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Research paper

Controlled extended octenidine release from a bacterial nanocellulose/ Poloxamer hybrid system

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ABSTRACT

Although bacterial nanocellulose (BNC) has been widely investigated in the last 10 years as drug delivery system, up to now no long-term controlled release of drugs could be realized. Therefore, the aim of the present work was the development of a BNC-based drug delivery system that provides prolonged retention time for the antiseptic octenidine up to one week with improved mechanical and antimicrobial properties as well as a high biocompatibility. BNC was modified by incorporation of differently concentrated Poloxamers 338 and 407 as micelles and gels that were extensively investigated regarding size, surface charge, and dynamic viscosity. Depending on type and concentration of the Poloxamer, a retarded octenidine release up to one week could be accomplished. Additionally, superior material properties such as high compression stability and water binding could be achieved. The antimicrobial activity of octenidine against *Staphylococcus aureus* and *Pseudomonas aeruginosa* was not changed by the use of Poloxamers. Excellent biocompatibility of the Poloxamer loaded BNC could be demonstrated after local administration in a shell-less hen's egg model. In conclusion, a long-term delivery system consisting of BNC and Poloxamer could be developed for octenidine as a ready-to-use system e.g. for long-term dermal wound treatment.

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1. Introduction

The unique natural hydropolymer bacterial nanocellulose (BNC) is an innovative bio-fabricated material, produced during fermentation by strains of the obligatory aerobic, Gram-negative bacteria *Komagataeibacter xylinus* in static culture [1]. Although the chemical formula is identical to plant cellulose, the most important difference is the diameter of the cellulose fibers that typically lies in the range of 20–100 nm. From the technological point of view, BNC is produced as an inherently stable three-dimensional hydropolymer consisting of about 1% cellulose and up to 99% water. The fiber diameter, the degree of polymerization and the network structure are responsible for the outstanding material properties such as high mechanical and thermal stability as well as softness [1,2].

The interest in BNC as drug delivery system dramatically increased during the last 10 years, as the nano-sized 3D-network of BNC is expected to hold a large amount of drug molecules due to its large surface area [3]. Active agents like small molecules [4–6], peptides [7] and proteins [8] as well as micro- and nanoparticles [9,10] including nanocrystals, precipitates or gels were integrated into the BNC network to accomplish a controlled drug release. Different drug loading strategies and functionalization methods were employed to combine material properties of BNC with the beneficial effects of drugs. Basically, *in situ* and *post* synthesis loading techniques can be distinguished where the active component is incorporated in the BNC nanofiber network during assembly or into the finally formed material after synthesis and purification, respectively [6,11,12]. The suitability of a method for a certain application depends on the physicochemical characteristics of the drug like molar mass and solubility, drug stability during each process step, modification of the BNC, and the intended drug release profile.

Typically, drugs were incorporated by sorption techniques under submerse conditions over several hours or days [8]. However, as drug loading is accomplished by diffusional or swelling controlled processes, the release often also follows these physical

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transport processes. Therefore, in many studies the drug release was found to be characterized by a biphasic profile consisting of a fast burst release within the first 2–10 h followed by a slow release phase up to 24 h [4,5]. The incorporation of nano- and microparticles to extent the release phase did also not exceed a release phase of 24–72 h [9]. However, for several pharmaceutical applications long-term release rates are required. As an example, for the application of BNC as active wound dressing less frequent changes could reduce pain and prevent tissue trauma. For the use of BNC as implant, bone or cartilage replacement an extended release of antibiotics or growth factors to treat infection or to attract the growing cells over several days after surgery, respectively, seems to be favorable.

Poloxamers are presented by the Food and Drug Administration guide as an inactive ingredient for many different preparations such as parenteral, oral, topical and ophthalmic formulations [13]. They are highly attractive due to their biocompatibility and low toxicity [13]. They have been introduced to pharmaceutical applications as amphiphilic surfactants composed of polyethylene oxide (PEO)/polypropylene oxide (PPO) arranged in a triblock structure as PEOx-PPOy-PEOx [13,14] that form micelles with a core of hydrophobic PPO blocks and a shell of strongly hydrophilic PEO in an aqueous environment. Depending on polymer concentration and temperature, micellar structures or coherent gels can be formed. Although local applications have been widely described, for a sustained local delivery Poloxamers were found to be critical. The rapid erosion in the physiological environment by dilution drops the concentration below the critical micellar or gelation concentration followed by a fast release of drugs [13,14].

Previously, we reported BNC as a drug delivery system for the antiseptic octenidine intended for the local treatment of acute wounds which requires a fast, short-term drug release within several hours. This could be realized by the incorporation of octenidine into the BNC network without any additional excipients. In contrast, in the present study a long-term release drug delivery system should be developed by the combination of the advantages of two materials, BNC and Poloxamers. As model drug octenidine has been selected again as it has been widely described before for the administration by BNC with well-known drug release kinetics and mechanisms. Loading techniques for drug and Poloxamers in BNC were developed to accomplish controllable release profiles up to one week. These hybrid systems were intensively characterized regarding their physicochemical and biological characteristics *in vitro* and *in vivo*.

2. Materials and methods

2.1. Preparation and characterization of BNC fleeces

The biosynthesis of bacterial nanocellulose was accomplished by static cultivation of *Komagataeibacter xylinus* DSM 14666 (culture collection of the Friedrich-Schiller-University Jena, deposited at the DSMZ, German Collection of Microorganisms and Cell Cultures, Braunschweig, Germany) in Hestrin-Schramm medium at 28 °C in 24-well plates (Greiner-Bio-one, Frickenhausen, Germany) as described before [8]. BNC fleeces were rinsed with deionized water, boiled in 0.1 N aqueous sodium hydroxide solution (NaOH, Carl Roth, Karlsruhe, Germany) for 30 min and washed again in water until a neutral pH was reached. Finally, they were sterilized by autoclaving (121 °C, 20 min, 2 bar) before storage at 4 °C. All BNC fleeces were characterized by examination of their different dimensions (diameter, thickness, volume, and weight) as described before [8]. Surface area and volume were calculated according to the geometrical formulas of a circular cylinder or a cuboid [8].

2.2. Preparation of octenidine and Poloxamer loaded BNC

Octenidine was purchased from Schuelke & Mayr (Norderstedt, Germany) as a stock solution containing 0.5% octenidine. The Kolliphor® F108 (Poloxamer 338) and F127 (Poloxamer 407) were obtained as a kind gift from BASF SE (Ludwigshafen, Germany). For the preparation of loading solutions the Poloxamers were dissolved in the octenidine stock solution under constant stirring (IKA® Werke, Staufen, Germany) at 4 °C in a temperature-controlled refrigerator for 24 h to ensure complete dissolution. Octenidine stock solutions containing equal amounts of water instead of the Poloxamers were used as controls. Poloxamers were used in two different concentrations representing values above the critical micelle concentration (so called CMC samples) and the critical gelation concentration (named as CGC samples) according to Table 1. For loading of BNC with octenidine and octenidine/Poloxamer dispersion, BNC fleeces were incubated in 10.0 mL loading solution under submersed conditions for 48 h on an orbital shaker (KS 4000 ic control, IKA®-Werke) at 70 rpm. For CMC samples, the fleeces were treated at room temperature using dispersions that were warmed-up after dissolution at 4 °C to 21 °C. In contrast, the CGC samples were loaded at 4 °C and heated to room temperature after the loading process. The amount of loaded antiseptic was calculated from the difference of the octenidine concentration before loading and the octenidine concentration of the loading solution after 48 h.

2.3. Quantification of octenidine

The quantification of octenidine was performed by ultraviolet and visible (UV/Vis) spectrophotometric measurements in 0.1 M phosphate buffered solution (PBS) pH 7.4 (Carl Roth) at 281 nm using the Beckman DU 640 spectrophotometer (Beckmann Instruments Inc., Fullerton, CA, USA). Detailed descriptions can be found at [4]. All experiments were run in triplicate and repeated once.

2.4. Laser light scattering experiments

The hydrodynamic diameter and the polydispersity indices of the undiluted octenidine/Poloxamer dispersions (CMC samples) were measured using the Zetasizer Nano ZS (Malvern Instruments, Herrenberg, Germany; Software: Zetasizer v7.2) in a minimal volume cuvette ZEN 0040 (BRAND, Wertheim, Germany) equipped with a 4 mW He-Ne laser (633 nm) at a scattering angle of 173° at 20 °C. Results were shown as the mean Z-average of six runs. The measurements of the zeta potential were performed in a Zetasizer cuvette DTS1060 (Malvern instruments) by measuring the electrophoretic mobility at 20 °C. The results were calculated with the Malvern software 7.2 and shown as the mean ± SD of three independent measurements.

2.5. Determination of CMC and CGC

To determine the CMC of the Poloxamers, a UV/Vis spectroscopic method was performed. A mixture of iodine/iodide was used as a stock solution containing 6.4×10^{-4} and 2.0×10^{-3} mol/L, respectively. Poloxamer concentrations in the range of 0.01–5% were tested. Samples (4 mL) of each Poloxamer concentration were mixed with 1 mL of the stock solution [15]. The mixture was stored under light exclusion for 12 h [16]. Afterwards, the absorbance measurements were carried out at 366 nm using the Beckman DU 640 spectrophotometer. The Poloxamer concentration which showed a sharp decrease in absorption was defined as the CMC value according to [15]. To determine the sol-gel transition temperature of the Poloxamers, the tube inverting method was employed [17,18]. Two mL Poloxamer solution were added

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