Applications of Bacterial Cellulose in Food, Cosmetics and Drug Delivery

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Abstract

Bacterial cellulose (BC) is a versatile biopolymer with better material properties, such as purity, high degree of porosity, relative high permeability to liquid and gases, high water-uptake capacity, tensile strength and ultrafine network. This review explores the applications of BC and its hydrogels in the fields of food, cosmetics and drug delivery. Applications of BC in foods are ranging from traditional dessert, low cholesterol diet, vegetarian meat, and as food additive and dietary aid to novel applications, such as immobilization of enzymes and cells. Applications in cosmetics include facial mask, facial scrub, personal cleansing formulations and contact lenses. BC for controlled drug delivery, transdermal drug delivery, dental drug delivery, protein delivery, tissue engineering drug delivery, macromolecular prodrug delivery and molecularly imprinted polymer based enantioselective drug delivery are also discussed in this review. The applications of BC in food and cosmetics provide the basis for BC-based functional foods, nutraceuticals, cosmeceuticals and medicated cosmetics. On the basis of current studies, the BC-based drug delivery could be further fine-tuned to get more sophisticated control on stimuli-responsive drug release. Along with the currently available literature, further experiments are required to obtain a blueprint of drug *in vivo* performance, bioavailability and *in vitro–in vivo* correlation.

Keywords

Bacterial cellulose
Cosmetics
Cosmeceuticals
Deracemization
Drug delivery
Food
Nutraceuticals
Protein delivery
Tissue engineering

Introduction

Biomaterials play a vital role in the daily life of humans (Czaja et al. 2007; Hubbell 1995; Ratner and Bryant 2004; Shoichet 2009). The importance of biopolymers in our food applications, and personal and medical care cannot be ruled out (Ellis and Smith 2008; Murphy 2001; Jay et al. 2008). Cellulose is the most abundant biopolymer on the surface of earth with 1.5×10^{12} tons annual production (Czaja et al. 2004; Klemm et al. 2005), and most commonly it is obtained from plants (Siró and Plackett 2010).

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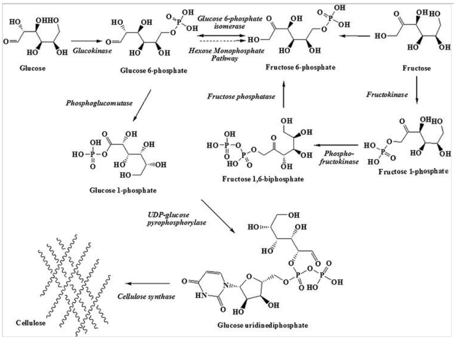
In addition to plant cellulose (PC), cellulose is also obtained through *in vitro* synthesis with the help of enzymatic pathways, the chemical synthesis from glucose derivatives and the biosynthesis by various microorganisms, such as algae and fungi (Klemm et al. 2005), as well as various aerobic non-pathogenic bacteria of the genera *Agrobacterium*, *Sarcina*, *Rhizobium* and *Acetobacter* (Dufresne 2013; Khan et al. 2007; Shezad et al. 2010). While studying acetic fermentations in 1886, Brown reported the bacterial cellulose (BC) in the form of a strong white gelatinous pellicle on the surface of a liquid medium, which had a thickness up to 25 mm. The microbe responsible for this BC membrane (BCM) was called *Bacterium xylinum* that was later on renamed as *Acetobacter xylinum* (*A. xylinum*) and at the moment is recognized as *Gluconacetobacter xylinus* (*G. xylinus*) (Brown 1886a, b).

G. xylinus is the most extensively used microorganism in the basic and applied studies for BC production because of its higher productivity, and capability to consume different sugars and other compounds as sources of carbon (Ross et al. 1991; Saxena and Brown 2012). *G. xylinus* cultivated under controlled conditions with suitable nitrogen and carbon sources, produces highly porous BC network structures in the form of sheets or pellicles, subject to the culturing approach (Lin et al. 2013; Pircher et al. 2014). The culturing conditions may be agitated or static, and batch, semi-continuous or continuous cultivation (Lin et al. 2013, 2014; Pircher et al. 2014; Sulaeva et al. 2015). Typically, the synthesis of BC occurs in four enzymatically catalysed steps: (a) glucose is phosphorylated to glucose-6-phosphate; (b) glucose-6-phosphate is isomerized to glucose-1-phosphate; (c) glucose-1-phosphate is converted to uridine diphosphate glucose (UDP–glucose); and (d) finally glucan chains are synthesized from UDP–glucose (Ross et al. 1991). After this, the parallel glucan chains are aggregated and crystallized to form microfibrils followed by aggregation of the latter to discontinuous bundles of cellulose fibres (Iguchi et al. 2000; Lin et al. 2013). After removal of the culture medium and complete washing, colourless, odourless and tasteless BC is obtained in the form of a gel. This gel finds several applications in our life (Lin et al. 2013). The biosynthetic pathway of BC in *G. xylinus* is shown in Fig. 1.

Fig. 1

Biosynthetic pathway of BC in *G. xylinus*.
Adapted with permission from Lin et al. (2013)



The auspicious properties associated with BC, such as exceptional mechanical characteristics, stress–strain behaviour, good light transmittance, *in situ* moldability, porosity, stability, biocompatibility, low immunogenic potential, and capability for cell adhesion, migration and proliferation (Helenius et al. 2006; Millon and Wan 2006; Qiu and Netravali 2014; Svensson et al. 2005) make it appropriate biomaterial for tissue engineering applications. These applications include, but are not limited to ~~artificial cartilage (Nimeskern et al. 2013; Svensson et al. 2005), artificial bone (Zimmermann et al. 2011), artificial cornea (Hui et al. 2009), heart valve prosthesis (Millon and Wan 2006), artificial blood vessels,~~artificial cartilage (Nimeskern et al. 2013; Svensson et al. 2005), bone (Zimmermann et al. 2011), cornea and blood vessels (Hui et al. 2009; Klemm et al. 2001; Wan et al. 2011), heart valve prosthesis (Millon and Wan 2006), nerve surgery (Klemm et al. 2001; Wan et al. 2011), meniscus implant (Bodin et al. 2007), artificial skin and skin tissue repair (Fu et al. 2012; Qiu and Netravali 2014).

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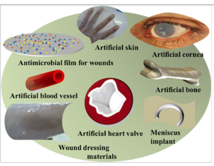
Some of these BC-based applications ~~of BC~~ are shown in Fig. 2.

Fig. 2

Applications of BC in biomedicine



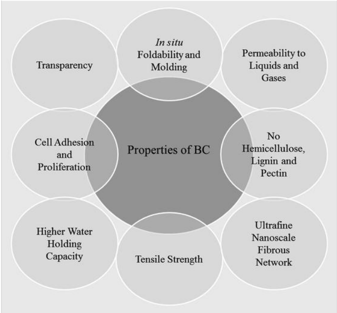
However, in the current review, we have focused mainly on the applications of BC in various fields, ranging from conventional food to modern functional foods, cosmetics, nutraceuticals, cosmeceuticals and drug delivery. This review will provide the readers an understanding of the role of BC as a functional additive, formulation stabilizer, biocatalysts platform, and ingredient for food, cosmetics and drug delivery systems. Furthermore, the review will be helpful for academic researchers and formulation scientists in food, cosmetics and pharmaceutical industries to give new insights to BC in terms of designing some novel BC-based functional foods, nutraceuticals, cosmeceuticals and drug delivery systems.

Better material properties of BC for food cosmetics and drug delivery applications

Although similar in chemical structure, BC has different and superior physical, mechanical and biological features to PC. Due to these superior properties, it finds applications in food, cosmetics, biomedicine and drug delivery (Lin et al. 2013). BC is biosynthesized in its purest form, which is entirely devoid of pectin, hemicelluloses and lignin (Chawla et al. 2009). Hence, BC is capable to be easily refined in comparison to PC (Shi et al. 2014b). As-synthesized, innate or pristine BC is highly porous in nature with high permeability to liquid and gases, and possesses high water-uptake capacity (more than 90 % of its weight) (Klemm et al. 2001). These characteristics of BC are due to the ultrafine network of the ribbon-shaped micro- and nanofibrils (Chawla et al. 2009), which are about 100-fold more thinner than the PC fibres. Such properties of BC make it suitable for application as formulation stabilizer, thickener, and for scrubbing and exfoliation without damaging the skin due to its soft texture of small fibres (Lin et al. 2015; Shi et al. 2014b). Moreover, the biocompatibility, low immunogenic potential and *in situ* foldability further enhance the applicability of BC in the field of biomedicine (Lin et al. 2016). These properties together with tensile strength (Campano et al. 2015) make BC a suitable candidate for dermal applications in cosmetics, and topical and transdermal drug delivery. Due to high water holding and ion exchange capacities, BC is an appropriate material for laxative effects and low cholesterol diet, respectively. Similarly, the transparency (Campano et al. 2015), along with high permeability to liquid and gases, makes BC an appropriate agent for facial mask, contact lenses and drug delivery to wound with ease of wound inspection (Czaja et al. 2006). The individual fibre strength of BC is almost comparable to that of Kevlar and steel (Yano et al. 2005), making it suitable candidate for applications, where high tensile strength is required, e.g., drug loaded bone cement. Several material characteristics of BC for applications under the scope of the current review are depicted in Fig. 3.

Fig. 3

Better material properties of BC



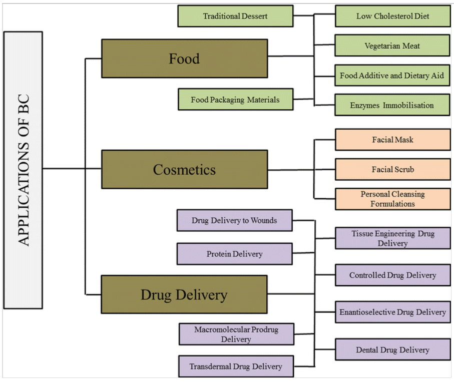
The material properties of BC can be further tailored by using various *in situ* techniques, such as addition of various substances, change in culturing conditions and the use of genetically modified strains, and *ex situ* strategies like physical and chemical modification, specialized drying conditions and electromagnetic irradiation (Krystynowicz et al. 2002; Lin et al. 2013, 2016; Olyveira et al. 2013; Petersen and Gatenholm 2011; Stoica-Guzun et al. 2007; Sulaeva et al. 2015; Yadav et al. 2010).

Applications of BC in food, cosmetics and drug delivery

Due to the abovementioned properties, BC finds various applications in foods, cosmetics and drug delivery. These applications are discussed with detail~~s~~ in the following ~~section~~sections and are summarized in Fig. 4.

Fig. 4

Food, cosmetics and drug delivery applications of BC



Food applications

Being a dietary fibre, BC is considered "generally recognized as safe" (GRAS) by the Food and Drug Administration (FDA) since 1992 (Shi et al. 2014b; Park et al. 2009). BC possesses manifold potentialities in food industries owing to its high purity, a variety of textures and shapes (e.g., particles, spheres, filaments, multi-shaped pulps, films and whiskers), capability to acquire *in situ* changes, such as colours and flavours of culture medium, and easy production process (Shi et al. 2014b). Keeping in view the abovementioned properties, BC can be used as adjuvant in foods and food industry.

Traditional dessert

One of the first uses of BC is the manufacturing of a Filipino traditional dessert with a smooth mouth feel that is called 'nata de coco', whereby coconut water is fermented for the biosynthesis of BC, then the BC is chopped into minute sections and immersed in syrup of sugar. This 'nata de coco' is used as a sweet candy dessert (Iguchi et al. 2000; Klemm et al. 2005, 2006). The 'nata de coco' has turned into a very well-liked food and is now quickly spreading worldwide in the form of a dessert or candy (~~Gama et al.~~Phisalaphong and Chiaoprakobkij 2012).

Low cholesterol diet

BC possesses higher water-holding and cation-exchange capacities than PC with significant serum lipids and cholesterol lowering effect. Thus, fat free, low-cholesterol and low-calorie food commodities can be made with BC (Chau et al. 2008). It might also be employed as a potential candidate to replace the fat in emulsified meat products (Lin and Lin 2004). BC has decreased the quantity of cholesterol in *in vitro* tests through absorption or binding (Stephens et al. 1990). Moreover, the BC gel itself is too tough for biting, but it may become edible by processing it with alginate and calcium chloride or with sugar alcohol. The textures of such BC resemble molluscs and fruit, such as squids and grapes, respectively. The addition of abovementioned substances make BC edible by holding the water in the gelatinous BC, thus making the BC gel easy for cutting off with the teeth. These facts make BC a new material for processed foods, low-calorie desserts and salads (Okiyama et al. 1992).

Vegetarian meat

Vegetarian meat may be prepared by using BC in combination with *Monascus* extract obtained from a natural red pigmented mould (Purwadaria et al. 2010). The composite is stable against changes in colour and morphology, and its flavour is much like natural meat (Jůzlová et al. 1996; Wonganu and Kongruang 2010). The vegetarian meat adds cholesterol-lowering effect to the other advantages of BC dietary fibres (Ng and Shyu 2004). Moreover, due to non-animal origin, this meat could be a suitable substitute to animal-based products for certain consumers with dietary restriction.

Food additive and dietary aid

BC has also been explored for its use as a potential gelling, thickening, suspending and stabilizing agent in the food industry (Shi et al. 2014b). BC also acts as a heat-stable suspending agent, and as a filler for the reinforcement of fragile food hydrogels, improving the worth of pasty foods by decreasing their stickiness (Okiyama et al. 1992). Moreover, BC (0.2–0.3 %) significantly increases the gel strength of Tofu (food made by coagulating and pressing soy milk), providing firmness and better texture. BC has also endowed Kamaboko (processed Japanese seafood) with better stiffness and brittleness, almost eliminating the springiness. This modified Kamaboko could better endure the aging process and human demand for sensory evaluation was still satisfied (Okiyama et al. 1993). Likewise, addition of BC, synthesized in agitated culture conditions, to chocolate drink prevented the precipitation of the cocoa due to the retention properties of BC mesh. There was a greater heat stability as the viscosity remained unchanged after the heat sterilization (Okiyama et al. 1993). Upon addition of BC into creamy condiment, the stickiness of the latter could be noticeably improved so that it would be easier to serve it quantitatively using a spoon (Shi et al. 2014b). Similarly, food items having BC can maintain their humidity for minimum storage period of 1 month. The contour of ice-cream having BC was maintained for at least 60 min after it was removed from freezer, which would otherwise melt over the same time in the absence of BC (Shi et al. 2014b). Hence, it is evident that BC could be extensively used in processed foods to improve the stability over a wide range of temperature, pH and freeze–thaw environments. These findings further clarify that BC could be widely applicable to processed foods to improve their quality and storage conditions.

Enzymes and cells immobilization

The production of high amount of food needs the use of modern technologies. Immobilization of enzymes and cells is one of such technologies. In case of certain food items, fermentation industry has been greatly assisted by the application of immobilized enzymes that can change several of their functioning parameters (Kilara et al. 1979; Fernandes 2010).

In the last decade, there has been ~~a growing interest in the use of cellulose materials~~an emergent interest in the use of cellulosic biomaterials in bioprocessing technologies (Koutinas et al. 2012). Pure BC has exclusive material properties differing from PC and ~~has therefore~~therefore has engrossed the attention as a new functional biomaterial (Petersen and Gatenholm 2011). In a research conducted by Wu and Lia (2008), glucoamylase was immobilized on BC beads. The BC beads in wet form having smallest size (500–1500 μm) were best for immobilization of enzyme in comparison to other types of BC beads. The stability of enzyme was increased against changes in lower temperature and pH values (Wu and Lia 2008). Likewise, the activity of immobilized enzyme via periodate oxidation method was increased by ca. 40 %. Being pH- and temperature-dependent, there was still ca. 46 % of the activity after 14 times of repeated use (Wu et al. 2013). Some other researchers used yeast for repeated batch fermentation for wine-making that was immobilized on BC. The immobilized yeast promoted the cost effectiveness of the manufacturing process by reducing the expenses for preparation of inoculum, whereby the yeast was recovered by simple separation at the end of the fermentation process (Nguyen et al. 2009; Ton and Le 2011). No significant difference was found for ethanol yield by yeast immobilized either on BC or calcium alginate (CA) (Montealegre et al. 2012). However, in another study, Kirdponpattara and Phisalaphong (2013) immobilized yeast using composites of BC with CA (BC-Al) with high chemical, thermal and mechanical stability, suitable porosity, pore size and hydrophilicity. Thus, in terms of ethanol production, the yeast immobilized on BC-Al substrate was more efficient than the suspended culture and culture immobilized on CA matrix. The efficient ethanol production can be ascribed to the water uptake capacity and properly interconnected porous structure responsible for appropriate mass transfer during the process (Kirdponpattara and Phisalaphong 2013).

BC-based composites can be used for various important enzymes and cells immobilization. Similarly, the immobilization of *Corynebacterium glutamicum* using BC as a support was carried out by adsorption and subsequent incubation for the synthesis of L-lysine (Tam and Huong 2014). The immobilized cells were used eight times for repeated fermentation. The lysine yield was 95 % in the eighth repetition of reusing immobilized cells. Regarding stability and cell viability, the immobilized cells had 80 % cell survival in sterile water (pH 7) stored at 40 °C for 30 days (Tam and Huong 2014).

Laccases obtained from different sources are extensively used in food industry (Osma et al. 2010). These laccases find applications in improving the organoleptic properties of foods, such as the colour of tea-based products, the stability of the beer and wines, the taste and flavour of cacao nib, and the flavour and colour of some vegetable oils. Laccase may also improve the quality of certain foods, such as sauces, pastes, puree, concentrates, and soups by the process of deoxygenation (Osma et al. 2010). Likewise, it has been used to decrease the bitterness and darken the colour of chopped olives (in olive–water mixture), control malodour of cysteine, and stabilize the colour and flavour of fruit juices. Using laccase, the mechanical, textural and bread-making properties of flour can be altered, and the elegancy of dough can be enhanced (Osma et al. 2010). In a study, Chen et al. (2015) immobilized laccase from fungus, i.e., *Trametes versicolor* on the BC sponge via cross-linking with glutaraldehyde and physical adsorption. The immobilized laccase through cross-linking showed wider pH range for good catalytic activity and higher stability in comparison to free as well as adsorbed one. The immobilized laccase retained 69 % of its original activity after 7 cycles (Chen et al. 2015).

Furthermore, BC has been used for immobilization of enzymes, such as horse radish peroxidase, glucose oxidase and laccase for biosensors, bioanalysis and enzymatic biofuel cell (Chen et al. 2011; Lv et al. 2016; Wang et al. 2010; Zhang et al. 2010), which is beyond the scope of this review.

From the aforementioned literature, it is evident that BC beads and cubes have potential for the immobilization of enzymes and cell systems for improving yield, quality and stability of food product in food industry. Moreover, these studies show the potentials of BC for the immobilization of other enzymes in techno-economically feasible manner for food production.

Food packaging

BC works as a food packing to confirm the safety and increase shelf-life of the products. Antimicrobial ingredients, ethylene and oxygen scavengers, and moisture and taint removers are all used in active BC-based packaging systems (Tomé et al. 2010). Moreover, modified BCM with tailored surface and barrier properties have been prepared by controlled heterogeneous esterification with hexanoyl chloride (Tomé et al. 2010). The esterified BCM showed an increased hydrophobicity, while maintaining the bulk structure of the pristine BC. The barrier properties was measured by its permeability to water vapour at different relative humidity, and humidified nitrogen, oxygen and carbon dioxide. About 50 % decrease in both water and gas ~~permeability through modified BCM was observed~~permeability was observed for the modified BCM (Tomé et al. 2010).

Furthermore, Jipa et al. (2012) designed biodegradable BC and sorbic acid (BC–SA) based monolayer and multilayer films by incorporation of SA as antibacterial agent. The study showed that concentration of both BC and SA affected the sensitivity to water, rate of SA release, and antibacterial activity of BC–SA mono- and multilayer film. There was no SA degradation during film preparation (Jipa et al. 2012). Faster SA release rate was observed at lower concentration, but it became significantly slower at higher SA concentration due to slower dissolution rate of the formed SA crystals. Moreover, SA release rate was faster from the monolayer films compared to the multilayer films. The antimicrobial effect of BC-SA was tested against *Escherichia coli* K12-MG1655, which indicated that the new BC films possess promising antimicrobial properties (Jipa et al. 2012).

Similarly, composite materials with antimicrobial activities were designed, whereby poly(vinyl alcohol) (PVA) acted as polymeric matrix and grinded BC as reinforcing fibres (Dobre et al. 2012). SA was used as an antimicrobial agent due to its recognized preservative function in the food industry. The designed film showed antibacterial effect against *Escherichia coli* (Dobre et al. 2012), which revealed that new composite film could be promising antimicrobial material for food packaging.

From the above discussion, it is evident that BCM is a promising and interesting biopolymer for the development of materials with potential applications in the packaging industry with antimicrobial property and durability.

Studies related to applications of BC in food and food industry are summarized in Table 1.

Table 1

BC applications in food

Food, related item or process	Form of BC	Purpose of BC	References
Nata de coco	BC slices	Main structure	Iguchi et al. (2000)
Low cholesterol diet	Powdered BC	Fat adsorbent	Chau et al. (2008), Lin and Lin (2004), Stephens et al. (1990)
Vegetarian meat	BC sheets	Structural component, fat adsorbent	Jüzlová et al. (1996), Purwadaria et al. (2010), Wonganu and Kongruang (2010)
Pasty food and jams	Aqueous paste	Heat-stable suspending and bulk forming agent	Okiyama et al. (1992)
Tofu	Aqueous paste	Gelling agent	Okiyama et al. (1993)
Kamboko	Aqueous paste	Hardening agent, texture modifier	Okiyama et al. (1993)
Chocolate drink	Aqueous paste	Stability against heat	Okiyama et al. (1993)
Ice-cream	Aqueous paste	Hardening agent, stability against freeze–thaw process	Okiyama et al. (1993)
Glucoamylase	Beads	Solid support to increase enzymatic activity	Wu and Lia (2008), Wu et al. (2013)
Wine	BC pieces	Solid support to increase activity of yeast	Montealegre et al. (2012), Nguyen et al. (2009), Ton and Le (2011)
Fungal laccase	BC sponge	Solid support to increase activity of laccase	Chen et al. (2015)
L-lysine	BC cubes	Solid support to increase activity and cell viability	
Food packaging	BC sheets, film and powdered BC	Hydrophobic and antimicrobial packaging	Dobre et al. (2012), Jipa et al. (2012), Tomé et al. (2010)

Cosmetics applications

Cosmetics are substances that are used to improve some of the organoleptic properties of the human body (Hasan et al. 2012). Cosmetics include products that are applied to the human body for altering the appearance, enhancing the attraction, and cleansing or beautifying the body parts without affecting the normal body functions or structure (Hasan et al. 2012). Currently, the majority of the cosmetics are used by customers to boost their beauty without bearing in mind the ill-effects on body, for example, toxicity concerns associated with parabens (Nagel et al. 1977; Darbre and Harvey 2008). In order to avoid harmful effects to the consumers, natural skin-care products are recommended, which utilize herbal or natural ingredients (Hasan et al. 2012).

In this context, cellulose fibrils are applied in cosmetics to stabilize oil-in-water (O/W) emulsion without the addition of any of surfactant. Such formulations may not be irritant to sensitive skin due to the absence of any surfactant (Hasan et al. 2012). BC has also been reported to be an exceptional non-allergenic biopolymer for use in the cosmetics. The various application of BC in cosmetics are discussed in the following sections.

Facial mask

BC facial masks are of great interest as cosmetic devices to treat dry skin due to its biodegradability, low toxicity and ability to hydrate the skin (Amnuaikit et al. 2011). In a study, one group of volunteers was asked to ~~apply~~put moist towels ~~to~~on the face for 25 min, while the second group was ~~assigned~~allocated to apply the translucent BC facial masks for the same period (Amnuaikit et al. 2011). During the subsequent week, the groups were interchanged to the alternative treatment. Skin dullness, texture, elasticity, sebum content, moisture content and desquamation levels were evaluated using a system used for routine skin counselling before applying and after 5 min of removing the towels and trial product (Amnuaikit et al. 2011). The user satisfaction about the BC mask was also investigated. The BC masks augmented the moisture contents of the skin significantly than moist towels upon a single treatment. No obvious effects on other characteristics of skin were observed. The ~~cellulose mask product~~BC facial masks rated around 4 out of 5 on the satisfaction rating scale (Amnuaikit et al. 2011). The BC mask ~~could be used as a natural cosmetic product for increasing moisture content of the skin~~can be used for increasing moisture content of the skin. The responses about user satisfaction in questionnaire-based study revealed that the BC facial mask was acceptable to consumer (Amnuaikit et al. 2011).

Similarly, BC with and without glycerine was evaluated for skin irritation potential in human subjects (Almeida et al. 2014). There was no significant difference in terms of transepidermal water loss (i.e., absence of barrier disruption) and erythema with zero clinical score, except for few subjects with mild skin irritation. Moreover, addition of glycerine gave a significantly higher skin moisturizing effect, suggesting its potentials for moisturizing facial mask (Almeida et al. 2014).

In a patent, BC facial mask was fabricated with holes for eyes, mouth and nose (Zhong 2008). The author claimed that such mask may be suitable for repeated or prolonged use for skin beautifying purpose, skin nutrition, and moisturizing and cosmetic effects (Zhong 2008). Similarly, facial mask composed of BC membrane containing ginseng extracts has shown promising results in terms of moist feel, overall user satisfaction and skin elasticity in women over 30 years of age (Lee et al. 2011). In another study, BC facial mask with sodium bicarbonate (5 g), monohydrated citric acid (4 g), ascorbic acid (0.5 g) and salicylic acid (0.05 g) has been used for exfoliative and brightening purposes (Legendre 2008). In this study, the author has also claimed BC mask with thermal plankton as a constituent for its anti-wrinkle effects (Legendre 2008).

BC gel with controlled release of silk sericin were developed with improved moisture holding capability in comparison to commercially available paper mask (Aramwit and Bang 2014). Upon peel test using porcine skin, it was revealed that BC-based gel was biocompatible and less adhesive (peeled without pain) than paper mask (Aramwit and Bang 2014). The prepared gel may find potential applications in medicated cosmetics as anti-wrinkle, antiaging and moisturizing facial mask.

Keeping in view the above studies, it is worth mentioning that in addition to the aforementioned application, BC-based membranes could also be used for treating various skin conditions including xerosis, atopic dermatitis and psoriasis, whereby moisturizing effect is needed in addition to pharmacotherapy.

Facial scrub and medicated cosmetics

A facial scrub containing powdered BC and natural ingredients including olive oil, ascorbic acid (Vitamin C), *Aloe vera* extract and powdered glutinous rice was formulated (Hasan et al. 2012). Using plate–plate rheometer, both commercial and formulated facial scrubs showed shear thinning behaviour (non-Newtonian liquid). The formulated facial scrub possessed relatively higher viscosity at lower shear rates in comparison to the commercial one, but both possessed nearly comparable viscosities at higher shear rates. The tested samples were capable of drying out after 10 min at ~30 °C (room temperature). This novel formulated facial scrub containing BC as major ingredient engrosses the attention of cosmetics formulators for the development of facial scrub with natural ingredients, making it safe for skin. Moreover, Lin et al. (2015) claimed cosmetic containing fragments of BC film in the range of 0.05–1.0 % by weight. By adding the fragments of BC in the cosmetic not only improved the transdermal permeation of active ingredients present in the cosmetic, but also provided skin moisturizing function, sebum absorption and skin exfoliation (Lin et al. 2015). It has also been claimed that due to high water holding capacity and good gas permeability, BC is an appropriate carrier for cosmetically active ingredients including moisturizers, such as salicylic acid or hyaluronic acid whitening agents, such as kojic acid or ursolic acid, anti-wrinkling agents (e.g., polypeptides, and exfoliator), growth factors, enzymes, or a combination thereof (Lin et al. 2015). Moreover, according to authors (Lin et al. 2015; Tournilhac and Lorant 2003), BC-based formulation can find extensive applications in designing the lip, skin and nail care products and long-lasting perfume.

Personal cleansing formulations

The purpose of personal cleansing formulations is remove dirt, reduce sebum and exogenous contaminants, and to control malodour and the skin microflora. In addition to hygienic benefits, surfactants in such formulations damage skin constituents and may entangle in the stratum corneum after washing (Kuehl et al. 2003; Walters et al. 2012). This can lead to allergic reactions and skin irritation, especially in case of sensitive skin (Draelos et al. 2013; Kuehl et al. 2003). In this regard, BC ~~produced~~biosynthesized in agitated culture conditions (Ag-BC) ~~showed~~exhibited the highest stabilizing effect for O/W emulsion among all the inspected cellulose-based materials (Ougiya et al. 1997). It was demonstrated that BC fine fibrils acted as a scaffolding structure and a mechanical barrier, interrupting the coalescence of oil droplets. Thus, the emulsion was stabilized without reducing the interfacial tension as occurs in the case of surfactants (e.g., sorbitan monolaurate). Due to its thinner fibrils, Ag-BC would protect a larger surface area of the droplets of oil in the form of mechanical barrier than any other cellulose-based material. Moreover, this emulsion was also stable against changes in temperature and pH, and against addition of salt in comparison with xanthan gum- and sorbitan monolaurate-based formulations. One of the potential applications of this O/W type emulsion could be the formulation of body parts cleansing products, especially for sensitive skin.

In a patent, a personal cleansing formulation consisting of liquid matrix, i.e., water, a lathering surfactant and an external structuring agent, comprising both BC network and a cationic polymer e.g., cationic starch derivatives and cationic cellulose derivatives or mixtures of these, was claimed to be formulated (Heath et al. 2012). The particles of these formulations were suspended in the liquid matrix with pH-values of less than ca. 4.0 or 7.0. Such compositions provided good lathering and easily rinse off properties without any unwanted filmy or slimy hand feel. The presence of particulate matters improve cleansing and exfoliation with conditioning benefits, and without any irritation or damage to the skin. A pH-value less than ca. 4.0 is especially preferred for salicylic acid formulations (Heath et al. 2012). Such formulation may be used for body cleansing for sensitive skin without any irritation, especially for body parts, where consumer's hand feel is important. Moreover, using compositions of such formulation at pH-value of less than ca. 4.0, salicylic acid formulation for personal cleansing can be formulated. Such formulations may be used to clear and prevent skin blemishes and pimples. These may also be used for the treatment of skin conditions with scaling or skin overgrowth (Heath et al. 2012).

Contact lenses

Other than optical indications, contact lenses find wide range of applications including cosmetic or decorative purpose (Rubinstein 2003; steinemann et al. 2005). BC is one of the potential candidates for fabrication of contact lenses due to its transparency, light transmittance, and permeability to liquid and gases. BC-based contact lens was fabricated by pouring high viscosity BC solution (in 1-butyl-3-methylimidazolium chloride) to a mould. Upon treating the solution with isopropyl alcohol followed by water, a clear BC membrane was precipitated, which spontaneously detached from the mould surface and the residual solvent diffused to the water. The hydrated BC contact lens retained its shape and transparency for a time of more than 8 weeks (Levinson and Glonek 2010). Similarly, transparent polymeric hydrogel was prepared by combining BC and 2-hydroxyethyl methacrylate polymer. The fabricated biomaterial possessed ca. 40 % (w/w) water content with good mechanical strength and integrity (Li et al. 2010) and had the ability to be used as contact lenses. Apart from optical and decorative purposes, these contact lenses can find potential applications for drug delivery to the cornea. Moreover, the ability of BC to take colour of the medium (Shi et al. 2014b) can be exploited for design of coloured and appealing contact lenses with transparent centre for the pupil, provided that the biocompatibility is not compromised by the colourant(s).

The applications of BC and BC-based products in cosmetics are summarized in Table 2.

Table 2

Applications of BC in cosmetics

Cosmetic product	Form of BC	Purpose of BC	References
Facial mask	BC sheets	Moisturizer	Amnuaikit et al. (2011)
Facial mask	BC-glycerine composites	Moisturizer	Almeida et al. (2014)
~~Facia~~Facial mask	BC membrane	Moisturizer	Zhong (2008)
Facial mask	BC-ginseng	Moisturizer and carrier	Lee et al. (2011)
Facial mask	BC with cosmetically substances	Moisturizer and carrier for the actives for exfoliative, brightening and anti-wrinkle purposes	Legendre (2008)
Facial mask	BC-sericin composites	Moisturizer and carrier for silk sericin	Aramwit and Bang (2014)
Facial scrub	Powdered BC	Viscosity enhancer	Hasan et al. (2012)
Facial scrub	BC fragments	Moisturizer, sebum absorber and skin exfoliator	Lin et al. (2015)
Carrier for cosmetically active ingredients	BC fragments	Prolongs the contact time of the cosmetically active ingredient with the skin surface	Lin et al. (2015)
Foundation make-up	BC fragments	Stable make-up with less number of touch-ups and lesser amount required	Lin et al. (2015)
Personal cleansing product	BC fibres (synthesized in agitated conditions)	Surfactant free emulsion for sensitive skin	Ougiya et al. (1997)
Personal cleansing product	BC particles	Cleansing and exfoliation	Heath et al. (2012)
Contact lenses	Regenerated BC sheet	Film-forming agent	Levinson and Glonek (2010)
Contact lenses	BC-based hydrogel	Film-forming agent	Li et al. (2010)

Drug delivery applications

Drug delivery to wounds

Studies have suggested that fluid, particularly exudates from chronic wounds may inhibit healing process (Vowden and Vowden 2003). An excessively wet environment may lead to wound and skin maceration resulting in prolonged wound healing, whereas a dry wound will also heal more gradually due to lack of moisture required for cell migration (Benbow and Stevens 2010). Hence, exudates reduction looks like a key parameter for normal healing process (Sulaeva et al. 2015). Being an excellent absorbent (Gayathry and Gopalaswamy 2014) and skin moisturizer (Amnuaikit et al. 2011), BC can be an ideal candidate for lowering or removing the wound exudates, while at the same time maintaining a moist environment (Sulaeva et al. 2015). However, innate BC is devoid of antimicrobial activity against the wound deteriorating pathogens.

To achieve such goals, a BC film with antibacterial property was fabricated, whereby a lyophilized BC film was dipped in a benzalkonium chloride (BZK) solution followed by further lyophilization (Wei et al. 2011). Water uptake capacity, a feature important for wound dressing system, was also attained with a swelling ratio of 37.3 and 26.2 for saline solution and deionized water, respectively. A prolonged (at least 24 h) stable antibacterial activity was achieved against *Staphylococcus aureus* along with a higher water uptake capacity. Thus, BZK-loaded BC film may act as a potential functional wound dressing system for treatment of acute traumas.

Recently, Pavaloiu et al. (2014b) studied the release of the antibiotic amoxicillin (AMX) from BCM at nearly neutral (7.4) pH conditions. The concentration of AMX significantly influenced the drug release (Pavaloiu et al. 2014b). Among the other factors, there was a significant contribution of glycerol (as plasticizer) to *in vitro* drug release. The common topical drug delivery enhancer cetyl trimethyl ammonium bromide did not show any positive impact on the in vitro release of the drug. This system might provide a suitable way for antibiotic delivery to the wound.

The antimicrobial activity of antibiotics with prolonged drug release behaviour from BC was assessed *in vitro* using ampicillin (AMP) and gentamycin (GM) (Kaplan et al. 2014). For the assessment of exudate retention, the water uptake capacity of the BCM was found to be 65.6 ± 1.6 % in phosphate buffer saline (PBS). The drug loading was 99 and 48 mg/cm^2 for AMP and GM, respectively. The BCM released only trace amount (0.107 % of AMP and 0.113 % of GM) within 24 h. Thus, with no burst release, the amount of drug released within 7 days was 28 and 17 % for AMP and GM, respectively. Furthermore, due to sufficient amount of the drug in prolonged release manner, the antibacterial activity against *Pseudomonas aeruginosa*, *Staphylococcus epidemidis*, *Staphylococcus aureus*, *Enterococcus feacalis* and *Escherichia coli* prevailed for as long as 3 days of incubation period (Kaplan et al. 2014). Furthermore, Rouabhia et al. (2014) covalently attached the GM to the surface of chemically modified BC, i.e., BC-RGDC-GM, where RGDC is a peptide composed of arginine, glycine, aspartic acid and cysteine. In addition to its bactericidal effect, BC-RGDC-GM was devoid of any toxicity for human skin fibroblasts (Rouabhia et al. 2014). Likewise, the *in vitro* release of tetracycline from BC was assessed as function of electron beam irradiation, which considerably decreased the diffusion of tetracycline (Stoica-Guzun et al. 2007). Hence, BC-based drug delivery to wound is a feasible way with its ability to absorb exudates as well. Furthermore, silver sulfadiazine (SSD) particles impregnated into BC revealed *in vitro* antimicrobial activity, human epidermal cells biocompatibility, and good epithelialization and wound healing ~~activity in rat models with burns~~ for burns in a rat model (Luan et al. 2012; Wen et al. 2015). A step further, a novel wound dressing system consisting of polyhexamethylene biguanide (PHMB) and the never dried BC (BC-PHMB) was evaluated for safety through *in vitro* cytotoxicity, haemolysis, sensitization in guinea pigs, irritation potential in rabbits and acute systemic toxicity (Serafica et al. 2010). In addition to good antimicrobial effects, wound healing in animal models showed that the BC-PHMB wound dressing rehabilitated 70 % of the wounds in comparison to 0, 20 and 50 % for the air-exposed, hydrogel treated and hydrocolloid treated wounds, respectively. Upon clinical effectiveness testing in humans, BC-PHMB showed promising results for wound healing of deep pressure wounds and venous leg ulcers (Serafica et al. 2010). Furthermore, in patient, this wound dressing system was more promising than the other commercial dressing in terms of bacterial load reduction and pain management (Haemmerle et al. 2012).

Though not a drug delivery system, BC has also been investigated as promising antimicrobial film for wound dressing with various agents, such as deacetylated chitosan (Butchosa et al. 2013), chitosan (viral protective membrane) (Wanling et al. 2012), montmorillonite (Ul-Islam et al. 2013), and nanoparticles of silver (Dobre and Stoica-Guzun 2013), copper (Pinto et al. 2013) and titanium dioxide (Khan et al. 2015). However, such metallic nanoparticles are infamous due to their possible concerns with human health, such as hepato-, neuro-, photo-, geno-, cyto- and dermal toxicity, formation of oedema, and hyperplasia (Koohi et al. 2011; Lu et al. 2010; Prabhu et al. 2010; Ray et al. 2009; Samberg et al. 2010; Wang and Wang 2014; Wang et al. 2014). The histopathological changes in the bones, hearts and kidneys of guinea pigs, and lack of studies about toxic effects with prolonged use of such nanoparticles further limit their practical applications (Korani et al. 2013).

Tissue engineering drug delivery

BC-based materials have also been demonstrated for drug delivery applications in the field of tissue engineering and regeneration. In this scenario, Mori et al. (2011) studied the release of antibiotics (GM and vancomycin) from a BC-based bone cement. It was demonstrated that ~~incorporating BC into the bone cement prevented compression and fracture fragility, improved fatigue life and increased antibiotic elution~~by incorporating BC into the bone cement, the compression and fracture fragility were prevented, while fatigue life and antibiotic elution were enhanced (Mori et al. 2011). Such antibiotic containing BC-based cements may have clinical relevance, when high levels of antibiotic release are required, while the mechanical properties of the cement are not compromised. In addition, bone morphogenetic protein-2 (BMP_2) loaded BC was investigated for localized delivery system with osteogenic potentials in tissue engineering (Shi et al. 2012). The system was enough biocompatible and was capable (*in vitro*) to differentiate the mouse fibroblast-like C2C12 cells into osteoblasts. Upon *in vivo* studies on subcutaneous implants, the BMP_2 loaded BC scaffold was capable for bone formation with higher calcium concentration than the pristine BC scaffolds (Shi et al. 2012). Hence, it can be concluded that BC is a good carrier for localized delivery of therapeutic candidates, such as BMPs in tissue engineering.

Controlled drug delivery

Frequent dosing, fluctuation in plasma drug concentration and patient non-compliance associated with shorter half-lives of drugs necessitate such drugs to be formulated into controlled release dosage forms. Researchers have made some attempts in order to control the drug release from a BC-based delivery systems. For this purpose, Amin et al. ~~(2012a, b)~~(2012a) reported the use of powdered BC to coat paracetamol tablets using a spray-coating technique (Amin et al. 2012a). The study demonstrated that BC formed high-quality, foldable, flexible and uniform soft films without adding any plasticizer that was comparable to the film of ethyl cellulose aqueous dispersion (Aquacoat ECD). *In vitro* drug release rate was dependent on the BC film thickness and was slower (200 min for maximum release) for coated tablets with 200 µm thick film, than uncoated tablets ~~(~~i.e., 100 min for maximum release~~)~~ (Amin et al. 2012a).

In another study, Păvăloiu et al. (2015) described the swelling behaviour of mono- and multilayer hydrogels based on BC and gelatin (BC-G). The findings indicated that the swelling of BC-G hydrogels was higher in acidic pH as compared to the basic one due to the polyelectrolyte character of gelatin. Moreover, the concentration of gelatin had a direct relation with the swelling of BC-G hydrogel, while the coating of hydrogel with additional BC has inverse effects on the swelling rate (Păvăloiu et al. 2015). Due to its swelling in acidic condition of the stomach, the hydrogels may find potential applications in gastro-retentive drug delivery.

Amin et al. (2014) studied the potential of stimuli-responsive BC-g-poly(acrylic acid-co-acrylamide) hydrogels synthesized by graft copolymerization using the microwave irradiation technique for oral controlled drug delivery (Amin et al. 2014). The hydrogels were suitable for drug loading due to the highly porous morphology. Being pH-responsive, swelling of hydrogels was less in acidic media, reaching maximum swelling at neutral pH. Similarly, the hydrogels exhibited lesser drug (theophylline) release in SGF than SIF (Amin et al. 2014). Hence, it was suggested that such type of hydrogels may be suitable for drug delivery to the lower parts of the gastrointestinal tract, e.g., peptides, proteins, and acid-labile drugs, and targeted delivery in colonic diseases.

In another sustained drug release study, BC-based hydrogels in combination with carboxymethyl cellulose (BC-CMC) were investigated for controlled drug delivery using ibuprofen sodium (IbuNa) as a model drug (Pavaloiu et al. 2014c). The results of this study showed that the CMC content and epichlorohydrin (cross-linker) concentration influenced the swelling and drug release properties of the hydrogels, which were governed by pseudo-Fickian diffusion. These preliminary findings suggested that BC-CMC hydrogels could be exploited as components in controlled drug delivery applications.

Likewise, mono- and multilayer films of BC, PVA and chitosan (BC-PVA-chitosan) have been reported for controlled release of IbuNa (Pavaloiu et al. 2014a). The drug release was pH sensitive, which followed the Fickian model of diffusion. Moreover, the rate of drug release was inversely proportional to the concentration of BC in the film with pronounced effect in case of multilayer films. Shi et al. (2014a) fabricated hybrid hydrogels of BC and sodium alginate (SodAl) as a dual-stimuli-responsive system. The pH and electric field stimulus-responsive swelling and drug release behaviours of the BC-SodAl hydrogels were investigated *in vitro* using Ibu as a model drug. The swelling ratio was lower at acidic pH (less than 8-fold), while higher at alkaline pH (more than 13-fold). The electric field of 0.5 V increased the swelling ratio from 8-fold (at 0 V) to 14-fold. The release of Ibu was slower in acidic conditions and faster in alkaline conditions (Shi et al. 2014a). Furthermore, the drug release from the BC-SodAl hybrid hydrogels could be boosted with the application of an electric stimulus (Shi et al. 2014a). The BC-SodAl hybrid hydrogels with both pH- and electro-response are therefore new auspicious candidates for oral controlled drug delivery.

Proteinaceous therapeutic candidates have an extended role in several fields of medicine, such as diagnostics, vaccines, inflammatory diseases and cancer (Malik 2008). The increased use of pharmaceutical proteins could be justified by some beneficial properties in comparison to small-molecule drugs (Vermonden et al. 2012). However, the subtle 3D conformation of proteins is a limitation to the use of such therapeutic candidates due to chemical and proteolytic degradation, aggregation and physical unfolding (Bruno et al. 2013; Manning et al. 1989, 2010; Yang 2015). This kind of instability always results in loss of bioactivity and frequently provokes an immune response (De Groot and Martin 2009; Kaliyaperumal and Jing 2009). Furthermore, oral administration of proteinaceous drugs is trickier due to acidic pH and high proteolytic activity of stomach that may lead to destabilization and degradation of the protein structure (Vermonden et al. 2012). In addition, first-pass effect of the liver, fast renal clearance and consequently the short half-lives of proteinaceous drugs require frequent intravenous administration that is associated with patient~~'s~~ discomfort, inconvenience and non-compliance (Harris and Chess 2003; Tang et al. 2004). Due to the abovementioned limitations, the delivery of proteins is an immense challenge in the field of modern medicine. Fabrication of hydrogels is one of the approaches for the improvement of pharmacodynamics and pharmacokinetics of proteinaceous drugs (in intact form) with improved patient's compliance (Peppas et al. 2004).

BC possesses abundant number of hydroxyl groups in addition to the hydrophilicity and biocompatibility (Pandey et al. 2014; Sulaeva et al. 2015). Such properties enhance the chemical modification capacity with a range of chemical groups, which could modulate the loading and release of drugs from the delivery system. BC has been employed for the oral delivery of protein by fabricating BC-based hydrogels. In this perspective, Ahmad et al. (2014) investigated stimuli-responsive BC-grafted polyacrylamide (BC-γ-PAM) hydrogels for oral delivery of proteins (Ahmad et al. 2014). In this case, BC-γ-PAM hydrogels were fabricated with the help of electron beam irradiation without any cross-linker, thus eradicating any potential toxic effects associated with it (Ahmad et al. 2014). The hydrogels showed potential for protection of bovine serum albumin (BSA) from gastric (acidic) environment with <10 % BSA release in simulated gastric fluid (SGF). Moreover, the released BSA was stable and bioactive with enhanced penetration across the intestinal mucosal tissue that was evident from *ex vivo* penetration experiment. The fabricated hydrogels were biocompatible, non-toxic and safe for *in vivo* applications (Ahmad et al. 2014).

Müeller et al. (2013) studied BCM for loading and release of BSA as a model protein for delivery systems. It was demonstrated that the protein release was controlled by diffusion. In this study, the never-dried BC had more protein loading than freeze-dried BC, which might be related to the changes in the fibrous network during the process of freeze-drying (Müller et al. 2013). The study also demonstrated that the integrity and bioactivity of proteins could be maintained during the process of loading and release. In another study, BC and polyacrylic acid (BC-PAA) hydrogels were investigated *in vitro* for controlled delivery of BSA as model protein (Amin et al. 2012b). The study demonstrated that BC-PAA hydrogels were pH-dependent with lower swelling ratios (<1000 %) below pH 5 and higher (>2000 %, being maximum) at pH 7. Consequently, BSA was released in SGF much slower (15 % at the end of 2 h) and faster in simulated intestinal fluid (SIF) (8 h to release maximum drug for lowest radiation dose and 13–14 h for the highest) (Amin et al. 2012b). The difference in release rates as function of pH were due to the different swelling rates of BC-PAA due to change in pH.

This clearly demonstrated the potential of BC for pH-responsive delivery system of proteinaceous and non-proteinaceous drugs. Such types of drug delivery systems have the capability for controlled oral delivery of peptides, proteins and acid-labile therapeutic candidates.

Enantioselective drug delivery

Approximately more than 50 % of the drugs in practice exist as racemates and about 90 % of these are marketed as racemic mixtures of an equimolar ratio of two enantiomers (Nguyen et al. 2006). Enantioselective drug delivery and deracemization are ~~a~~ key processes in modern medicine~~s~~ and are predominantly significant in the field of pharmaceuticals, as the different diastereomers or enantiomers of a therapeutic candidate often have different bioactivities (Nguyen et al. 2006). Therefore, it is necessary to promote deracemization in pharmaceutical industry and clinical settings to eliminate the unwanted isomer from the product and deliver the desired isomer for optimal treatment, as well as a rational therapeutic control over the patient. In this domain, Bodhibukkana et al. (2006) fabricated BC-based molecularly imprinted polymeric (MIP) matrix system for the enantioselective delivery of ~~from the racemic mixture of propranolol~~*S*-propranolol (from its racemic mixture) through transdermal route. In this study, MIP matrix system with specific enantioselective binding sites for ~~drug~~*S*-propranolol was ~~obtained~~fabricated by *in situ* copolymerization of methacrylic acid~~, using~~in the presence of ethylene glycol dimethacrylate as cross-linking agent (Bodhibukkana et al. 2006). *S*-propranolol was used as a template molecules, which was removed later on. This MIP matrix system exhibited an enantioselective transport of *S*-propranolol. The enantioselectivity for S-propranolol was also revealed by the *in vitro* release of enantiomers employing the skin of rat (Bodhibukkana et al. 2006). Thus, the BC-based MIP membrane might have great potential for application in enantioselective drug delivery system through transdermal route in clinical settings, and deracemization of racemates of propranolol and other racemic drugs.

Dental drug delivery

Dental caries may promote to dental pulp infection, which needs a procedure, known as root canal treatment (RCT), of the affected tooth. The major aim of RCT is to thoroughly decontaminate the root canal system. The morphology of root canal is too complex to access in many humans. In addition, relapse of dental pulp infections is likewise common. In conventional RCT, a paper point made of PC or cotton pellet is employed in order to dry and sterilize the dental root canal. For such sterilization, high absorbency for residue, high biocompatibility and efficient intracanal medication delivery is desired. To achieve this, Yoshino et al. (2013) designed a pointed form of BC with its usability as a novel biomaterial for RCT (Yoshino et al. 2013). BC ~~in pointed form~~point exhibited outstanding ~~expansion and absorption~~absorption and expansion ~~than~~in comparison to the conventional paper points, with a higher tensile strength in wet form. Moreover, BC releases more drug than that from conventional paper points. Owing to the abovementioned finding, BC-drug composite has great potentiality for dental drug delivery and treatment of RCT.

Transdermal drug delivery

Transdermal drug delivery provides an attractive alternate route to both oral drug delivery and hypodermic injection (Prausnitz and Langer 2008; Prausnitz et al. 2004). Since remote times, folks apply different ingredients on the skin for therapeutic purposes, and in the current age, several transdermal formulations have been developed for delivery of drugs to systemic circulation (Prausnitz and Langer 2008). For the same purpose, BCM with and without plasticizer has the potential for transdermal delivery of therapeutic candidates due to absence of barrier disruption and erythema (Almeida et al. 2014). In addition, skin moisturizing effect and good skin tolerance further strengthens the reputed interest of BCM as source for transdermal drug delivery (Almeida et al. 2014). There are few reports that describe the application of BCM for transdermal drug delivery. The rate of drug release can also be tailored by controlling the porosity of BC by physical or chemical means and also by changing the hydrophilicity of the environment. For example, a study was carried out by Olyveira et al. (2013), whereby gamma-irradiated and non-irradiated BCM was studied for *in vitro* drug release in a diffusion cell. It was shown that irradiated BCM has higher pores density than non-irradiated samples, and thus exhibited slower diffusion than the latter one (Olyveira et al. 2013). Likewise, Stoica-Guzun et al. (2007) assessed the effect of electron beam irradiation on the release of tetracycline from BCM as transdermal delivery system. This study showed that electron beam irradiation considerably decreased the *in vitro* diffusion of tetracycline. These findings suggest the potential of BCM in the form of transdermal patches (Stoica-Guzun et al. 2007). Hence, it is concluded that the drug release by diffusion can be tuned by treating BCM with ionizing radiations, giving a new way for physical control over drug release.

Likewise, for therapeutic feasibility in terms of transdermal delivery system, BCM was assessed for the *in vitro* permeation of lidocaine hydrochloride (LHC) and Ibu (model drugs) through human epidermis. The study showed that LHC loaded BCM gave lower permeation rate than that of conventional formulations (Trovatti et al. 2012). In contrast, the permeation study for Ibu quite poled apart, as the *in vitro* permeation rate was almost threefold higher for Ibu-loaded BCM than that of Ibu gel or an Ibu solution in PEG400 (Trovatti et al. 2012). Diclofenac sodium (DS), belonging to the class of NSAIDs, was loaded into BCM (Silva et al. 2014). Using glycerol as plasticizer, BCM was explored as novel nanostructured transdermal delivery systems for DS salt. The drug containing BCM was quite homogeneous and flexible having substantial swelling behaviours. Using human epidermal membranes, *in vitro* diffusion studies showed that DS loaded BCM had permeation rate comparable to marketed patches of DS and significantly lower than that of a commercial gel formulation (Silva et al. 2014). The simplistic preparation method having easy application and the comparable drug release profile clearly demonstrated the enormous potentialities of utilizing BCM in transdermal delivery of DS and other drugs. In a similar context, Pandey et al. (2013) utilized BC dispersion and solution for the preparation of superabsorbent BC-PAM cross-linked hydrogels by microwave irradiation. The hydrogels exhibited a swelling behaviour (maximum at pH 7). The swelling rate was much higher (ca. 2300–2500 %) for hydrogels prepared from BC solution than that of BC dispersion (ca. 900 %). Moreover, the hydrogels sustained the release of theophylline in buffers (pH 7.4) for 24 h (Pandey et al. 2013). The study demonstrates the application of this hydrogel for transdermal delivery of theophylline. However, there is still a need for the *in vitro* drug permeation studies to ~~further~~ make the feasibility clearer.

In a recent study, Huang et al. (2013) investigated the BCM for the *in vitro* controlled drug release of an alkaloid of isoquinoline group, i.e., berberine. In addition to the transdermal controlled drug release experiments, BCM was also tested in SGF, SIF, and acidic and alkaline solutions. The drug release rate was slower in low-pH fluids (such as SGF), intermediate in alkaline fluid and the highest in near-neutral conditions (such as SIF). The drug release was controlled by diffusion. This type of pH-dependent drug release can be correlated to the swelling of BCM at different pH values (Huang et al. 2013). From these findings, it is evident that BC and BC-based hydrogels are feasible for successful application in transdermal drug delivery, and to modulate the percutaneous drug bioavailability.

Briefly, in most of the studied systems with BC, the release of the therapeutic candidates was controlled by diffusion. The rates of drug release were temperature- and pH-dependent, where the latter affects the swelling of the nanofibres drastically and thus the porosity of the material is altered (Huang et al. 2013; Pandey et al. 2013).

Macromolecular prodrug delivery

Besides gastric irritation (Radi and Khan 2006), one of the major concerns associated with Ibu is the shorter half-life that needs its most frequent dosing with associated side effects (Wright 2002). To avoid these concerns, researchers have tried some novel pH-dependent conjugates of non-steroidal anti-inflammatory drugs (NSAIDs) with different macromolecules (Hussain et al. 2009; Peng et al. 2006). BC gives more opportunities for modification by different methods due to the presence of abundant surface hydroxyl groups (Stenstad et al. 2008). One of such attempts was made by Shi et al. (2013), who developed a novel BC-based conjugates of Ibu by esterification between –OH and –COOH groups of BC and Ibu, respectively (Shi et al. 2013). BC-Ibu as a macromolecular prodrug had the capability to control the drug release via the process of hydrolysis of the ester bond under different pH-conditions. The drug release profiles were dependent on the ester bond hydrolysis, faster in alkaline and acid solution, but relatively slower in neutral pH (Shi et al. 2013). Such pH-dependent drug release suggests a great potential of BC-Ibu as a more effective and stable prodrug candidate. However, this strategy can be further applied to other NSAIDs with carboxyl functional group for the preparation of prodrugs. For example, aspirin could be conjugated to BC to avoid gastric irritation and to target colonic cancer, if the ester bond is sufficiently stable in acidic pH.

All the studies discussed above regarding BC-based drug delivery are summarized in Table 3.

Table 3

Applications of BC in drug delivery

Purpose	Therapeutic candidate(s)	Strategy	Finding	References
Drug delivery to wound				
	BZK	Drug loaded BCM	Prolonged drug release and antimicrobial activity	Wei et al. (2011)
	AMX	Drug loaded BCM	AMX- and glycerol-dependent *in vitro* drug release	Pavaloiu et al. (2014b)
	AMP, GM	Drug loaded BCM	Good water uptake capacity, no burst release and prolonged drug release with antibacterial effects	Kaplan et al. (2014)
	GM	Covalently attached to the surface of RGDC-modified BCM	Antibacterial effects without toxicity for human skin fibroblasts	Rouabhia et al. (2014)
	Tetracycline	Drug loaded BCM	Antibiotics release was sustained by electron beam-irradiation	Stoica-Guzun et al. (2007)
	SSD	BCM	*In vitro* antimicrobial activity, human epidermal cells biocompatibility, *in vivo* epithelialization and wound healing activity	Luan et al. (2012), Wen et al. (2015)
	PHMB	BCM	No *in vitro* cytotoxity or haemolysis; no sensitivity, irritation potential or acute systemic toxicity in animals; good antimicrobial effects; promising for *in vivo* wound healing, and more pain reduction than the commercial dressing	Serafica et al. (2010), Haemmerle et al. (2012)
	Deacetylated chitosan, chitosan montmorillonite	BCM	Antimicrobial effects	Butchosa et al. (2013), Wanling et al. (2012), Ul-Islam et al. (2013)
	Metallic nanoparticles (silver, copper, titanium dioxide)	BCM	Antimicrobial effects	Dobre and Stoica-Guzun (2013), Pinto et al. (2013), Khan et al. (2015)
Tissue engineering drug delivery				
	GM vancomycin	BC-based bone cement	~~Presence of BC in the bone cement prevented compression and fracture fragility, improved fatigue life and increased antibiotic elution~~The compression and fracture fragility were prevented, while the fatigue life and antibiotic elution were improved	Mori et al. (2011)

Purpose	Therapeutic candidate(s)	Strategy	Finding	References
	BMP_2	BC-based protein composite	Biocompatible, and capable of *in vitro* fibroblast differentiation and bone formation	Shi et al. (2012)
Controlled drug delivery				
	Paracetamol	BC coated tablets	The flexible BC film sustained the drug release	Amin et al. (2012a)
	–	BC-based hydrogels with gelatine	Potentials for gastro-retentive drug delivery due to more swelling in acidic conditions	Pǎvǎloiu et al. (2015)
	Theophylline	BC-based hydrogels	Lesser drug release in SGF than SIF	Amin et al. (2014)
	IbuNa	BC-based hydrogels	pH-dependent sustained drug release	Pavaloiu et al. (2014c)
	IbuNa	BC-based hydrogels	pH-dependent sustained drug release	Pavaloiu et al. (2014a)
	Ibu	BC-based hydrogels	pH- and electro-dependent drug release	Shi et al. (2014a)
	Propranolol	MIP matrix	Selective transport and release of *S*-propranolol	Bodhibukkana et al. (2006)
	BSA	BC-based hydrogels without cross-linker	Devoid of cross-linker associated toxicity, protection of BSA from gastric conditions, *in vitro* sustained release of BSA, which was stable after loading and release	Ahmad et al. (2014)
	BSA	BCM	More BSA loading in never-dried BCM, and integrity and bioactivity of BSA was maintained after loading and release	Müller et al. (2013)
	BSA	BC-based hydrogels	Lower swelling and lower drug release in acidic pH in comparison to alkaline pH.	Amin et al. (2012b)
Dental drug delivery				
	Trypan blue	BC point	Greater drug release in comparison to paper point	Yoshino et al. (2013)
Transdermal drug delivery				
	Insulin	BCM	Gamma-irradiated BCM has slower insulin release than non-irradiated BCM	Olyveira et al. (2013)
	Tetracycline	Drug loaded BCM	Electron beam-irradiated BCM has slower tetracycline release than non-irradiated BCM	Stoica-Guzun et al. (2007)
	Ibu, LCH	Drug loaded BCM	Slower permeation of LCH than conventional formulations, faster permeation of Ibu than conventional formulations	Trovatti et al. (2012)
	DS	Drug loaded BCM	Permeation rate was comparable to commercial patches and significantly lower than commercial gel	Silva et al. (2014)
	Theophylline	BC-based hydrogels	Sustained release of theophylline	Pandey et al. (2013)
	Berberine	BCM	Drug release was slower in acidic pH, intermediate in alkaline pH and highest in neutral pH	Huang et al. (2013)
Macromolecular prodrug delivery				
	Ibu	pH-dependent ester conjugates	Sustained release of Ibu (faster in alkaline and acid pH, while slower at neutral pH)	Shi et al. (2013)

Conclusion and future prospects

The current review demonstrates that BC is a natural biomaterial with 'GRAS' status, biosynthesized by non-pathogenic bacteria. BC has great potential for application in food, cosmetics and drug delivery systems, in addition to the aforementioned biomedical applications. Nevertheless, there are a limited number of available studies in the field of foods and cosmetics, and there still exists adequate scope for the advanced research in these areas in more detail. For example, cholesterol lowering studies on animals and humans need further attention. Studies on food and cosmetics pave the way for potential applications of BC in nutraceuticals and cosmeceuticals. In terms of nutraceuticals, BC can be further employed in the form of fortified food by adding certain nutritional entities, such as vitamins and minerals to the existing and the new BC-based food items. The traditional dessert may also act as a sweetened vehicle for oral drug delivery, particularly for children. Moreover, due to its bulk-forming and water retention capacity, the fibrous nature of the BC-based food products can be assessed for its laxative effect in the treatment of constipation. BC can be used in O/W emulsion without surfactant, as a substitute to PC and PC-derivatives. This emulsion could be used for cleansing, makeup, and care or treatment of the lips, skin and the eyelashes, as well as treating certain medical conditions of the skin. Furthermore, a comparison between BC produced under static and agitated conditions should be carried out for pure BC in terms of water uptake for sweat retention in cosmetics, exudate retention in wounds, drug loading, drug release, and ~~for~~ physical and chemical modifications.

In the modern era, most of the people rely on cosmetics in one way or the other. By addition of antioxidants and therapeutic agents to BC-based cosmetics, a paradigm shift is expected from conventional cosmetics to cosmeceuticals and medicated cosmetics. It is noteworthy that due to its transparency, light transmittance and biocompatibility, BC and/or its hydrogels can be used for the fabrication of disposable and multiple use contact lenses for cosmetic purpose and optometry, and as ~~ocular~~ implants for ocular drug delivery.

BCM provides a good tool for delivery of antibiotics to the wound with potentials for exudates retention and moisturizing environment that are favourable for wound healing. These studies lack experiments on wound models to study the favourable properties of pristine and antibiotics loaded BCM for *in vivo* wound healing.

The fabrication of BC-based hydrogels has been tested with several polymeric matrices, such as PAA, PVA and PAM. However, many other polymeric biomaterials could be tested while considering specific interactions between carriers and drugs that might tailor the drug release. Despite of several studies regarding the oral delivery of proteins, only BSA as model protein has been studied. There still exists a space for research ~~on the~~about loading, release and stability studies of other proteins with therapeutic value.

Regarding transdermal drug delivery, BC-based delivery systems have shown promising results in term of biocompatibility (pure BC) with skin, and *in vitro* drug diffusion studies. However, further *in vivo* studies for skin irritation potentials of drug loaded BC and *in vivo* bioavailability of drugs from the BC-based delivery systems with and without penetration enhancer(s) are needed.

As discussed in some of the abovementioned studies, drug release is controlled by the process of pH-dependent diffusion, which could be further tailored by additional physical treatments or chemical modifications. Such approaches would enable a sophisticated control over the drug release, particularly in a response to body stimuli, such as temperature above normal, i.e., fever condition and tumour micro-environment. Moreover, BC-based nanogels would be helpful for invasive targeted delivery of proteinaceous and non-proteinaceous drug, provided that such nanogels are biodegradable *in vivo*. Such nanogels could also be used in the form of biomolecule-sensitive ~~hydrogels~~ delivery systems, e.g., glucose-sensitive hydrogels for delivery of insulin. Moreover, such biodegradable hydrogels can also be used for targeted drug delivery to tumour (acidic pH), provided that suitable nanogels are formed that are more sensitive to slight changes for invasive drug delivery. In addition, due to the presence of several-OH groups on its surface, BC has also potential for the formation of macromolecular prodrug by covalent conjugation. The Ibu conjugates can be further tested *in vitro* in the presence of enzymes (microbial esterases and cellulases) and in ~~vivo~~ animal models to predict the *in vivo* performance. Moreover, this approach can be further tailored for pH-dependent (more stable in acidic environment) sustained release of other therapeutic candidates associated with gastric irritation (e.g., NSAIDs). The abundant surface free –OH groups can also be used for surface functionalization of BC for targeted drug delivery, for example, colon-specific drug delivery.

BC alone or in composite form with biocompatible polymer(s) may also find interesting applications in subcutaneous implantable devices for the delivery of therapeutic candidates, where prolonged therapy is desired, such as hormonal replacement therapy and contraception.

In case of MIP, the technique could further be tailored by designing specific MIP ~~to attain~~for enantioselective drug delivery ~~for~~with better patient~~'s~~ outcomes, and for enantiomer differentiation and deracemization. Moreover, MIP-based nanoparticulate columns with improved surface area can be designed for efficient enantiomer separation, analysis and deracemization.

In case of all drug delivery systems, discussed in this review, there is a need for further ~~in vivo~~ studies using various animal models and/or human volunteers for getting a clearer idea about the *in vivo* performance, bioavailability and *in vitro–in vivo* correlation (IVIVC) of the prepared delivery systems.

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