Carbohydrate Polymers 150 (2016) 330–352

Contents lists available at ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Review

Advances in biomedical and pharmaceutical applications of functional bacterial cellulose-based nanocomposites

Hanif Ullah[a,c], Fazli Wahid[b], Hélder A. Santos[c,*], Taous Khan[a,*]

[a] Department of Pharmacy, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[b] Biotechnology Program, Department of Environmental Sciences, COMSATS Institute of Information Technology, Abbottabad 22060, Pakistan
[c] Division of Pharmaceutical Chemistry and Technology, Faculty of Pharmacy, University of Helsinki, FI-00014 Helsinki, Finland

ARTICLE INFO

Article history:
Received 22 January 2016
Received in revised form 25 April 2016
Accepted 11 May 2016
Available online 14 May 2016

Keywords:
Bacterial cellulose
Bioengineering
Biomedical application
Composites
Nanocellulose

ABSTRACT

Bacterial cellulose (BC) synthesized by certain species of bacteria, is a fascinating biopolymer with unique physical and mechanical properties. BC's applications range from traditional dessert, gelling, stabilizing and thickening agent in the food industry to advanced high-tech applications, such as immobilization of enzymes, bacteria and fungi, tissue engineering, heart valve prosthesis, artificial blood vessels, bone, cartilage, cornea and skin, and dental root treatment. Various BC-composites have been designed and investigated in order to enhance its biological applicability. This review focuses on the application of BC-based composites for microbial control, wound dressing, cardiovascular, ophthalmic, skeletal, and endodontics systems. Moreover, applications in controlled drug delivery, biosensors/bioanalysis, immobilization of enzymes and cells, stem cell therapy and skin tissue repair are also highlighted. This review will provide new insights for academia and industry to further assess the BC-based composites in terms of practical applications and future commercialization for biomedical and pharmaceutical purposes.

Contents

* Corresponding authors.
E-mail addresses: helder.santos@helsinki.fi (H.A. Santos), taouskhan@ciit.net.pk (T. Khan).

http://dx.doi.org/10.1016/j.carbpol.2016.05.029
0144-8617/

1. Introduction

Cellulose is the most abundant biopolymer on earth that is frequently obtained from the plant sources (Finkenstadt, 2005; Saxena & Brown, 2012). It is the main structural component of plant cell wall and has an extraordinary commercial reputation in paper, textile and pulp production units (Gandini, 2008; Huber et al., 2012; Klemm, Heublein, Fink, & Bohn, 2005). Cellulose is also biosynthesized by some oceanic animals (tunicates), and thus called as tunicin (Zhao and Li, 2014). Other major pathways for cellulose production are *in vitro* enzymatic synthesis and chemosynthesis from glucose derivatives. The most important pathway of cellulose production is through different microbes, such as algae, fungi (Klemm et al., 2005) and various aerobic non-pathogenic bacteria of the genera *Agrobacterium, Sarcina, Rhizobium* and *Glucoacetobacter* (formerly *Acetobacter*) (Khan, Park, & Kwon, 2007; Petersen and Gatenholm, 2011; Shezad, Khan, Khan, & Park, 2010; Shoda and Sugano, 2005).

In 1886, Brown reported bacterial cellulose (BC) for the first time as a sturdy gelatinous white pellicle on a liquid medium surface during the acetic fermentations (Brown, 1886a, 1886b). The BC membrane was produced by *Bacterium xylinum* with a thickness about 25 mm (Brown, 1886a, 1886b). Later on, this bacterium was renamed as *Acetobacter xylinum* (*A. xylinum*), then as *Gluconacetobacter xylinus* (*G. xylinus*) and presently it is known as *Komagataeibacter medellinensis* (Matsutani et al., 2015; Yamada et al., 2012; Yamada, 2014).

Although BC is produced in laboratories in small scale for research, there are some commercial outlets for BC. Besides, traditional nata de coco (Iguchi, Yamanaka, & Budhiono, 2000), a German company, Fzmb GmbH is considered one of the largest producers of BC for cosmetics and biomedical applications (Keshk, 2014a). In addition, Xylos Co. in USA is a producer of Prima Cel™, a type of BC used for wound dressing. Other brands of BC include Gengiplex® and Biofill® (Keshk, 2014a) used as physical barrier for tissue regeneration. BC is also produced and used by many food industries in Asian countries (Budhiono, Rosidi, Taher, & Iguchi, 1999; Ng and Shyu, 2004). Sony Corporation, Japan in association with Ajinomoto, Japan and other firms fabricated the first BC-based diaphragm of audio speaker. Ajinomoto, Japan also sells wet BC (Chawla et al., 2009; Czaja, Krystynowicz, Bielecki, & Brown, 2006).

1.1. Biosynthesis of BC

G. xylinus has been employed as model microbe for basic and applied studies on BC due to its higher production yields and its ability to consume variety of sugars and other compounds as carbon source (Ross, Mayer, & Benziman, 1991; Saxena and Brown, 2012). In laboratory, glucose is usually added to the fermentation medium and the biosynthesis of BC takes place in four enzymatic steps: (1) phosphorylation of glucose by glucokinase to glucose-6-phosphate, (2) isomerization of glucose-6-phosphate to glucose-1-phosphate by phosphoglucomutase, (2) conversion of glucose-1-phosphate to uridine diphosphate glucose (UDP-glucose) by UDP-glucose pyrophosphorylase, (4) and the synthesis of cellulose from UDP-glucose by cellulose synthase (Ross et al., 1991). The activity of cellulose synthase in *G. xylinus* is regulated by an allosteric activator c-di-GMP (Ross et al., 1987; Saxena & Brown, 2012), which is also found in other bacteria (Saxena and Brown, 2005). Cellulose synthases from different organisms have been found with sequence similarities (Nobles and Brown, 2004).

BC is biosynthesized in the form of a ribbon that projects from the pole of bacterial rod. The ribbon elongates at a rate of 2 μm/min. A single *G. xylinus* cell synthesizes a ribbon composed of 10–100 microfibrils (Brown, 1985, 1996). There are 50 individual sites for BC synthesis, organized in a row along the longitudinal axis in close association with the outer envelope of bacterial cell. The assembly of BC microfibrils is a two-step process: polymerization of glucose residue to form β-1, 4-glucan chain (in the plasma membrane) and crystallization of glucan chain to cellulose in extracellular medium (Brown, Willison, & Richardson, 1976). Moreover, crystallization and polymerization are coupled processes directed by bacterial cell and the rate of crystallization determines the rate of polymerization (Benziman, Haigler, Brown, White, & Cooper, 1980). In addition, the assembly of the cellulose crystallite is proposed to occur in two steps:formation of sheets of glucan chain by van der Waals forces followed by stacking of the sheets to give crystalline structure (Cousins & Brown, 1995; Cousins & Brown, 1997a, 1997b).

1.2. Effect of bacterial strain on the properties and production of BC

Currently, several microorganisms have been reported with the ability to produce BC having numerous physicochemical properties for biological applications (Lee, Buldum, Mantalaris, & Bismarck, 2014). For example, *Salmonella* spp. and *Escherichia coli* (*E. coli*) were reported for the production of BC; however, the amount of BC produced by these bacteria is lower than that of *G. xylinus* (Lin, Calvar et al., 2013). In order to increase the production of BC, *E. coli* was transformed with BC producing capability similar to *G. xylinus*. The production of gluconic acid during BC biosynthesis decreases the pH of the medium leading to decreased production of the former. In order to avoid this, De Wulf, Joris, and Vandamme (1996) genetically engineered, mutant *G. xyinus*, limiting its ability for gluconic acid production. As a result, the pellicle size was doubled as compared to the wild type *G. xylinus*. Similarly, glutamate dehydrogenase deficient mutant strain of *G. xylinus* BPR 2001 (GD-1) does not produce gluconic acid, but produces twice as much BC than the parent strain (Shigematsu et al., 2005). Moreover, mutant type *G. xylinus* produces cellulose II in which the glucan chains are arranged antiparallel in comparison to parallel arrangement of glucan chains (cellulose I) produced by wild type *G. xylinus* (Kuga, Takagi, & Brown, 1993). The average length of glucan chain in cellulose II was about 10 times the width of the strand that suggests the folding of glucan chain, thus arranged in antiparallel manner. Using sucrose or glucose as a source of carbon, the main product of *G. xylinus* is