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Bacterial Cellulose Film Coating as Drug Delivery System: Physicochemical, Thermal and Drug Release Properties

(Penyalutan Filem Selulosa Bakteria sebagai Satu Sistem Penyampaian Dadah: Sifat-sifat Fizikokima, Terma dan Pelepasan Dadah)

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ABSTRACT

There has been an increasing interest in the use of natural materials as drug delivery vehicles due to their biodegradability, biocompatibility and ready availability. These properties make bacterial cellulose (BC), from nata de coco*, a promising biopolymer for drug delivery applications. The aim of this study was to investigate the film-coating and drug release properties of this biopolymer. Physicochemical, morphological and thermal properties of BC films were studied. Model tablets were film coated with BC, using a spray coating technique, and* in vitro *drug release studies of these tablets were investigated. It was found that BC exhibited excellent ability to form soft, flexible and foldable films without the addition of any plasticizer. They were comparable to Aquacoat ECD (with plasticizer) in tensile strength, percentage elongation and elasticity modulus. Differential scanning calorimetry (DSC) BC showed a high T_g value indicating thermally stability of films. These results suggest that BC can be used as novel aqueous film-coating agent with lower cost and better film forming properties than existing film-coating agents.*

Keywords: Bacterial cellulose; drug delivery; DSC; film-coating; Young's modulus

ABSTRAK

Penggunaan bahan semula jadi sebagai satu pendekatan penyampaian dadah semakin mendapat perhatian disebabkan sifatnya yang bioterurai, bioserasi dan mudah diperoleh. Kepelbagaian sifat ini menjadikan selulosa bakteria (BC) daripada nata de coco*, menjanjikannya sebagai satu biopolimer untuk aplikasi penyampaian dadah. Kajian ini dilakukan bertujuan untuk menyelidiki sifat penyalutan filem dan pelepasan dadah biopolimer tersebut. Kajian fizikokimia, morpologi, dan terma BC telah dilakukan. Penyelidikan ke atas model tablet yang disaluti BC menggunakan kaedah penyalutan secara semburan dan kajian pelepasan dadah secara* in vitro *dari tablet telah dilakukan. Adalah didapati BC menunjukkan keupayaan yang hebat untuk membentuk filem yang lembut, fleksibel, mudah dilipat tanpa menambah sebarang bahan pemplastik. Ianya setanding dengan Aquacoat ECD (dengan bahan pemplastik) daripada segi kekuatan tensil, peratus pemanjangan dan modulus keelastikan. Pengesanan pembezaan kalorimeter (DSC) BC menunjukkan satu nilai T_g yang tinggi membuktikan kestabilan filem secara terma. Hasil keputusan mencadangkan BC boleh digunakan sebagai agen penyalut filem akues yang baru pada kos yang rendah dan bersifat pembentukan filem lebih baik berbanding agen penyalutan filem yang sedia ada.*

Katakunci: DSC; modulus Young; penyalutan filem; penyampaian dadah; selulosa bakteria

INTRODUCTION

The use of natural polymers for drug delivery is an active area of research because they are readily available, relatively inexpensive, potentially degradable and biocompatible (Säkkinen et al. 2002; Satturwar et al. 2004; Yuasa et al. 2002). The increased use of film-forming materials as vehicles for medicaments, specialized coatings on medications or as packaging agents has prompted the researchers to develop novel materials for these applications. In the last decade several biopolymers like polysaccharides, obtained from renewable resources were developed as alternatives to remnant resources (Fulzele et al. 2002; Halib et al. 2009).

Film coating of tablets protect the integrity of the core material against environmental factors, masks the taste, provide a tough and high quality finish to minimize possible damage from mechanical handling and regulate the drug release. Aqueous film coating is currently preferred in pharmaceutical industry due to the higher costs, health and safety issues associated with organic solvents (Rangaiah et al. 1997). Cellulose and acrylic polymers are primarily used in pharmaceutical coatings due to their good film-forming properties. Tackiness, cracking and interaction with drug core are the limitations associated with existing polymeric film coating agents which create the need for novel polymers with better film-forming characteristics (Abu Diak et al. 2007; Tarvainen et al. 2002).

One such biopolymer of great interest is bacterial cellulose (BC) or microbial cellulose. It is an unbranched polysaccharide, comprised of linear chains of β-1, 4-glucopyranose residues and is generally produced by microorganisms as carbon source for their growth (Chen 2009; Vandamme et al. 1998; Zou et al. 2009). Microorganisms (*Acetobacter, Achromobacter, Aerobacter, Agrobacterium* and *Pseudomonas*) when cultured under specific conditions produce cellulose, which has molecular structure identical to cell-wall plant cellulose but differs in crystalline arrangement and properties (Vandamme et al. 1998). Among all microorganisms, *Acetobacter xylinum* (*Gluconoacetobacter xylinum*), an aerobic, non-pathogenic, rod shaped and gram-negative bacteria, is the most efficient cellulose-producing specie (Klemm et al. 2001; Shoda & Sugano 2005).

Cellulose produced by *Acetobacter xylinum* strains does not contain any impurities associated with plant sources such as hemicellulose, pectin and lignin (Kurosumi et al. 2009). It exhibits many unique structural and biochemical properties such as ultrafine nanofiber network structure (1.5-nm width) (Patel & Suresh 2008), bioadaptibility (Hong & Qiu 2008), inert, biodegradability, hypoallergenity, bioconsistency and chemical stability (Amin et al. 2010; Grzegorczyn & Slezak 2007; Moreira et al. 2009). BC possesses good water absorbance and increase capacity due to its reticulated structure, which provides large surface area and a capacity to absorb water (approximately 200 times its weight) (Patel & Suresh 2008; Wippermann et al. 2009). Additionally, BC exhibits desirable mechanical properties, including high tensile strength, elastic modulus and high wet strength due to its uniform and ultrafine fibrous network structure. It can be sterilized without any changes to its structure and properties (Czaja et al. 2007; Hu et al. 2009; Wan et al. 2009).The above-mentioned properties make BC a suitable candidate for application as tablet film coating agent.

To the best of our knowledge, no studies have been reported on the use of BC as a film coating material for tablets. This study characterizes BC as a tablet film-coating material with modified drug release behavior.

Materials and Methods

Materials

Polyvinyl pyrrolidone was supplied by BDH, UK. Micro granular cellulose and triethyl citrate were purchased from Sigma-Aldrich, Germany and aquacoat ECD was supplied by FMC Biopolymer, USA. *Nata de coco*, as a source of bacterial cellulose, was obtained from local food industry, purified and then identified as described in *British Pharmacopoeia 2010*.

Preparation of Bacterial Cellulose Powder

Nata de coco was washed and soaked in distilled water until neutral pH was achieved. The samples were then blended in a wet blender, poured into trays and freeze dried until a constant weight was achieved. The cellulose sheets were then micronized by using a pulveriser (Pulverisette 14, Frisch, Germany) to produce a fluffy cellulose powder. IR spectrum of BC powder was then recorded over the range of 4000-500 cm^{-1} using FTIR spectra 2000 (Perkin Elmer) at room temperature.

Preparation of Bacterial Cellulose Dispersions

Bacterial cellulose dispersions 1 to 6% w/v were prepared in distilled water with continuous stirring by a mechanical homogenizer (Ika, Brazil) at a speed of 11,000 rpm for 5 h. The resulting homogeneous dispersions were allowed to hydrate, de-foam and equilibrate overnight in a water bath (JP Selecta, Spain) at 25°C.

Rheological Studies

The viscosities of BC dispersions were determined by using a rotational, programmable digital viscometer (DV-III, Brookfield Engineering USA). Approximately 10 mL of all dispersions were placed in a small cylindrical sample adapter and left to equilibrate for 10 min. Sample adapter was then fitted into a water jacket connected to a circulating water bath to maintain the temperature at 25°C. Five replicates were taken for all dispersions and the average was calculated.

Determination of Minimum Film Forming Temperature (MFFT)

The minimum film-forming temperature (MFFT) was determined to understand the effect of temperature on film formation. Thirty millilitre samples of 1 % w/v BC dispersion were casted in glass Petri dishes and dried at 8, 20, 40, 60 and 70°C in a controlled temperature chamber (Binder GmbH, Germany). The samples were observed for the presence of film at regular time intervals.

Preparation of Free Films

Bacterial cellulose 1 % w/v and Aquacoat ECD (plasticized with 20 % w/w triethyl citrate) dispersions were poured in glass Petri dishes (9 cm diameter) to cast dry films of 100-120 μm thickness. The Petri dishes were placed in oven, set at 60°C for 24 h to produce coalescence. The films were then maintained at 25ºC with 60 - 70% relative humidity for 24 h. The resulting free films were stored in desiccators.

Differential Scanning Calorimetry (DSC)

The glass transition temperature (T_g) of the free films was determined by using differential scanning calorimeter (DSC 822e, Mettler Toledo, Switzerland). Approximately 3 mg of film was sealed in a standard aluminium pan for non-volatile samples. The samples were first heated to 150°C for the removal of moderately bound moisture, cooled to 0°C and then scanned over a temperature range of 0-250°C

at a heating rate of 10°C/min. Three measurements were used to calculate mean.

SCANNING ELECTRON MICROSCOPY (SEM)

The surfaces of BC free films, uncoated tablets, coated tablets and cross-section of coated tablets were examined under a scanning electron microscope (Leo1450 VP, Leo, Germany). The samples were mounted on an aluminum stub with a double-sided carbon tape and coated with gold for 120 s in a sputter coater (SC500, BioRad, UK) under argon atmosphere. Samples were observed at acceleration voltage of 15 kV.

MECHANICAL PROPERTIES

The samples were cut into 4 mm width × 20 mm length by using a rectangular cutting die. The free films were evaluated for their mechanical properties by using Instron Universal Testing Instrument (Instron 5567, USA) with 500N load cell. The measurements were taken at a crosshead speed of 5 mm/min, 25 ± 2°C and relative humidity of 60 ± 5%. Percent elongation at break, tensile strength and Young's modulus were determined.

MOISTURE PERMEABILITY OF FREE FILMS

The free films were cut by using a circular template of 1.5 cm in diameter and mounted on the brim of permeation cells made of individual glass vials containing 20 g of calcium chloride each as desiccant. The films were sealed and tightened to the vials by rubber rings to provide an exposed surface area of 0.95 cm^2. The vials were then placed in a desiccator containing supersaturated solutions of potassium nitrate, sodium bromide and potassium acetate to provide the relative humidity of 93, 57.5 and 23%, respectively. Vials were weighed at regular time intervals for 14 days. Water vapor transmission rate was calculated by using the following equation:

$$Q = WL/S \quad (1)$$

where W is increase in the desiccant weight per 24 h, L is the film thickness (cm), S is the exposed surface area (cm^2) and Q is the water vapor transmission rate (g/cm^2/24 h).

TABLET COATING PROCESS

BC aqueous dispersion 1 % w/v was sprayed on to generic paracetamol uncoated tablets by using a bench-top tablet and spheroid coater (Caleva, UK). The coating process parameters are shown in (Table 1). The coating process was divided into wet and dry cycle of 1 min and 30 s respectively. After the specified coating time, the tablets were dried for 30 min. The tablets with a coating weight gain of approximately 5-9 % were produced and stored in glass containers.

TABLE 1. Tablet coating process parameters.

Coating Parameter	Value
Frequency	17 Hz
Amplitude	3 mm
Temperature	60 °C
Air flow	4.5 m/min
Spray time	15 and 28 min
Spray rate	20 mL/hr

IN VITRO DRUG RELEASE STUDIES

Drug release studies were performed on uncoated and film-coated paracetamol tablets using tablet dissolution tester (DT 620, Erweka, Germany). The tests were carried out on six tablets using 900 mL of phosphate buffer as a dissolution medium at a temperature of 37°C, 50 rpm paddle speed and pH5.8. At specified time intervals, 5 mL samples were withdrawn and replaced with fresh media. The amount of paracetamol in the dissolution medium was determined spectrophotometrically (UV-1601, Shimadzu, Japan) at a wavelength of 243 nm.

RESULTS AND DISCUSSION

PREPARATION OF BC POWDER

FTIR spectrum of prepared BC powder showed peaks at 3440 cm^{-1}(O-H stretching), 2926 cm^{-1} (C-H stretching), 1163 cm-1 (C-O-C stretching) and 1040 (C-O stretching). Peaks at 1300 cm^{-1} and 1440 cm^{-1} indicated C-H and CH_2 bending respectively (Hussain 2008). As shown in Figure 1, the FTIR spectrum of BC powder (b) prepared from *nata de coco* (from local food industry) is a typical signature of BC (Klemm et al. 2001) and pure cellulose powder.

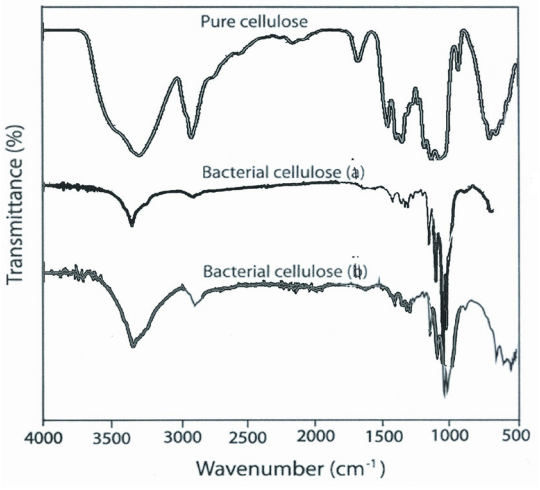

FIGURE 1. FTIR spectra of pure cellulose (micro granular cellulose) from Sigma, bacterial cellulose (a) from Klem et al. (2001) and bacterial cellulose and (b) from nata de coco

RHEOLOGICAL STUDIES

Viscosity of an aqueous dispersion effects spray ability, wetting, spreading and coalescence. This ultimately affects the quality of the end product. Viscosity of the BC polymeric dispersions was directly related to the concentration of the polymer (Figure 2(a). A linear correlation exists between viscosities of BC and its concentration at lower concentration but as the concentration increased, a change in the rheological profile was observed and the viscosity increased sharply indicating a non-Newtonian flow behavior of BC. The higher viscosity of BC dispersions, as compared to Aquacoat ECD (66.4 cp) might be attributed due to the larger particle size and hydrophilic nature of BC. As shown in Figure 2(b), the dispersion viscosity exhibits an indirect relation with the viscometer speed (shear rate) which indicates the pseudoplastic (shear thinning) behavior. As a result no major difficulties were expected during spray coating with BC dispersion. As the particle size of BC increased, the viscosity of BC dispersions also increased (Figure 2(c)) and this may be attributed to the hydrophilicity of BC. In addition to that, the particles are irregular needle-like or plate-shaped structure (as shown by SEM study), which could contribute to the increased in viscosity (Shotton & Ridgway 1974).

MINIMUM FILM FORMING TEMPERATURE

Bacterial cellulose was found to be capable of film casting at all tested temperatures. BC films were opaque and homogenous in appearance, intact and were easily detached from the casting surface. Films dried at 40, 60 and 70 ºC were soft, flexible and foldable without any observed fracture. They exhibited a glossy surface from the casting side and were superior to Aquacoat ECD films, which were very brittle and required a plasticizer (triethyl citrate. However, films formed at lower temperatures (8, 20 and 25°C) were thicker and weaker as compared to films prepared at 40, 60 and 70°C. To ensure optimal conditions for film formation, the coating temperature should be at 10-20°C above the MFFT (Cole et al. 1995).

DIFFERENTIAL SCANNING CALORIMETRY (DSC)

Glass transition temperature (T_g) of BC films was found to be 191°C (Figure 3) which is higher than reported by George et al. (2005) for native (13.94°C) and NaOH treated (41.41°C) BC membrane but it was lower than the benzoylated bacterial cellulose (280°C) as reported by Wang et al. (2008). Higher T_g is advantageous because minimal aging is expected at storage temperature (which is well below the T_g) (Béchard et al. 1995). No melting or degradation peaks were detected over the temperature range of 0 - 250ºC. The high thermal stability might be attributed to the high crystallinity, highly orientated cellulose chains within fibrils, and pure cellulosic form (Chen Kim et al. 2009; Hsieh et al. 2008).

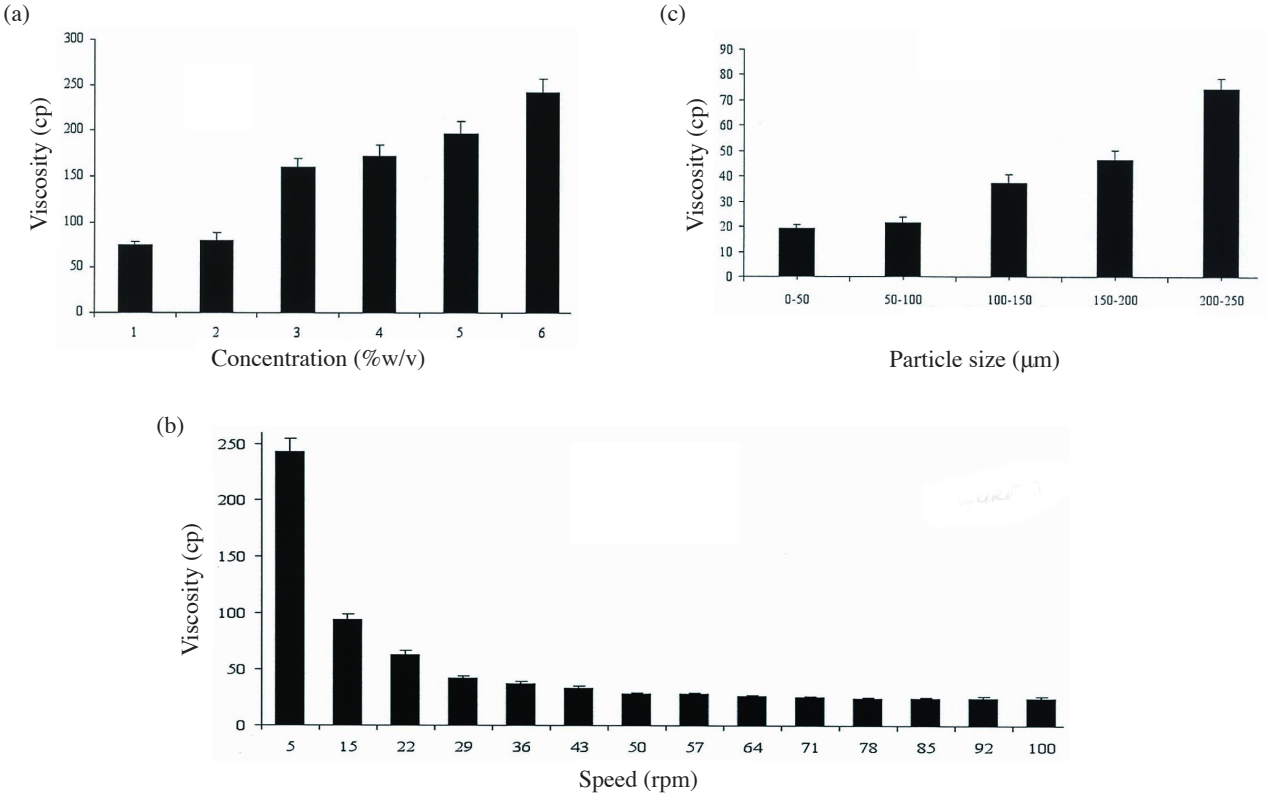

FIGURE 2. Relationship between viscosity of BC dispersion with (a) concentration, (b) shear rate and (c) particle size

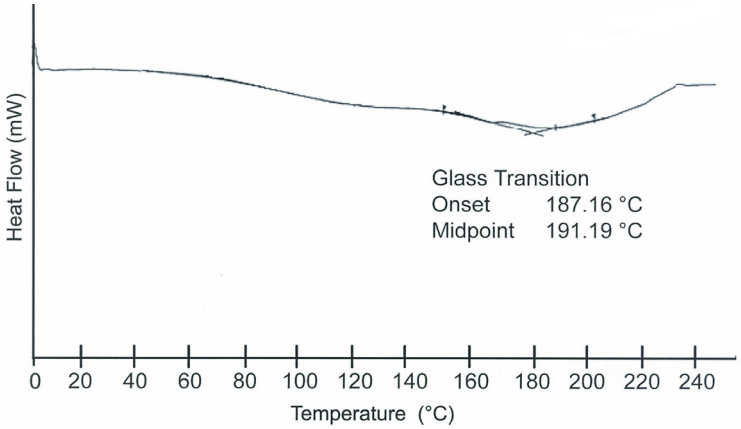

FIGURE 3. DSC thermogram of BC free film

SCANNING ELECTRON MICROSCOPY (SEM)

The SEM images of BC powder, BC film surface, coated tablet surface and cross section of coated tablets are shown Figure 4. The SEM images demonstrated a uniform, moderately smooth and intact coating without any defect. Examination on the BC film's surface under an electron microscope showed that BC films were homogenous without any cracking or pores.

MECHANICAL PROPERTIES

To gauge the performance of the films, the mechanical properties such as tensile strength, elastic modulus (indicating stiffness and rigidity) and tensile strain at breakage/elongation are often determined. An ideal film should be hard, tough and extendible, characterized by high tensile strength, high elastic modulus and moderate elongation (Cole et al. 1995; Kwok et al. 2004). In terms of tensile strength, elasticity modulus, % elongation and tensile strength to elastic modulus (σ/E), BC free films were found to be comparable to Aquacoat ECD which required plasticizer (Table 2). The lower values of some BC parameters may be attributed to the particle size used as discussed earlier in the rheological studies.

Nishi et al. (1990) reported that BC sheets could have Young's modules in excess of 15 and obtained improvement in modulus up to 30 GPa by treatment with alkaline and oxidative solutions. Maximum stress,

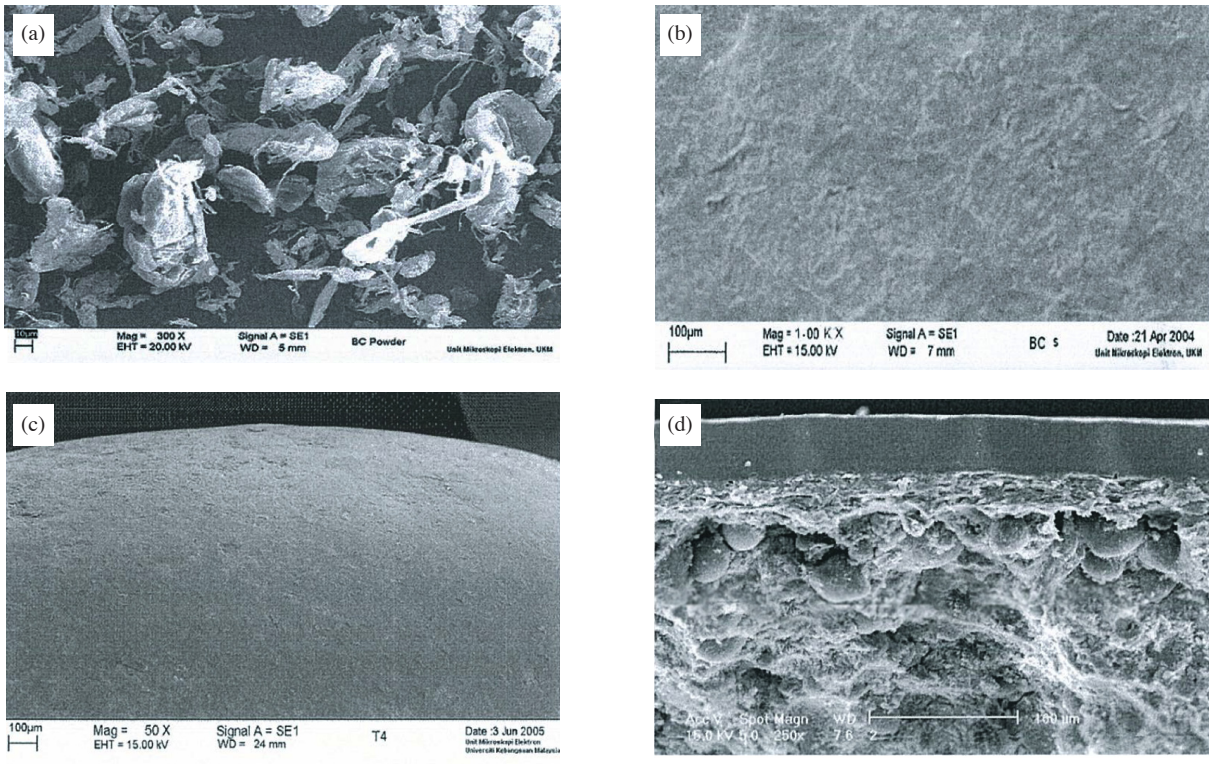

FIGURE 4. The SEM images of (a) BC powder, (b) BC film surface, (c) coated tablet surface and (d) cross section of coated tablet

maximum elongation and Young's modulus for neat BC sheets were reported to be 241.42 ± 21.86 (MPa), 8.21 ± 3.01%, 6.86 ± 0.32% (GPa), respectively by Grande et al. (2009). Saibuatong and Phisalaphong (2010) reported tensile strength, Young's modulus and elongation at break to be 5.32 (MPa), 161.80 (MPa) and 3.7%, respectively, for BC sheets (Saibuatong & Phisalaphong 2010).

TABLE 2. Mechanical properties of BC and Aquacoat ECD free films

Property	Material	
	BC	Aquacoat ECD
Thickness (μm)	100 ± 4.1	120 ± 1.3
Tensile strength σ (MPa)	146 ± 1.4	194 ± 1.2
% elongation	7.4 ± 1.6	5.2 ± 1.2
Modulus of elasticity E (MPa)	454.6 ± 4.7	379 ± 2.8
σ/E value ($\times 10^{-2}$)	3.2	5.1

WATER VAPOR PERMEABILITY

The effect of the film on the stability of the coated product was determined by water vapor transmission rate studies (WVTR), which describes the barrier properties, tightness, homogeneity, and integrity of the polymeric films (Tarvainen et al. 2003). WVTR study indicated that the permeability of the BC films was increased with increasing relative humidity (Table 3). In addition, the WVTR decreased with increasing film thickness (100 to 200 μm) at the same relative humidity.

Saibuatong and Phisalaphong (2010) reported the WVTR of dry BC films at 90% relative humidity to be 1616.5 g/m^2/day. Increase in the degree of swelling and the high hydrophilicity of BC films could be attributed to water vapor permeability of BC membranes. More water molecules binding to the surface of the membranes led to greater transportation through the membrane (Phisalaphong et al. 2008; Saibuatong & Phisalaphong 2010). From the above observations, it can be concluded that any adjustment on film thickness and incorporation of other hydrophobic polymers would improve the bacterial cellulose barrier properties.

TABLET COATING

BC is an edible and non-toxic biopolymer that has potential for diverse applications in many different fields. However, from the available references there are no reports on its use as a tablet film coating material. The tablets were coated with BC dispersions without major shortcomings like nozzle blockage, tablet agglomeration and adhesion of tablets to the walls of coating apparatus. Further reduction of particle size will provide larger surface area, which could result in enhanced coating efficiency and quality. The roughness of the coating surface was due to the particle size of BC. A cross-section of coated tablets (Figure 4) exhibits a distinct layer of tablet core and a homogenous film of coating material around the core.

IN VITRO DRUG RELEASE STUDIES

All films remained intact for approximately 0.5 h without any clear rupture, however swelling was observed. The drug release from uncoated tablets was faster as compared

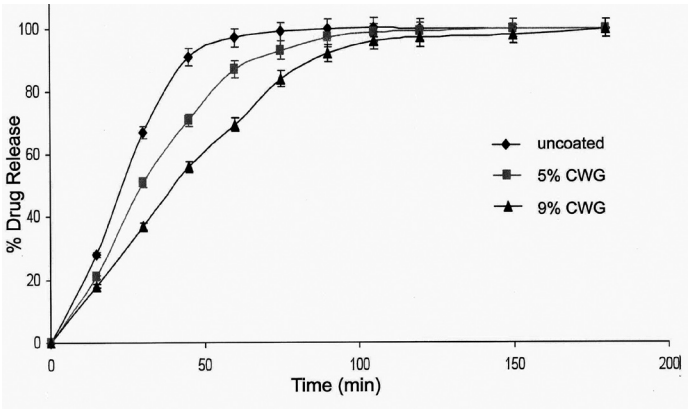

FIGURE 5. Drug release profile of uncoated and coated tablets

TABLE 3. Water vapor transmission rate of BC films

Film thickness (μm)	WVTR (g/cm^2/2H) at RH		
	23 %	57.5 %	93%
100 ± 3.7	$4.97 \times 10^{-5} \pm 0.38$	$6.75 \times 10^{-5} \pm 0.53$	$7.9 \times 10^{-5} \pm 0.67$
200 ± 5.4	$3.17 \times 10^{-5} \pm 0.34$	$4.87 \times 10^{-5} \pm 0.44$	$6.42 \times 10^{-5} \pm 0.59$

to the coated tablets. Coated tablets with 9% CWG showed slow release than both uncoated and 5 CWG coated tablets (Figure 5). These results suggest that a total built-up coat induces a slight retardation of drug release. The observed drug release profile of BC coated tablets may be due to the particle size and swelling properties, which create larger voids. These findings suggest that BC can be used as a tablet film coating material with adjustments in particle size and blending with other polymers or additives.

Conclusion

Bacterial cellulose is edible, non-toxic and biocompatible biopolymer. This study demostrate that bacterial cellulose forms aqueous dispersions for spray coating of drug tablets with relatively good film-forming properties, can be further improved by careful formulation with other additives such as different plasticizers or polymers. Further reduction of particle size can also improve coalescence, with improved film quality. The produced films were strong, almost opaque. BC thus has potential application for non-functional pharmaceutical film coating and for sustained release drug delivery system.

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