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Bacterial cellulose: Application as drug delivery system

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ABSTRACT

Bacterial cellulose (BC) is a very interesting biopolymer to the biomedical application, including drug delivery system, due to unique characteristics as such as high degree purity and of porosity, relatively high permeability to liquid and gases, high holding water capacity, tensile strength, and randomly oriented three-dimensional fiber network. Several authors described the use of BC membranes or copolymers to use as drug delivery system. The aim of the present mini-review was to show the wide and vantages application of the BC and its copolymers for use as controlled drug delivery system.

Introduction

Polymeric drug delivery systems may be designed in many forms, including matrices, composites, pure membranes and copolymers in which the bioactive compound must be dispersed or dissolved (1,2). The route of administration, carrier formulation, release mechanism and physicochemical properties of the drug molecule may influence the rate of release and, therefore, should be considered when selecting a suitable polymer for this purpose (2,3). In addition, the polymers used for the development of drug delivery systems must be chemically inert and present appropriate physical and chemical characteristics (2). In the last years, BC (Figure 1), a very interesting biopolymer, has been widely applied in transdermal drug delivery as membranes, being commonly used in the fabrication of matrix-type patches due singular properties (4), such as high degree purity and of porosity, relative high permeability to liquid and gases, high holding water capacity, tensile strength and randomly oriented three-dimension fibers network, viscoelasticity and poroelasticity (5,6).

BC can be produced by several organisms species, (7,8) with special emphasis to cellulose produced by bacteria of the genus *Gluconacetobacter*, recently named *Komagataeibacter* (Figure 2), especially the species *K. xylinus* and *K. hansenii* (6,9,10), using a variety of natural and synthetic culture media with several carbon sources of different origins (11,12). Nevertheless, BC membranes maintain a physical barrier that reduces pain, bacterial infection and allows drug transfer into the wounded region (13–15). These BC membranes characteristics constitute an important aim to development of studies for application this biopolymer as drug delivery system (16–18).

The aim of the present mini-review was to show the wide and vantages application of the BC and its copolymers for use as controlled drug delivery system.

Application of bacterial cellulose as a drug delivery system

In recent years, several drug delivery systems based in BC membranes for various pharmaceutical applications have been proposed including antimicrobial, and anticancer agents, small molecules, inorganic nanoparticles and a metal complex (19).

Studies developed by Stoica-Guzun et al. (20) demonstrated the delivery of the antibiotic tetracycline encapsulated on BC matrix comparing irradiated (doses of 5 or 15 kGy) to non-irradiated BC membranes an *in vitro* study demonstrating that electron beam radiated over BC-tetracycline system promoted faster drug release rate.

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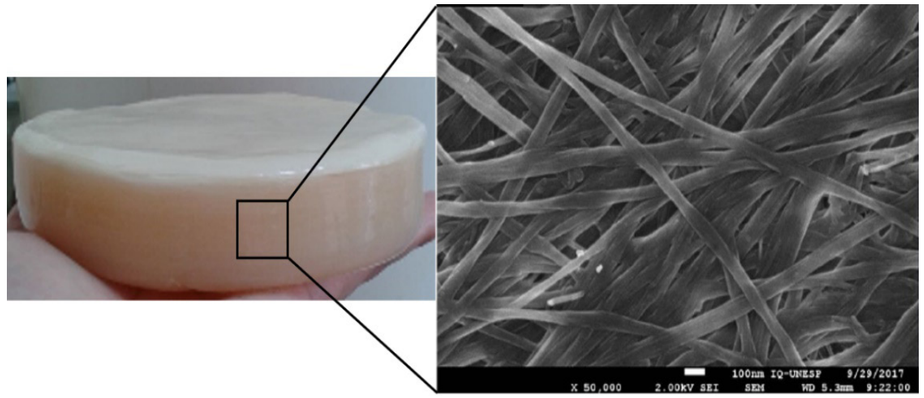

Figure 1 – Swollen BC membrane and Scanning Electron Microscopy (SEM) BC membranes randomly oriented three-dimension fibers network (50.000x)..

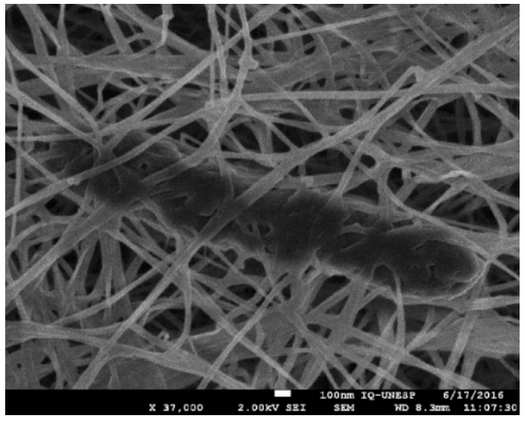

Figure 2 - Scanning Electron Microscopy (SEM) *G. hansenii* ATCC 23769 (37.000x)

Antimicrobial bacterial cellulose-silver nanoparticles composite membranes obtained by *in situ* preparation of silver nanoparticles from hydrolytic decomposition of silver nitrate solution using triethanolamine as reducing and complexing agent exhibited strong antimicrobial activity against Gram-positive *S. aureus* and Gram-negative *E. coli* and *P. aeruginosa* bacteria Gram-positive *S. aureus* (21).

In another work, Kaplan et al. (22) performed a comparative study to evaluate the in vitro release behavior of gentamicin (GM) and ampicillin (AMP) by BC membranes. These authors demonstrated that membranes exhibited sustained release capacity of AMP and GM in 7 days and the amounts of antibiotic released by BC reached the proportion of dose required to inhibit the growth of *E. coli*, *E. feacalis*, *S. aureus* and *P. aeruginosa.*

In study using the Box-Behnken statistical design to study the release of amoxicillin (AMX) from the BC, BC / glycerol and BC / hexadecyltrimethylammonium bromide enhancer showed that amoxicillin concentration had a greater influence on drug release and a significant contribution was also observed for the linear and quadratic terms of the glycerol concentration, the linear concentration of potentiator, and the interaction between the concentration of glycerol and concentration of the enhancer. These results show that independent variables affevct the release of AMX from BC membranes (23).

In vitro antibacterial assay using BC composite membranes prepared with tetracycline hydrochloride (BC-TCH) demonstrates that this composites displayed excellent antibacterial activity solely associated with the loaded TCH drug (24).

A study using immobilized lysozyme onto BC nanofibers (BCNF) produced by physical absorption method was performed to evaluate the antimicrobial activity and other properties of immobilized lysozyme and also morphological characteristics of BCNF. This result demonstrates that the antimicrobial activity of lysozyme against *S. aureus*, *E. coli*, *L. monocytogenes*, *Y. entrocolitica*, *Aspergillus niger,* and *Saccharomyces cerevisiae* were increased after immobilization evidencing the potential for the use of BCNF as lysozyme delivery system (25).

Transparent antimicrobial silver nanoparticles/bacterial cellulose (AgNPs/BC) membranes produced by reducing silver nitrate as a precursor in the presence of sodium tripolyphosphate and *in situ* impregnation into the BC membranes. The AgNPs/BC membranes were nontoxic and showed good biocompatibility on peripheral blood mononuclear cells due to the controlled silver ion release. According to the results, it is suggested that the AgNPs/BC membranes can be applied for many antimicrobial purposes such as antibacterial wound dressing (26).

In a study, using bilayer BC membrane produced by *G. hansenii* ATCC 23769, from sugar-cane molasses carbon sources, impregnated with ceftriaxone (CRO), was demonstrated a higher capacity for retention and release of CRO when compared to the commercial BC membranes (18).

In a recent study, Volova et al. (27) demonstrated

pronounced antibacterial activity against *E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*, and the BC/ antibiotics amikacin and ceftriaxone composites were more active than BC/AgNp. *S. aureus* was the most susceptible to the effect of BC composites.

Lazarini et al. (18), obtained a dissimilar BC membrane with high drug delivery capacity by *G. hansenii* variety achieve after application of different culture temperatures. The BC membrane produced by variety acquired from the culture at 35º C produced membranes with dissimilar degrees of interweaving and fibers thickness and high dry mass yield. This BC obtained was impregnated with CRO and maintained release capacity for 72 hours.

A new hybrid material based on bacterial cellulose containing silver phosphate microparticles on one side of the matrix and high ciprofloxacin loading has been developed by Bayón et al. (28). The AgP-MPs developed by the self-assembly technique on only one side of the bacterial cellulose surface provide a novel and promising composite material with excellent antimicrobial activity against both Gram-positive *S. aureus* and Gram-negative *E. coli* bacteria. The BC membranes obtained showed relevant properties such as non-adhesive hydrogel dressing capability, high skin tissue compatibility, excellent water uptake ability, high mechanical strength, and air permeability.

In a study designed to prepare surface modified BC matrices by treatment with acetic anhydride, freeze drying, and oven drying, the BC was loaded with model drugs selected based on their aqueous solubility, faintly water-soluble famotidine and highly water-soluble tizanidine. The chemical structure, the concentration of the drug loaded, the concentration of the surface modifier and the modifications pre and post-loading of the drug altered the physicochemical properties of the BC matrices, which in turn affected the drug release behavior. The obtained results demonstrated that the surface modifications were found to be effective for controlling the drug release properties demonstrating the potential these BC matrices for applications as modified drug delivery system (29).

Results obtained in recent study, development by Lima Fontes (30), BC/ carboxymethylcelullose (BC/CMC) biocomposites with different DS-CMC (DS from 0.7 to 1.2) were loaded with methotrexate (MTX), drug used treatment of psoriasis, an autoimmune disorder of skin, in order to evaluate their impact as a drug delivery system. All samples showed a typical burst release effect in the first 15 min of a test, however, the BC/CMC (DS0.9) biocomposite promoted a slight lowering of MTX release rates, suggesting that the DS of CMC can be considered the key factor to modulate the BC properties.

A novel hybrid biomaterial composed bacterial cellulose hydrogel and nanostructured lipid carriers (NLCs) for application as local drug delivery implant for cancer therapy using doxorubicin (Dox) as drug model were described by Cacicedo et al. (31). NLCs loaded with cationic Dox (NLCs-H) or neutral Dox (NLCs-N) were fully characterized and their cell internalization and cytotoxic efficacy were evaluated *in vitro* against MDA-MB-231 cells. Both NLCs internalized via the endocytic pathway while allowing a sustained release of the Dox, which in turn rendered IC50 values below of those of free Dox. Thereafter, a combination of NLCs-H and NLCs-N loaded into BC (BC-NLCs-NH) was analyzed *in vivo* into an orthotopic mouse model. BC-NLCs-NH showing a significant reduction in tumor growth, metastasis incidence and local drug toxicities. These results demonstrate the potential use of BC-NLCs-NH as local drug delivery system.

Conclusion

After reviewing published data, it was evident that BC membrane and copolymers showed high potential pharmaceutical use with advantage application for the controlled drug delivery system justifying the increase of the interest of the researchers in the development of products based in BC to this application.

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