Rendering cellulose fibers antimicrobial using cationic β-cyclodextrin-based polymers included with antibiotics

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Abstract Cationic β-cyclodextrin polymer (CPβCD) and its complexes with butylparaben and triclosan were reported in this paper. 2D NMR confirmed that the host-guest complexes were formed by including antibiotics inside the cavities of CPβCDs, which significantly improved the water solubility of the antibiotics. Results of inhibition zones and shaking flask methods of antimicrobial-modified cellulose fibres showed that both antibiotics/CPβCD complexes had excellent antimicrobial activities when applying on the cellulose fibers whereas triclosan appeared to more effective. Morphology of untreated and treated bacteria revealed by AFM suggested that the antibiotics/CPβCD complexes inhibited bacteria through affecting the metabolism of the bacteria instead of damaging the cell membrane. Due to the strong electrostatic association, CPβCD polymers adsorbed on the surface of cellulose fibres almost completely within the range of dosages investigated.

Keywords Cationic β-cyclodextrin polymers · Antibiotics · Cellulose fiber · Inclusion complexes · Antimicrobial activity · AFM

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Introduction

Infection control is of utmost importance in a variety of situations that require a high level of hygiene, such as medical devices, healthcare products, water purification systems, hospitals, dental office equipments, food packaging, food storage, household sanitation, etc. (Patel et al. 2003). Antimicrobial properties, which destroy or inhibit the growth of microorganisms and make commonly used materials bioactive, are extremely important to the industry because of their ability to address health concerns. Therefore, antimicrobial modification for various raw materials has been extensively developed and applied.

Cellulose is a naturally occurring polysaccharide and the most abundant renewable organic raw material in the world. Its derivatives have many important applications in fiber, paper and packaging

industries. To endue this material with antimicrobial property is a current need of society, especially for the products used in the occasions that need a high degree of safety for the civilian population.

Cyclodextrins (CDs) are a series of cyclic oligo-saccharides consisting of six to eight glucose units linked by α-1, 4 bonds. Among them, the β-form, consisting of seven glucose units, is the most important and widely used one. The cyclodextrin anatomy takes the form of a toroid or a hollow tapering cone. The internal hydrophobic cavities in the CDs facilitate the inclusion of a wide variety of guest molecules in aqueous solution (Szejtli 1998).

The unique feature of CDs that gained much attention is their ability to host a guest compound in its internal cavity, thereby improving the physical and chemical properties of the guest compound. A number of applications of CDs involve the formation of inclusion complexes in liquid and solid phases (Benito et al. 2004; Moozyckine et al. 2001; Sheremata and Hawari 2000), and recently on gaseous phase (Ahn et al. 2001). Organic and inorganic molecules of appropriate size can be included into the cyclodextrin cavity to form inclusion complexes. When the hydrophobic cavity of the cyclodextrin is filled partially or wholly with another molecule or substrate, "inclusion complex" occurs where water molecules located within the lipophilic central cavities are replaced by lipophilic guest molecules (Loftsson and Duchene 2007). Several factors to which a guest can be incorporated in the central cavity of the cyclodextrin include steric effect, release of high-energy water, and hydrophobicity. The naturally occurring CDs serve as scaffoldings on structures on which functional groups and other substituents can be assembled with controlled geometry. This feature results in improved procedures for molecular recognition (Harada et al. 1997) and chemical separation (Murai et al. 1996) through guest binding.

Over the past decades, β-CD has been successfully applied in many industrial products, technologies and analytical methods. However, the drawbacks of β-CD, such as poor water solubility (1.85 g/100 mL H_2O) and the relatively small size of the cavity (diameter, 7 Å), limit its application. To address these problems, various CDs derivatives have been developed.

Chemical modifications have been attempted to alter the undesired physicochemical and safety properties of the parent CDs. The modifications are mostly derivatives attached through the three available hydroxyl groups on each glucopyranose unit. Among them, cyclodextrin-based polymers are of interest due to their high solubility in water and capability to include compounds with large molecular structures in particular. For example, the polymers containing β-CD were found to bind to large substrates having two guest parts more efficiently than β-CD due to the cooperation of two adjacent β-CD moieties on a polymer chain (Harada et al. 1980, 1981). In our previous study (Li et al. 2004), we successfully synthesized a range of novel cationic β-CD polymers (CPβCDs) which showed improved physicochemical and hemolytic properties to permit them to be used as drug carriers in pharmaceutical applications. It was found that CPβCDs of relatively high molecular weight and low cationic charge density exhibited good drug inclusion and dissolution abilities.

In this work, the CPβCDs were used to form complexes with antibiotics. Their structure and physicochemical properties were investigated. There were two antibiotics used in this work. One is triclosan (2,4,4′-Trichloro 2′-Hydroxydiphenyl Ether), another is butylparaben (p-hydroxybenzoic butyl ester). They are nonionic, white, odorless and tasteless crystalline powders. They can inhibit growth of a wide range of bacteria, yeast and molds. The antimicrobial mechanism of triclosan is to block the synthesis of lipids and inhibit the enzyme enoyl-acyl carrier protein reductase (Buschmann and Schollmeyer 2002), while the mechanism of butylparaben may be linked to the mitochondrial depolarization depletion of cellular ATP (adenosine 5′-triphosphate) through uncoupling of oxidative phosphorylation (Lu et al. 2002). Both of the antibiotics have very low toxicity and are Food and Drug Administration (FDA)-approved. They have been widely used as disinfecting active ingredients in cosmetic, drug and food industry. A drawback which limits the application of these nonionic compounds is their extremely low water solubility (only about 10–20 mg/L).

The purpose of this work was to prepare and characterize novel antibiotic inclusion complexes which can render cellulose paper products antimicrobial properties. Both triclosan and butylparaben have

the right size and are suitable to be included in β-CD. Based on our preliminary work, it has been found that water solubility of triclosan and butyparaben can be significantly improved after forming the inclusions complexes with cationic β-CD polymers (Guan et al. 2007a, b). Another advantage we choose CPβCDs is that the cationic charge will help the adsorption or retention of the antibiotic complexes on negatively charged wood fibers. To further improving our understanding of rendering cellulose fibres antimicrobial using CPβCD complexes, modified moreover, an atomic force microscope (AFM) was utilized to reveal the antimicrobial mechanism and the adsorption of CPβCD on cellulose fibres was determined to investigate the interaction between the polymer and fibres.

Experimental

Materials

β-Cyclodextrin (β-CD), epichlorohydrin (EP) and choline chloride (CC) were purchased from Sigma–Aldrich. Triclosan and butylparaben were obtained from Fluka Chemika. All reactants were used as received without further purification. The bleached sulfite pulps were supplied by Fraser papers in Edmundston, New Brunswick, Canada. The received pulps were cleaned with distilled water for three times prior to being stored at a high consistency (25.7%wt) in a refrigerator. Phosphate aqueous saline (PBS), LB (Lunia–Bertani) agar and LB broth were purchased from Aldrich. Deionized-distilled water was used throughout.

Preparation and characterization of cationic β-cyclodextrin polymer and its complexes with antibiotics

Cationic β-cyclodextrin polymers (CPβCDs) were synthesized by one-step condensation (Li et al. 2004) and the molar ratio of the reactants (β-CD/EP/CC) was fixed at 1/5/2 in this work. The specific procedures for preparing CPβCDs were the same as those we reported previously (Guan et al. 2007a). The antibiotics/CPβCDs complexes were prepared by mixing equimolecular of antibiotics and CPβCDs

and grinding manually for 10 min (Arias et al. 1997; Mura et al. 2002). Then, the mixed powder was dissolved in water to form the complexes.

Solubility of CPβCDs and antibiotics included in CPβCDs was determined by measuring UV absorbance (GENESYS[TM] 10S Spectrophotometer, Thermo Electron Co.) of the saturated solutions at a wavelength of 282 or 256 nm and compared with the calibration curve at 20 °C. Gel permeation chromatography (GPC) (Pump: Waters 600E System Controller; Detector: Waters 410 Differential Refractometer) with Ultrahydrogel 250 and 500 columns was used to determine the molecular weights of CPβCDs. The tests were carried out at 40 °C and the flow rate at 0.7 mL/min. 0.05M sodium sulfate aqueous solution was used as an eluent. NMR (a Varian Unity 400 spectrometer) in D_2O at 25 °C was used to characterize the molecular structure.

Characterization of antimicrobial activities

Minimum inhibitory concentration (MIC) of antimicrobial agents was determined by the serial dilution method. Hand sheets of the sulfite pulps with a grammage of 60 g/m^2 were prepared according to TAPPI test methods T205. The paper sheet samples for antimicrobial tests were prepared via two approaches. One was blending virgin pulps with different ratios of modified pulps by adsorption. The other method was to spray antibiotics solution directly on the surface of handsheets without any pretreatments on cellulose fibers. Inhibitory effects of paper with antibiotics were tested by inhibition zones method and shaking flask method, respectively. Inhibition zones method is a typical antimicrobial test used extensively in many fields. In this work, 0.1 mL of bacterial suspension (10^8 CFU/mL) was plated and spread on agar plates firstly and a roundish sheet of paper samples (Φ 10–15 mm) was further put on the surface of agar. Then the dishes were put into an incubator at 37 °C for 24 h. The antibacterial activity was evaluated via measuring the diameter of inhibition zones. Shaking flask method is a kind of quantitative test and used for the evaluation of the antimicrobial activity of textile products normally. The procedure is as follows: 0.10 g paper scraps and 5 mL bacterial culture (10^6 CFU/mL) were mixed and shaken at 200 rpm at 37 °C for 1 h. After shaking, various dilutions were made successively

and then 0.1 mL of this culture was seeded on LB agar in a petri dish. The plates were incubated at 37 °C for 24 h and the number of colonies was counted. Three repeats were carried out for each sample. The growth inhibition of cell can be quantified by the following equation:

$$\text{Growth inhibition of cell } = \frac{A - B}{A} \times 100\%$$

where A and B are the number of the colonies of the control and treated samples, respectively.

Morphology of bacteria revealed by AFM

Atomic force microscope (AFM) was used to investigate the morphology of *E. coli* treated by antibiotics solutions. The sample was prepared by depositing a drop of bacteria suspension (10^3 CFU/mL) on a clean silicon wafer (Universitywafer, 66 N. St., South Boston) and semidried at room temperature in a desiccator. AFM measurements were performed using a Nanoscope IIIa from Veeco Instruments Inc., Santa Barbara, CA. The images were scanned in Multimode mode in air using a silicon tapping probe (NP-S20, Veeco Instruments) with a resonance frequency of about 273 kHz.

Determination of dynamic adsorption of the CPβCD polymer on cellulose fibres

The dynamic quantification of the adsorption of CPβCD polymer on cellulose fibres was carried out by adding various amounts (10–270 mg/g on oven-dried fibre) of CPβCD polymers to fiber suspensions. The consistency of the fibre and temperature were fixed at 3% and 40 °C, respectively. Meanwhile, the control samples without pulp fibers were prepared similarly. The adsorption duration was varied from 1–30 min. After sampling, the suspensions were filtered, and the supernatants were collected at different time intervals for analysis. The same volume was taken from each sample and its control. Then, the samples were titrated using a particle charge Detector Mutek PCD 03 (Herrsching, Germany) with PVSK solution (0.5 mN). The amount of the adsorption was calculated based on the concentration difference between the CPβCD polymer in supernatant and its control sample.

Results and discussion

Synthesis and characterization of CPβCDs and its complex with antibiotics

The scheme of synthesizing CPβCDs and forming host-guest complex with antibiotics is shown in Fig. 1. During the reaction, EP plays an important role for imparting cationic charge to βCD and polymerizing to CPβCDs by reacting with hydroxyl groups in βCDs and CC. Theoretically, various hydroxyl groups in βCDs could react with EP, whereas the one connected with methylene is easier to be consumed. The mean inner diameter of cavity of β-CD is about 7 Å, and it is possible to assist the antibiotics with small size (e.g., $M_w = 194$ for butylparaben and $M_w = 289.5$ for triclosan) to enter the cavities of CPβCDs to form the host-guest complex as shown in Fig. 1. Molecular weight of CPβCDs ($M_w = 5,620$) was almost five times of that of βCD ($M_w = 1,135$) according to GPC results, that indicated five βCD molecules was contained in one CPβCDs averagely. Cationic charges introducing to CPβCDs increased the water solubility dramatically
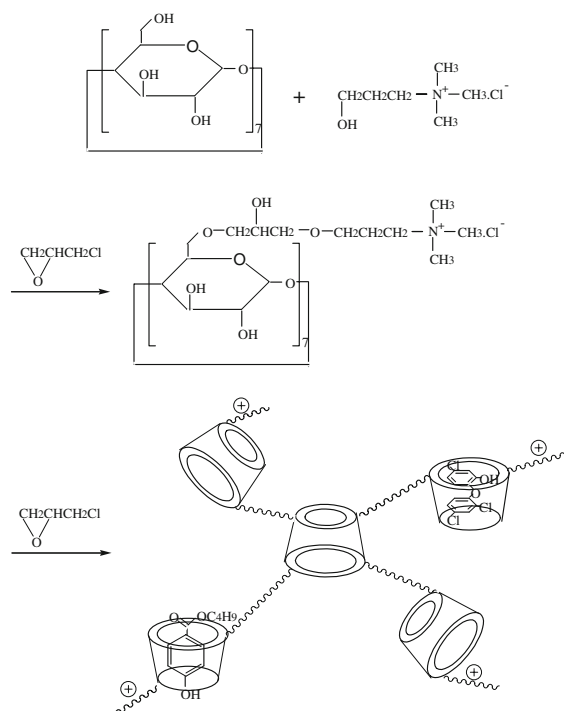
Fig. 1 Synthesis of CPβCDs and its inclusion with antibiotics. **a** triclosan/CPβCDs **b** butylparaben/CPβCDs

to 41.26 g/100 mL from 1.85 g/100 mL of unmodified βCD. Meanwhile, the extremely low water solubility of antibiotics (about 20 mg/L for butylparaben and 10 mg/L for triclosan at 25 °C) can be significantly increased by inclusion with CPβCDs which is linear increased with the CPβCDs concentration. At the CPβCD concentration of 6.0% (w/v), the water solubility of butylparaben or triclosan was increased, respectively to 2.80 or 1.64 g/L. The improvement of water solubility of butylparaben is greater than that of triclosan because the smaller size of butylparaben facilitates its entering into the cavities of CPβCDs for complex inclusion.

The inclusion of antibiotics into CPβCDs was confirmed by 2D NMR spectra of antibiotics/CPβCDs complexes. 2D NMR shown in Fig. 2 was used not only to give the chemical shifts of various protons listed in Table 1 but also to reveal the correlation between them. The correlation peaks in the spectra can be divided in two groups, originating from the neighbourhood of the protons in the CPβCDs or antibiotics (ones in dash rings) and the interaction of the protons between the antibiotics and the CPβCDs (ones in dash boxes). The cross-peaks in Fig. 2a indicate a very close interaction of CPβCDs (3.5–3.8 ppm, CH) and triclosan (6.9–7.7 ppm, all five aromatic protons). Similar results can be found in Fig. 2b, which demonstrate the interaction of CPβCDs

Table 1 ^{1}H chemical shifts of CPβCDs and the antibiotics (ppm)

Proton	CPβCD	Butylparaben	Triclosan
H-1	5.115	7.738	7.069
H-2	3.676	6.529	6.711
H-3	3.561	4.223	6.648
H-4	3.553	1.721	6.560
H-5	3.808	1.393	6.404
H-6		0.921	7.432

(3.5–3.8 ppm, CH) and butylparaben (0.9–1.6 ppm, protons of alkyl groups; 6.9–7.8 ppm, aromatic protons). The results confirmed the inclusion of the antibiotics in the cavities of CPβCDs.

Antimicrobial activity of antibiotics/CPβCDs complex

Minimum inhibition concentration (MIC) of CPβCDs was higher than 2,000 ppm, indicating that the antimicrobial activity of CPβCD itself is very weak and can be ignored. MIC values of triclosan and butylparaben included in the CPβCDs were 0.24 and 20.3 ppm, respectively. Both antibiotics showed excellent antimicrobial activities, whereas triclosan is a much more effective antibiotic compound than
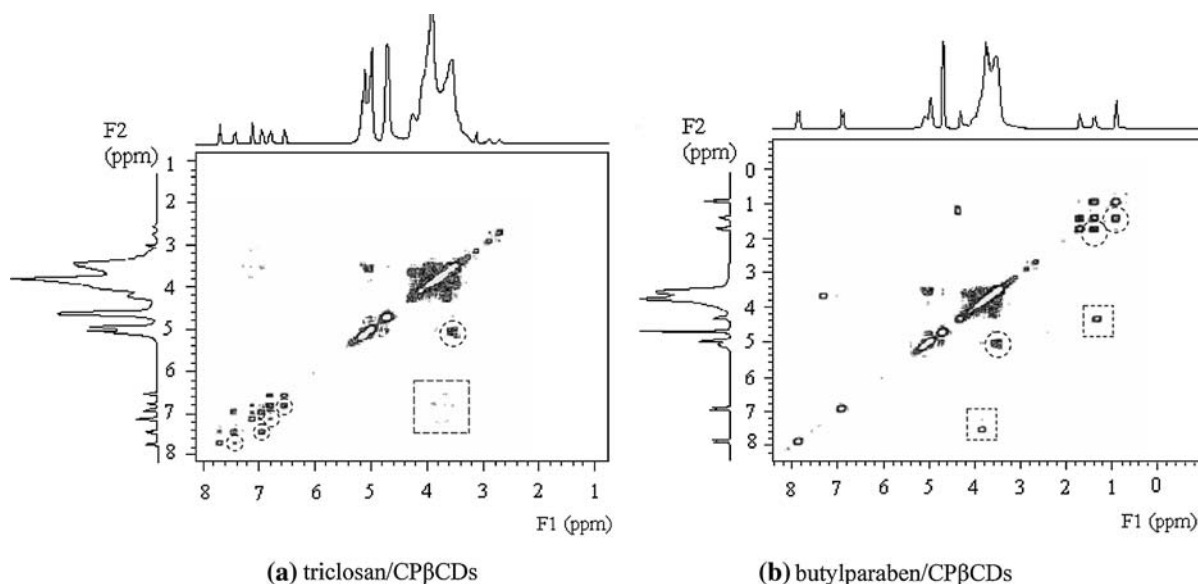
Fig. 2 2D gCOSY NMR spectra of antibiotics/CPβCDs in D$_2$O at 25 °C. **a** triclosan/CPβCDs; **b** butylparaben/CPβCDs

butylparaben. In order to investigate the application of these antibiotics/CPβCDs complexes on paper products, inhibition zones method and shaking flask method were employed to assess their antimicrobial activities. The results of inhibition zones method against *E. coli* and against *Salmonella* are listed in Table 2. The blank paper sheet was used as a negative control. Triclosan and butylparaben have excellent bacteriostasis for the common bacteria and fungi. It can be seen from Fig. 3, there are obvious inhibition zones in the plates of triclosan and butylparaben samples, while there are no visible rings in the plate of blank sample. The results implied that *E. coli* were killed by triclosan or butylparaben diffused out of the sheets. From Table 2, it can be also found that the diameters of inhibition zones with spraying samples are larger than those of the adsorbed samples at the same antibiotics concentration, which is attributed to the surface concentration of antibiotics in the spraying samples tends to be higher.

The effects of antibiotics concentration and contacting time with the shaking flask method are shown in Fig. 4. The growth inhibition increased with the increasing of both antibiotics concentration and contacting time. The growth inhibition of triclosan is higher than that of butylparaben when the concentration of antibiotics is lower than 0.5%, and growth inhibition of both antibiotics reach about 100% at the concentration higher than 0.5%, indicating that almost all the bacteria were killed. Triclosan showed higher antimicrobial activity than butylparaben at a low concentration, which is consistent with the results of MIC. On the other hand, butylparaben
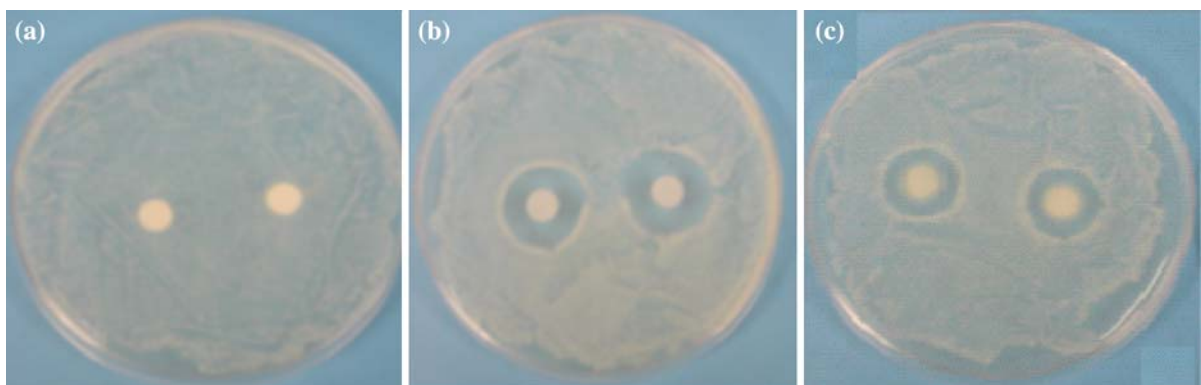
Table 2 Antimicrobial activities of diffusion method

| Sample	Antibiotics content[b] (% wt)	Diameter of inhibition zone (mm)[c] (against *E. coli* 11229)	Diameter of inhibition zone (mm)[c] (against *Salmonella*)
Blank	0	0	0
Triclosan/CPβCD	0.5	6.8	7.2
Triclosan/CPβCD	1.0	24.8	22.6
Triclosan/CPβCD[a]	0.5	–	23.0
Butylparaben/CPβCD	0.4	5.0	6.2
Butylparaben/CPβCD	1.0	7.3	9.3
Butylparaben/CPβCD[a]	0.5	–	12.3

[a] Samples were prepared by spraying antimicrobial agent on the paper

[b] The antimicrobial agent content means triclosan or butylparaben weight percentage based on wood fibers (o.d.)

[c] The diameter of inhibition zones equals to the diameter difference between the ring and the paper sheet

Fig. 3 Antimicrobial activity of paper against *E. coli* ATCC11229 (ring-diffusion or inhibition zone method). **a** blank; **b** triclosan 0.5%wt; **c** Butylparaben 0.4%wt
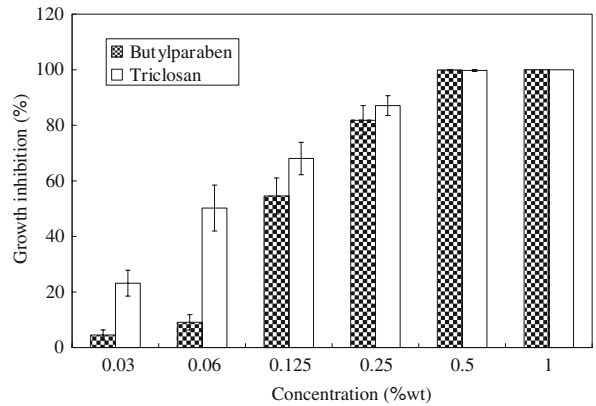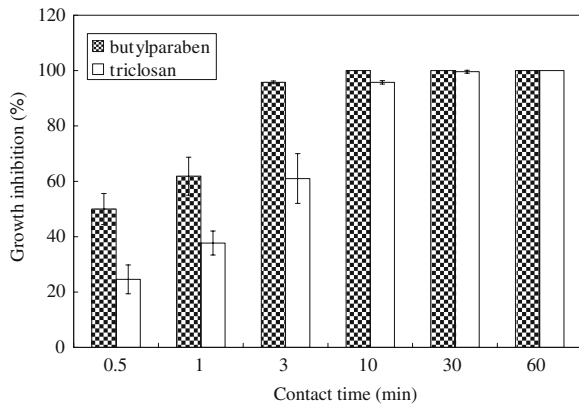
Fig. 4 Effect of antibiotics concentration (based on cellulose fibers) and contact time on the growth inhibition of *E. coli* ATCC 11229. Shaking time was fixed at 1 h. The number of colonies of blank control was 2.2×10^6 CFU/mL. **a** Topography image **b** section image

exhibited faster inhibition effect than triclosan when contacting time was shorter than 10 min. This is mainly because that the molecular size of butylparaben is smaller than that of triclosan, thus facilitating butylparaben to enter into or release from the cavities of CPβCDs. Moreover, the solubility of butylparaben is relatively high. Therefore, the butylparaben/CPβCDs complexes could deactivate the bacteria in a relatively shorter time than triclosan/CPβCDs complexes at appropriate concentrations.

Antimicrobial mechanism of antibiotics/CPβCDs complex revealed by AFM

AFM was applied to reveal the antimicrobial mechanism of antibiotics/CPβCDs complex by observing the morphology of *E. Coli* treated by the complex. As can been seen from Fig. 5, after being treated by butylparaben/CPβCDs complex, *E. Coli* still kept the integrated membrane and no obvious indentation observed. From the section analysis, the height of
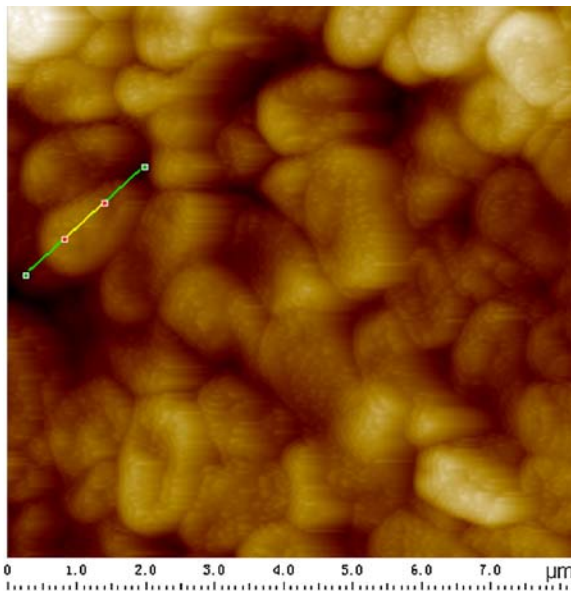

(1) Topography image
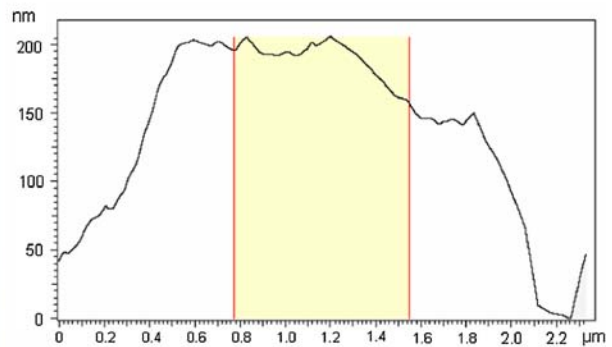
(2) section image

Fig. 5 Morphology of *E. Coli* treated by butylparaben/CPβCDs complex

treated bacteria was not deceased, implying the integration of cell membrane after the treatment. Similar image was observed for the *E. Coli* treated by triclosan/CPβCD complexes. The results suggested that the antimicrobial mechanism of triclosan or butylparaben and CDβCPs complexes is different from that of other cationic antibiotics or polymer (e.g., guanidine polymers discussed in our previous work, Guan et al. 2007b; Qian et al. 2008), which tend to destroy the cell membrane and eventually deactivate the bacteria. The role of triclosan is to block the synthesis of lipids and inhibit the enzyme enoyl-acyl carrier protein reductase (Buschmann and Schollmeyer 2002); while the antimicrobial mechanism of butylparaben may be linked to the mitochondrial depolarization depletion of cellular ATP (Adenosine triphosphate) through uncoupling of oxidative phosphorylation (Lu et al. 2002). On the other hand, the cationic groups on the CPβCDs facilitate the antibiotics to approach the anionic-charged bacterial membrane via electrostatic attraction and therefore improve the antimicrobial activity of antibiotics.

Dynamic adsorption of CPβCD polymers on cellulose fibres

To further verify the strong adsorption of CPβCD on cellulose fibres, dynamic adsorptions were investigated. The adsorption of CPβCD polymers on fibres as a function of time is shown in Fig. 6. As can be
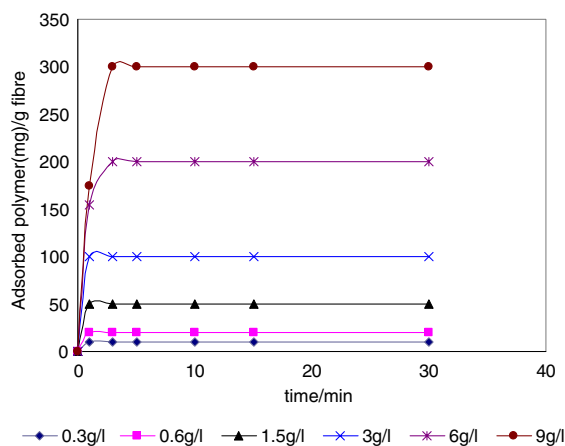
seen, the rapid adsorption occurred for all samples within the concentration range investigated, and the adsorption reached the stead-state within 3 min or shorter. The saturated or steady-state adsorption for all dosages assessed in the current work was proportional to the amounts of polymer added. It is clear that the CPβCD polymers almost completely adsorb on the fibres in the range of polymer concentration investigated, thereby ensuring their effectiveness in rendering cellulose fibre antimicrobial. The strong adsorption of CPβCD is attributed to both cationic charges and small hydrodynamic sizes of the polymers. As a result, the polymers not only adsorb on the fibre surfaces, but also readily penetrate into the pores of fibre walls or entire amorphous region of the cellulose fibres, thus leading to the large capacity of cellulose to absorb the CPβCDs.

Conclusions

The antibiotics/CPβCDs complexes of butylparaben and triclosan were successfully prepared; and the inclusion of antibiotics into the cavities of CPβCDs was confirmed by 2D NMR. Water solubility of the antibiotics was significantly improved after forming the cationic inclusion complexes. The antibiotics/CPβCD complexes showed excellent antimicrobial activities when applying on the cellulose fibers. The growth inhibition increased with the increasing of both antibiotics concentration and contacting time. Triclosan possess the higher antimicrobial efficiency than butylparaben at the same antibiotic concentration, whereas butylparaben exhibited faster inhibition effect than triclosan in a short of contacting time. Morphologies of the untreated and treated bacteria revealed by AFM suggested that the antibiotics/CPβCDs complexes inhibited bacteria through affecting the metabolism of the bacteria instead of damaging the cell membrane.

Fig. 6 Dynamic adsorption of the CD polymer on cellulose fibres at various dosages (polymer concentration is indicated in the legend); fibre consistency: 3%; volume of fibre suspension for each sample: 100 mL

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