Journal Of Nanomedicine & Nanotechnology
OPEN ACCESS Freely available online
ISSN: 2157-7439
Mini Review

Bionanocellulose: A Trending Natural Nanomaterial for Groundbreaking Applications in Regenerative Medicine

Vanessa Raddatz, Katrin Petzold-Welcke, Dieter Klemm

KKF-Gesellschaft, Hans-Knöll-Str. 6, 07745 Jena, Germany

ABSTRACT

The concern of this mini review is to feature the natural nanomaterial bionanocellulose (BNC) and its potential as a novel type of biomaterial for applications in regenerative medicine. The hydrogel BNC is characterized by high purity, dimensional stability and good surgical handling. A fundamental current progress is the biotechnological design of shape, dimensions, nanofibernetwork and surface properties of the BNC materials. The corresponding template-based technology allows the tailoring of implants for quite different organs such as urgently needed small diameter blood vessel substitutes, bile duct and ureter implants. Further application fields are advanced wound dressings and drug delivery.

Keywords: Bionanocellulose; Regenerative medicine; Visceral implants; Cardiovascular implants; Wound dressing; Drug delivery

INTRODUCTION

Nanocelluloses: As natural nanomaterials with unique characteristics

Nanocelluloses combine the outstanding properties of the natural material cellulose with the specific characteristics of nanomaterials. They are characterized by at least one dimension in the nanometer range. The family of nanocelluloses can be divided into three areas that differ significantly in terms of starting material, manufacturing process and product properties. These types are: cellulose nanofibers, cellulose nanocrystals and bionanocellulose (BNC). BNC, also named as bacterial nanocellulose, biotech nanocellulose and microbial cellulose, is the only cellulose type that is produced biotechnologically by acetic acid bacteria from low molecular educts such as glucose in form of nanofibernetworks [1]. This results in specific features of this nanomaterial with high application potential, especially in the medical field. The unique characteristics of BNC are: high purity (no foreign substances or other functional groups than -OH), high biocompatibility, high mechanical strength and a nanofibernetwork with an interconnecting and open micropore system (natively containing 1 % cellulose, 99 % water). These characteristics can be influenced further by type of synthesis technology, cultivation conditions, additives and post processing steps such as different drying methods (freeze-drying leads to aerogels, air-drying leads to a reduction of pore size and finally pore collapse) [2–5].

Preparation and design of bionanocellulose materials

The formation of BNC can be realized using different methods resulting in different properties of the hydrogels. The most commonly used one is the static cultivation. The principle is based on the inoculation of a culture medium, frequently used is Hestrin-Schramm, by a bacterial strain, mostly of the genus Komagataeibacter. Under defined static cultivation conditions (time, temperature) a BNC hydrogel is formed on the surface of the medium [6]. This method is limited in shape, thickness (hindered nutrient supply) and additives cannot be incorporated homogeneously as well as surface and network properties can only be affected by the used strain or post processing. A variant that overcomes the limited thickness and allows additives to be distributed homogeneously throughout the network is spraying the culture medium onto a statically produced BNC membrane [7–9].

To meet the challenging requirements for its medical use, the demand for process-controlled design of function determining properties, such as shape, surface and nanofibernetwork structure, is growing. A novel technology, called Mobile Matrix Reservoir Technology (MMR Tech), enables the design of these factors [10,11]. The MMR Tech is a dynamic technology characterized by BNC formation on a template. This template is moving vertically in defined time intervals between the culture medium (containing bacteria of the genus Komagataeibacter) and the air space of a bioreactor. In contact with the oxygen-containing atmosphere, the BNC formation takes place on the surface of the template. Since the surface is constantly wetted with fresh medium, the

Correspondence to: Dieter Klemm, KKF-Gesellschaft, Hans-Knöll-Str. 6, 07745 Jena, Germany, E-mail: d.klemm@kkfpolymers.de

Received: June 09, 2021; **Accepted:** June 23, 2021; **Published:** June 30, 2021

Citation: Raddatz V, Petzold-Welcke K, Klemm D (2021) Bionanocellulose: A Trending Natural Nanomaterial for Groundbreaking Applications in Regenerative Medicine. JNMNT Res. 12:7

layer thickness is not limited. After finishing biosynthesis the BNC hydrogel is detached from the template, purified and post processing steps can be added. The template shape (e.g. flat, tubular, X-shape, Y-shape) and its material (e.g. wood (bamboo), glass, textiles, metals, polymers) can be adapted to the requirements of the product (Figure 1) [12].

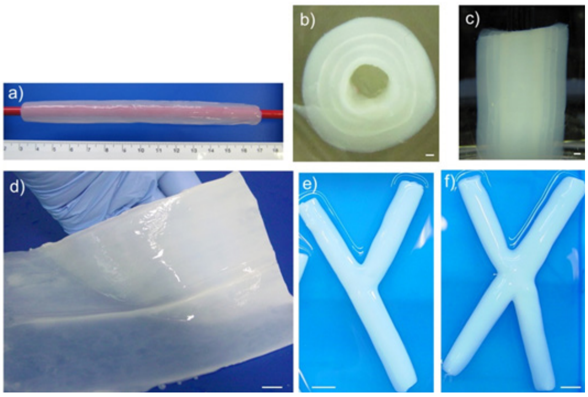

Figure 1: Overview of products made by MMR Tech, a) never-dried BNC tube (99 % water content) on a red glass rod. Length >100 mm, inner diameter: 5 mm, wall thickness: 1 mm, b) photography of the cross-section of a multilayered BNC tube, scale bar: 1 mm, and c) lateral view of this BNC tube. The wall thickness of the shown tube is of extra-large size for better demonstrating the layers, scale bar: 1 mm, d) never-dried BNC membrane with dimensions up to 200 x 100 x 3 mm, scale bar: 10 mm, e) never-dried hollow BNC-Y-piece, scale bar: 10 mm, f) never-dried hollow BNC-X-piece for demonstration of 3D structures, scale bar: 10 mm [12].

The only limitation is that the template has to be wettable by the culture medium and is non-toxic for bacteria. Depending on the template surface and the dipping mode, surface properties and nanofibernetwork architecture can be designed. BNC coatings can also be achieved by remaining the BNC on the templates surface. The MMR Tech also allows building up multilayer structures and the incorporation of additives (dispersed or dissolved) homogeneously in the nanofibernetwork of each layer [12].

The applicability of BNC-based implant materials has already been evaluated in prospective, randomized multicenter clinical trials for repair of dural defects. BNC implants showed noninferiority compared to commercially available dural replacements, offered superior handling qualities and a hypothetical advantage concerning prion and other infectious agent exposure [13]. These results underline the high application potential of BNC as novel implant materials and the need to advance medical research in this field. Moreover, the MMR Tech opens up many advantages for products with specific properties in the medical field, such as implants, wound dressings and drug delivery systems.

Tubular bionanocellulose implants for visceral and cardiovascular surgery

The preparation of tubular BNC with adjustable inner diameters is particularly interesting for visceral surgery and cardiovascular implants.

Due to cancer or destruction during surgical interventions, there is a great demand for biomaterials to replace destroyed parts of ureter, esophagus and bile duct in visceral surgery. In years of research cooperation with the group of Prof. Dr. Utz Settmacher and Prof. Dr. Falk Rauchfuss (Clinic for Visceral and Vascular Surgery, University Hospital Jena, Germany), the development of tubular BNC implants, prepared by MMR Tech, for bile duct repair was successful. Animal studies (pig) have shown that approximately three months after implantation of the BNC tube, regeneration of the damaged bile duct is promoted by the body's own cells. Then, the implant can be removed non-invasively [14–16].

The design of tubular BNC implants is also essential for cardiovascular applications, since cardiovascular diseases are still the leading cause of death worldwide [17]. Especially when it comes to the replacement of small-lumen blood vessels with an inner diameter of less than 6 mm, there are currently no alternatives to autologous vessel transplantation. The MMR Tech offers the opportunity to synthesize BNC tubes with a variable inner diameter in the range of 2.5 up to 30 mm and with different structured inner surfaces (facing the blood) depending on the used template type (Figure 2) [12].

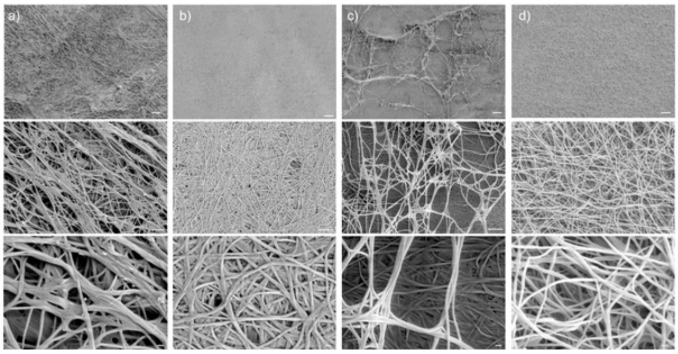

Figure 2: Scanning electron microscopic image of BNC tubes synthesized by MMR Tech from K. xylinus DSM 32384 (top line: 600x, scale bar: 10 µm, middle line: 5,000x, scale bar: 2 µm, lower line: 20,000x, scale bar: 200 nm), a) inner surface of BNC tube directed to bamboo template, b) outer surface of BNC tube, synthesized on a bamboo template, directed to the air space, c) inner surface of a manually inverted BNC tube, synthesized on a bamboo template, d) inner surface of BNC tube directed to air space, synthesized inside a hollow cylinder [12].

Using hollow cylinders (Figure 2d), the BNC tube is synthesized inside this template type. The inner surface of the tube is created in contact with air without structure-damaging influence of a template. These tubes can be produced with a smooth inner surface to reduce adhesion of blood cells. The nanofibernetwork (loose or dense) can also be adapted by varying the dipping mode and the bacterial strain. Each layer of the multilayered tubes can be influenced. The properties can be further modified by incorporation of additives and drying (air-drying additionally compacts the surface) [12]. In cooperation with the research group of Prof. Dr. Jens Wippermann (Clinic for Cardiac and Thoracic Surgery of the Magdeburg University Hospital, Germany), tubular BNC implants prepared by MMR Tech with different inner surfaces were examined regarding their haemocompatibility in an artificial blood circuit (Chandler Loop) [18–20]. The tubes were attached to heparinized polyvinyl chloride tubes, loaded with human blood and rotated at 37 °C. To determine the distribution of adhering platelets by scintigraphy, platelets were labeled with 111indium oxide. The BNC tubes, formed in hollow cylinders, showed the lowest roughness and are characterized by superior performance with <10 % leukocyte and <50 % thrombocyte loss to compared grafts (>65 % leukocyte and >90 % thrombocyte loss). Scintigraphy analyzes showed the least radioactivity for these types, indicating a reduced platelet adhesion. Nevertheless, all nanocellulose types showed enhanced complement activation [21]. In summary, these results elucidate the necessity to invest further research in these BNC implants. First results in animal studies (sheep, arteria carotis) display good surgical handling and a stable multilayered structure during surgery and for months in the organism for the BNC tubes prepared by MMR Tech. This study also showed that the patency rate of the implants still needs to be improved [22].

Bionanocellulose membranes for wound dressings and drug delivery systems

BNC membranes are particularly interesting in the field of wound dressings and drug delivery systems based thereon. The hydrogels offer besides high purity and good biocompatibility a nanofibernetwork with a high mechanical strength. These properties enable wound exudate to be absorbed while maintaining a moist wound environment for healing. Water retention properties can be improved further by embedding additives such as alginate leading to an extended wear time [23]. The nanofibernetwork is also suitable for incorporation of active ingredients that promote wound healing. Depending on the physicochemical characteristics of these drugs, the structural design of BNC and the drug loading strategy, different release profiles can be achieved. Mostly hydrophilic (especially antibiotics [24–26] and antiseptics [27,28]) and water-soluble substances are used, which correspond to the hydrophilic character of the BNC. However, loading strategies for hydrophobic substances are also being investigated, including improvement of the solubility of drugs [29,30], incorporation of disperse multiphase systems [31,32] and surface modification of BNC [33]. As presented in [12], work focusing on drug delivery systems based on BNC scaffolds is in progress in the research group of Prof. Dr. Dagmar Fischer (Department of Chemistry and Pharmacy, University Erlangen, Germany). To determine swelling behavior as well as drug loading and release profiles the design of BNC characteristics is necessary. Shape, surface porosity (partial drying leads to different pore sizes), nanofibernetwork structure (loose, dense), water content, and chemical and mechanical modifications (introduction of additional functional groups, straighten or shrinkage of the nanofibernetwork), are variables that can be adapted here to the intended demands. The MMR Tech facilitates a process-controlled design of these parameters and, more importantly, the construction of multilayered membranes directly during biosynthesis, which can be influenced individually, as mentioned before. With these materials there are completely new possibilities to influence drug release kinetics by building up gradients within the membrane.

CONCLUSION AND OUTLOOK

The high potential of bionanocellulose (BNC) as biotechnological designable implant materials open up new possibilities for regenerative medicine. By the process parameters of the currently established technology, the functional implant properties for replacement and repair of human organs can be tailored. The technology can supply the research market by corresponding products to advance implant development. In near future, the development of applicable BNC medical devices should be possible, especially in the background of "first in man" dura mater implants.

ACKNOWLEDGEMENT

The preparation of the mini review is based on a corresponding invitation, which in turn refers to the article in Carbohydrate Polymers. Only the named authors were involved in the mini review. The underlying article in Carbohydrate Polymers contains an acknowledgement.

REFERENCES

1. Klemm D, Lindström T, Abitbol T, Kralisch D.The nanocellulose family. In: Thomas S, Pottathara YB. Nanocellulose based composites for electronics.Amsterdam.2021.1–14.

2. Gama M, Gatenholm P, Klemm D.Bacterial nanocellulose: A sophisticated multifunctional material.2013.

3. Klemm D, Kramer F, Moritz S, Lindström T, Ankerfors M, Gray D, et al. Nanocelluloses: A new family of nature-based materials. Angew Chem Int Ed Engl. 2011;50(24):5438–66.

4. Klemm D, Cranston ED, Fischer D, Gama M, Kedzior SA, Kralisch D, et al. Nanocellulose as a natural source for groundbreaking applications in materials science: Today's state. Materials Today. 2018;21(7):720–48.

5. Nishi Y, Uryu M, Yamanaka S, Watanabe K, Kitamura N, Iguchi M, et al. The structure and mechanical properties of sheets prepared from bacterial cellulose. J Mater Sci. 1990:2997–3001.

6. Schramm M, Hestrin S. Factors affecting production of cellulose at the air/liquid interface of a culture of Acetobacter xylinum. J Gen Microbiol. 1954;11(1):123–129.

7. Hornung M, Ludwig M, Gerrard AM, Schmauder H-P. Optimizing the Production of Bacterial Cellulose in Surface Culture: Evaluation of substrate mass transfer influences on the bioreaction (part 1). Eng. Life Sci. 2006; 6(6):537–545.

8. Hornung M, Ludwig M, Schmauder HP. Optimizing the production of bacterial cellulose in surface culture: A novel aerosol bioreactor working on a fed batch principle (part 3). Eng. Life Sci. 2007; 7(1):35–41.

9. Luo H, Dong J, Yao F, Yang Z, Li W, Wang J, et al. Layer-by-Layer assembled bacterial cellulose/graphene oxide hydrogels with extremely enhanced mechanical properties. Nanomicro Lett. 2018; 10(3):42.

10. Fried W, Klemm D, Kopsch V, Koth D, Kramer F, Moritz S, et al. Process for producing hollow bodies from microbial cellulose, WO2013113675A1. 2013.

11. Klemm D, Kopsch V, Koth D, Kramer F, Moritz S, Richter T, et al. Vorrichtung zur Herstellung von Hohlkörpern aus mikrobiellem Polymer. Germany, DE102012201272B4. 2013.

12. Klemm D, Petzold-Welcke K, Kramer F, Richter T, Raddatz V, Fried W, et al. Biotech nanocellulose: A review on progress in product design and today's state of technical and medical applications. Carbohydr Polym 2021; 254:117313.

13. Rosen CL, Steinberg GK, DeMonte F, Delashaw JB, Lewis SB, Shaffrey ME, et al. Results of the prospective, randomized, multicenter clinical trial evaluating a biosynthesized cellulose graft for repair of dural defects. Neurosurgery. 2011;65(5):1103-1104.

14. Klemm D, Rauchfuss F, Kramer F, Petzold-Welcke K, Richter T, Ruhe C, et al. Design of biocellulose implants for first successful bile duct regeneration. 251st ACS National Meeting & Exposition. San Diego, United States. 2016.

15. Rauchfuss F. Biocellulosis as scaffold for tissue regeneration in modern surgery. 225th ACS National Meeting & Exposition. New Orleans, United States. 2018.

16. Rauchfuss F, Settmacher U, Klemm D, Fried W, Richter T, Petzold-Welcke K, et al. Medical implant based on nanocellulose, WO2017021468A1. 2017.

17. World Health Organization (2020) The top 10 causes of death.

18. Scherner M, Reutter S, Klemm D, Sterner-Kock A, Guschlbauer M, Richter T, et al. In vivo application of tissue-engineered blood vessels of bacterial cellulose as small arterial substitutes: Proof of concept? J Surg Res. 2014;189(2):340–347.

19. Schumann DA, Wippermann J, Klemm DO, Kramer F, Koth D, Kosmehl H, et al. Artificial vascular implants from bacterial cellulose: Preliminary results of small arterial substitutes. Cellulose. 2019;16(5):877–885.

20. Wippermann J, Schumann D, Klemm D, Kosmehl H, Salehi-Gelani S, Wahlers T. Preliminary results of small arterial ubstitute performed with a new cylindrical biomaterial composed of bacterial cellulose. Eur J Vasc Endovasc Surg. 2009; 37(5):592–596.

21. Wacker M, Kießwetter V, Slottosch I, Awad G, Paunel-Görgülü A, Varghese S, et al. In vitro hemo- and cytocompatibility of bacterial nanocelluose small diameter vascular grafts: Impact of fabrication and surface characteristics. PLoS One 6. 2020;15(6):e0235168.

22. Weber C, Reinhardt S, Eghbalzadeh K, Wacker M, Guschlbauer M, Maul A, et al. Patency and in vivo compatibility of bacterial nanocellulose grafts as small-diameter vascular substitute. J Vasc Surg. 2018;68(6S):177S-187S.

23. Sulaeva I, Hettegger H, Bergen A, Rohrer C, Kostic M, Konnerth J, et al. Fabrication of bacterial cellulose-based wound dressings with improved performance by impregnation with alginate. Mater Sci Eng C Mater Biol Appl. 2020:110619.

24. Mori R, Nakai T, Enomoto K, Uchio Y, Yoshino K. Increased antibiotic release from a bone cement containing bacterial cellulose. Clin Orthop Relat Res. 2011;469(2):600-6.

25. Shao W, Liu H, Wang S, Wu J, Huang M, Min H, et al. Controlled release and antibacterial activity of tetracycline hydrochloride-loaded bacterial cellulose composite membranes. Carbohydr Polym. 2016; 145:114–20.

26. Ye S, Jiang L, Wu J, Su C, Huang C, Liu X, et al. Flexible amoxicillin-grafted bacterial cellulose sponges for wound dressing: In vitro and in vivo evaluation. ACS Appl Mater Interfaces. 2018;10(6):5862–5870.

27. Adepu S, Khandelwal M. Bacterial cellulose with microencapsulated antifungal essential oils: A novel double barrier release system. Materialia. 2020;9(6):100585.

28. Marquele-Oliveira F, da Silva Barud H, Torres EC, Machado RTA, Caetano GF, Leite MN, et al. Development, characterization and pre-clinical trials of an innovative wound healing dressing based on propolis (EPP-AF®)-containing self-microemulsifying formulation incorporated in biocellulose membranes. Int J Biol Macromol. 2019; 136:570-578.

29. Trovatti E, Freire CSR, Pinto PC, Almeida IF, Costa P, Silvestre AJD, et al. Bacterial cellulose membranes applied in topical and transdermal delivery of lidocaine hydrochloride and ibuprofen: In vitro diffusion studies. Int J Pharm. 2012; 435(1):83-7.

30. Gupta A, Keddie DJ, Kannappan V, Gibson H, Khalil IR, Kowalczuk M, et al. Production and characterisation of bacterial cellulose hydrogels loaded with curcumin encapsulated in cyclodextrins as wound dressings. European Polymer Journal. 2019; 118:437–50.

31. Karl B, Alkhatib Y, Beekmann U, Bellmann T, Blume G, Steiniger F, et al. Development and characterization of bacterial nanocellulose loaded with Boswellia serrata extract containing nanoemulsions as natural dressing for skin diseases. Int J Pharm. 2020;587:119635.

32. Numata Y, Mazzarino L, Borsali R. A slow-release system of bacterial cellulose gel and nanoparticles for hydrophobic active ingredients. Int J Pharm. 2015;1-2:217–25.

33. Beekmann U, Karl B, Zahel P, Käfer D, Schmölz L, Lorkowski S, et al. Manufacturing of modified bacterial cellulose as tailor-made anti-inflammatory wound dressing. 4th International Symposium on Bacterial Nanocellulose. Porto, Portugal. 2019.