable processes.[6] However, it’s wide variety of applications and its potential, led scientists from all over the world to look for sustainable and ecologically friendly options to obtain cellulose. There is a high potential even more to be discovered regarding materials from biological origin. Diverse applications of each new discovered material are the object of study by researchers from all over the world. This varied and exhaustive analysis resulted in the appearance of potential products with high added value and very low environmental impact.[7] These cellulosic estructures are called Nan fibrillated Cellulose (NFC) and refers to cellulose fibers that have been fibrillated to achieve agglomerates of cellulose microfibril units; NFCs have nanoscale (less than 100nm) diameter and typical length of several micrometers.[5] Several denominations exist for describing such material and most often Nano and Micro Fibrillated Cellulose (NFC/MFC) are used.[8] Mechanical disintegration is the method of choice for the Nan fibrillated cellulose. In this process it is possible to obtain a long and flexible nanocellulosic material.[9] Following a sustainable trend, many alternatives emerge to obtain NFC whose source transcends wood cheeps. Vegetable residues from other industries such as, palms, bagasse, wheat straw and soybean residues, pulps among others, are now explored alternatives. In Argentina two main fonts are bagasse from sugar cane process and soy hulls.[8] As it is known, cellulose can not only be obtained from plant sources. Recently, other ways beyond the plant kingdom have attracted attention. This new route for the production of micro and nano cellulose fibers opens a plethora of possibilities regarding applications and distinctive characteristics of the material that are currently studied.[10]

This review presents the advances made in the alternative production of this material which, due to its broad advantages over other polymers, represents a sustainable, green and economic alternative to replace non-biodegradable products. The replacement of non-active pharmaceutical ingredients in the design of pharmaceutical formulations is a key issue in particular because as a raw material, cellulose already forms part of pharmacopoeias throughout the world, narrowing the gap between laboratory-scale studies and its production for commercialization.

Bacterial Nano Cellulose

Cellulose is commonly produced with a desired size by the top-down enzymatic, mechanical and chemical treatments of cellulosic precursors, in which cotton, wood, annual plants or other agricultural residues can be used. In contrast, cellulose can be obtained by a bottom-up approach, where is biosynthesized from glucose using the direct action of specific bacterial strains.[11] Bacteria species such as *Pseudomonas fluorecens*, Gluconacetobacter xylinus, Gluconacetobacter hansenni produce cellulose as one of its metabolites. Gluconacetobacter xylinus is one of the first studied as Bacterial Nano Cellulose (BNC) producer and has become a model system for the study of the biosynthetic mechanisms of BNC.[12] The mechanism of cellulose production by the bacterium G. xylinus is the construction of a interface air/culture medium film nanofiber.[13,14] BNC is a primary metabolite synthesized in the interior of the bacterial cell that is later twisted into nanofibrils that is mechanically amplified to form micro fibrils.[15,16] During biosynthesis of cellulose chains, van der Waals forces and hydrogen bonding between hydroxyl groups and oxygen of adjacent molecules promote parallel stacking of multiple cellulose chains forming elementary fibrils that further aggregate into larger microfibrils.[17] BNC has distinctive characteristics due mainly to its size and fibrillar disposition that introduces modifications in its biological and physicochemical properties such as biocompatibility and biodegradability. In addition, the fibers are lighter, have greater optical transparency, their surface is chemically adaptable because it allows the annexation of multiple functional groups, enhancing their mechanical properties.[18] Among the potentialities of BNC are some highly relevant pharmaceutical applications such as biomedical implants or scaffolds, translucent films, controlled release systems, antimicrobial dressings and patches with barrier action.[19–21] Enzymes immobilization, tissues engineering. Among the most interesting applications are bone, cartilage, corneas, artificial skin, and dental materials and implants.[15] Also they exhibit high chemical resistance to dilute acids and alkalis solutions, organic solvents, proteolytic enzymes and antioxidants as well.[11] Chemical modification of the cellulosic structure to improve interactions with living tissues could enlarge the utilization of nanocelluloses in biomedical devices tremendously.

Biosynthesis a bottom-up approach

There are two fundamental methods for the production of bacterial nano cellulose developed so far: a) Static cultivation is useful when production in the form of a film is required. With this method, a monolayer of BNC of white color and variable thickness is obtained according to the incubation times and culture media composition, and b) Stirred cultivation, is useful when a dispersion or suspension of cellulose micro fibrils in the heart of the liquid is required. It can appear as fibers or conglomerates of irregular size.[22] there are currently several methodologies for large-scale BNC production. Increasing the production efficiency is one of the main objectives for researchers and so far, results have been obtained that support the demand for BNC production at laboratory scale. However, it is necessary to satisfy a greater demand for the product and further improve the yields obtained, modifying the growth media, in order to reduce costs and increase productivity. Low cost medium that allows improving the yield of BNC could be a viable solution for the design of prototypes in a wide variety of fields of application. One of the cellulose producer bacteria is *Pseudomonas fluorecens*.[23] these bacteria present a convenient behaviour as cellulose biofactorie. The space for cellulose attachment is between air and liquid interface, which when colonized, provides bacteria with access for both the gaseous (e.g. oxygen) and liquid (e.g. nutrient) phases.[23] All so, these attachments facilitate its harvest from reactor surface, diminish handling errors and improve production recovery process. These main factors represent advantages thinking on scaling up process, but media commercial growing is expensive for industrial development. Previously, many authors reported the use of waste from other industries as a carbon source for the bacterial cellulose production.[24–26] however, although these practices are very interesting and useful, adds additional steps to the process of product purification. Organic and inorganic molecules as well as physical stressors are factors that positively or negatively affect the BNC synthesis. Then, the selected cultivation medium may also affect yield, structure, cohesiveness, crystallinity and amorphicity degree among other properties from BNC beyond the production method. Refined sugars and protein sources, although costly, are the most commonly used substrates for commercial production of metabolites by fermentation process.[27] The trend towards environmental sustainability and development of renewable resources has significantly increased interest. A research team developed a new growing media designed as a clean production experience by recovering residual bacterial cell from *Pseudomonas fluorecens*. By redesigning a growth media for increase bacterial cellulose production replacing all protein and carbon sources for heat pre-treated residual bacterial cells.[28,29] An interesting option in situ during growing static cultivation is that the cellulose-producing microorganisms can be grown in culture medium with some sources, such as fruit syrup, that allow to produce cellulose to acquire the nature flavor and pigment of the fruit.[30] There are still many options to explore in reference to top down production and research groups around the world are developing variants that confer distinctive characteristics to the BNC. They also offer pharmaceutical and chemical researchers and industrials many intellectual property opportunities.

Application as non-active pharmaceutical ingredient

Commercial and intellectual interests are steal focus on active pharmaceutical ingredients (APIs) like solid forms. The solid forms of a drug, which can be crystalline, co-crystalline, solvate or amorphous, can have different solubility, bioavailability, stability and processing characteristics.[31] Its applicability results in an exhaustive study and a strong commercial interest in the investigation of pharmacological substances in solid state with respect to other types of molecules. The perspectives regarding the application of BNC in the field of health care, as well as in the design of new drugs are incalculable, particularly in this instance where the profiles of new drugs are advancing rapidly and the development of innovative pharmaceutical forms becomes in a technological need.[32] Polymers like polystyrene, rubber, plastic, polyvinylchloride are used extensively in the pharmaceutical industry, for the manufacture of vials, closures, tubing, injection sets, flexible blood bags.[33] originally the use was limited to primary packaging, secondary packaging and accessories, but they were not considered part of the pharmaceutical form. The development of pharmaceutical technology and the exploration of new drugs encouraged the symbiosis of polymer chemistry and pharmaceutical sciences. Cellulose derivatives have the advantage of easily accepting chemical surface modifications. These modifications confer characteristics such as biological compatibility, biodegradability, robustness and other features such as low production cost that make them the products of choice for the pharmaceutical industry.[34] BNC represents a new perspective on non-active pharmaceutical ingredients, since it allow novel amphipathic chemical modifications. The cellulosic derivatives

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are useful for the controlled release of drugs in solid formulations such as capsules and tablets. They also fulfil various functions in the technological development of solid pharmaceutical forms acting as non-active pharmaceutical ingredients and favouring the rheological characteristics in suspensions and emulsions.[35] Methylcellulose (MC) is acts as diluent and disintegrating agent for API release on solid dosage forms.[36] Hydrophilic matrix systems adopt hydroxypropyl cellulose (HPC), hydrophobic matrix system use often ethyl cellulose (EC). Also, liquid and semi-solid pharmaceutical dosage forms are important physicochemical systems for medical treatment which require rheological control and stabilizing excipients as essential additives, carboxymethyl cellulose (CMC),[37] is use for adjust the syrups viscosity. Nan particles made up of polysaccharides and polysaccharide-attached derivatives are useful as vectors for active pharmaceutical ingredients (APIs) that require controlled release at the target site.[38] these self-assembled nano-structures are produced from the modification of polysaccharides using amphiphilic molecules as the obtaining method. The amphiphilicity is necessary to complete the process of self-assembly property, since the monomers are assembled by modifying the hydrophobic/hydrophilic balance.[39] The electrostatic interaction of ionic polysaccharides of opposite charges is another alternative for self-assembly.[40] Chemical modification of the cellulosic structure to improve interactions with living tissues could enlarge the utilization of BNC in biomedical devices tremendously.[11]

Likewise, drugs with inadequate water solubility and/or dissolution rate along with hydrolytically medicines involve more complex development techniques in BNC, nevertheless provide a vast area for applications which has still to be studied.[41] Another issue to take account is toxicity, BNC reveals absolutely no side effects as well as genotoxicity in vitro.[41] The toxin levels of bacterial cellulose nanofibres have been effectively examined in vitro via cell viability and also flow cytometric assays along with in vivo choosing mice surgeries.[42] Also, bacterial cellulose exhibits absolutely no side effects in the human being umbilical vein endothelial cell culture, fibroblasts, as well as chondrocytes.[43] The in vitro analysis additionally reveals that 95% of the mesenchymal stem cells accumulate to cellulose membrane.18 Also, hydrophobic ally modified celluloses are GRAS materials that are widely used as excipients in the pharmaceutical industry.[44,45] Even though BNC has been demonstrated as nongenotoxic and noncytotoxic, further studies are required to completely address such issue.[46]

Conclusion

Nan celluloses are natural materials with at least one dimension in the nano-scale.[47,48] they combine important cellulose properties with the features of nanomaterials and open new horizons for materials science and its applications. Its everyday life use could be profitable in fields of practical application particularly as a product packaging, papers as well as paperboard, food products factory, health care and additionally sanitation products, paints, cosmetics, and so on. BNC are highly promising platforms for the synthesis of biocompatible nanocarriers of small molecule and macromolecular drugs for biomedical applications.[49] The various processing procedures for BNC have already been fully optimized for many years, and good strategies that possibly focus on a more significant scale are being established.[50] Around the globe, research groups and, increasingly, companies are extensively working to expand the market for nanocellulose products and to open up totally new application areas. Key aspects for future development include the design of nanocelluloses for specific user requirements, the reduction of production costs, and the customization/functionalization using post production steps and different types of compounding/processing.

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Conflict of interest

Authors declare there is no conflict of interest.

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