Journal of Dentistry 80 (2019) 23–29

Contents lists available at ScienceDirect

Journal of Dentistry

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

Strong antibacterial dental resin composites containing cellulose nanocrystal/zinc oxide nanohybrids

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A R T I C L E I N F O

Keywords:
Caries
Streptococcus mutans
Bacteria
ZnO
Mechanical properties
Composite materials

A B S T R A C T

Objective: The aim is to explore the reinforcing and antibacterial effect of cellulose nanocrystal/zinc oxide (CNC/ZnO) nanohybrids on dental resin composites (DRCs).
Methods: CNC/ZnO nanohybrids were prepared through precipitating Zn^{2+} on the surface of CNC and then introduced into the DRCs. The mechanical properties of DRCs including compressive strength, flexural modulus, flexural strength, and Vickers microhardness were characterized. The antibacterial activity of DRCs to *Streptococcus mutans* was determined and the morphology of *Streptococcus mutans* on the surface of DRCs after incubation was observed. The morphology of fractured surface after flexural test and Zn content in DRCs were analyzed.
Results: Compared with DRCs without CNC/ZnO nanohybrids, DRCs containing 2 wt.% CNC/ZnO nanohybrids possess higher compressive strength and flexural modulus and there is no significantly statistical difference ($P > 0.05$) on the flexural strength and Vickers microhardness. The excess use of CNC/ZnO nanohybrids decreases the mechanical properties of DRCs except flexural modulus. DRCs containing CNC/ZnO nanohybrids show excellent antibacterial properties and a 78% reduction in bacterial number is obtained when 2% CNC/ZnO nanohybrids are added.
Conclusion: The small amounts of CNC/ZnO nanohybrids have a positive influence on the mechanical and antibacterial properties of DRCs.
Significance: The prepared DRCs are promising to address bulk fracture and secondary caries.

1. Introduction

Dental caries, a highly frequent oral disease, is the result of continually demineralizing by acid produced by bacteria [1,2]. Dental resin composites (DRCs) have become the prevalent restorative materials to cure dental caries, due to their excellent esthetics, acceptable biocompatibility and convenient operation [3]. However, DRCs are easier to accumulate biofilm and plaque compared with traditional amalgam which can release antibacterial ions such as Ag^{+} [4], increasing the occurrence risk of secondary caries [5]. It has indicated that 50–70% of composite restorations results from the replacement of the failed restorations [6], while secondary caries is one of the main causes for the failure of composite restorations [7].

The introduction of antibacterial properties into the DRCs is a promising method to address this problem. Releasing (such as Ag and chlorhexidine) [8–10] and non-releasing (such as quaternary ammonium methacrylates, QAMs) [11] antibacterial agents have been studied in dental restorative materials [12]. These additives endow DRCs excellent antibacterial properties, however, other performances of DRCs such as mechanical properties [13,14] and appearance [15] could be compromised, which limits their practical application. ZnO has already been applied to some commercial oral restorative products. Compared with Ag, ZnO possesses more similar colour to natural tooth, which is suitable as dental filler to give DRCs antibacterial properties [16]. The direct addition of ZnO nanoparticle could not improve the mechanical properties effectively [16]. Therefore, cellulose nanocrystal/zinc oxide (CNC/ZnO) nanohybrids were prepared and introduced into DRCs in this study. CNC extracted from natural plants is biocompatible, transparent, and abundant. It has been widely studied in the area of biomaterials as a reinforcing agent [17–19], possessing axial elastic modulus of 110–220 GPa, transverse elastic modulus of 10–50 GPa, and tensile strength of 7.5–7.7 GPa [20,21]. The hypothetic

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https://doi.org/10.1016/j.jdent.2018.11.002
Received 2 October 2018; Received in revised form 26 October 2018; Accepted 6 November 2018
0300-5712/

advantage of the nanohybrids is to integrate the reinforcing effect of CNC and antibacterial activity of ZnO together. The formula of studied DRCs mainly consisted of resin matrix, inorganic filler, and photo-initiator systems. The effect of different amounts of CNC/ZnO nanohybrids on the mechanical and antibacterial properties of the above DRCs was investigated.

2. Materials and methods

2.1. Materials

Bisphenol A glycerolate dimethacrylate (*Bis*-GMA), triethylene glycol dimethacrylate (TEGDMA), camphorquinone (CQ), ethyl 4-dimethylamino benzoate (4-EDMAB), and 3-methacryloxypropyl-trimethoxysilane were obtained from Sigma-Aldrich, USA. Microcrystalline cellulose (MCC), $Zn(NO_3)_2{\cdot}6H_2O$, NaOH, HCl (37%), citric acid, and absolute ethanol were obtained from Sinopharm Chemical Reagent Co., Ltd., China. Micro-SiO_2 (average size 1 μm) and nano-SiO_2 (Aerosil® OX50, average size 40 nm) were obtained from Zhejiang Tongda Weipeng Electric Co., Ltd. and Degussa, respectively. The *Streptococcus mutans* was provided by stomatological laboratory of Shanghai Jiao Tong University School of Medicine.

2.2. Preparation and characterization of CNC/ZnO nanohybrids

2 g MCC was soaked into 100 mL mixed acid consisting of 90 mL 3 mol/L citric acid and 10 mL 6 mol/L HCl, and the mixture was mechanically stirred at 1000 r/min at 80 °C for 6 h. Then the mixture was washed with distilled water and centrifuged at 10,000 r/min at 10 °C for 10 min. The washing process was repeated 3 times and CNC functionalized with −COOH (CNC−COOH) was obtained. The CNC−COOH was dispersed into distilled water to prepare 100 mL suspension liquid. 0.1 mol/L $Zn(NO_3)_2{\cdot}6H_2O$ solution was made previous and 22.41 mL of above solution was added into the suspension liquid and stirred homogeneously. The pH of the mixture was adjusted to about 7 using 0.5 mol/L NaOH solution. Then the mixture was heated to 80 °C and 8.96 mL 0.5 mol/L NaOH solution was added dropwise to precipitate Zn^{2+} under magnetic stirring of 800 r/min. After reacted for 30 min, the sample was sufficiently washed using distilled water to remove the remaining zinc species and other byproducts. Then the sample was collected and freeze-dried for 48 h. The powder of CNC loading Zn$(OH)_2$ (CNC/$Zn(OH)_2$) was obtained. At last, the CNC/$Zn(OH)_2$ powder was dried in a vacuum oven at 100 °C for 24 h to transform $Zn(OH)_2$ to ZnO.

The morphology of original MCC and prepared CNC/ZnO was observed using a field emission scanning electron microscope (FE-SEM, S-4800, Hitachi, Japan) and transmission electron microscope (TEM, JEM-2100, Japan), respectively. The structure was characterized using an X-ray diffraction (XRD, D/Max-2550 PC, Japan) with 2θ range of 5–80°and a Fourier transform infrared spectroscopy (FT-IR, Nicolet 6700, USA) with a resolution of 4 cm^{-1}.

2.3. Preparation of dental resin composites

The formula and preparation of DRCs were based on a previous study [15]. The CNC/ZnO nanohybrids as functional additive was added into the DRCs with different amounts (0, 2, 4, 6, and 8 wt.%). The resin matrix was firstly prepared through mixing *Bis*-GMA and TEGDMA at a mass ratio of 1:1. Then CQ and 4-EDMAB were added into the resin matrix in the dark at room temperature, which accounted for 0.2 wt.% and 0.8 wt.% of resin matrix, respectively. The modified micro-SiO_2 (5.5 g), modified nano-SiO_2 (1.5 g) and CNC/ZnO nanohybrids (0, 0.2, 0.4, 0.6, 0.8 g) were added into the resin matrix (3 g) containing photo-initiator systems in turn and blended using a Speedmixer (DAC 150.1 FVZ-K) at 3000 r/min for 5 min. Finally, the pasty samples were transferred onto a three roll mixer (EXAKT 80E) to blend thoroughly.

2.4. Characterization of dental resin composites

2.4.1. Mechanical properties

Composites paste was filled in specified molds (flexural test 2 mm × 2 mm × 25 mm, compressive test Φ 4 mm × 6 mm, Vickers microhardness test Φ 6 mm × 4 mm) and then each side of samples was cured for 60 s. All prepared samples were polished before test. A universal testing machine (Instron 5900, USA) was applied to test flexural (span 20 mm, crosshead speed 0.75 mm/min, n = 6) and compressive (loading rate 1 mm/min, n = 6) properties. A Vickers indentation technique (FV-700, Future-Tech Corporation, n = 3) was applied to test Vickers microhardness at a load 0.5 Kgf for 5 s.

The statistical significance of mechanical data was evaluated using one-way analysis of variance (ANOVA) and $P < 0.05$ was considered statistically significant.

2.4.2. Antibacterial properties

The antibacterial activity of DRCs was determined according to the standard ASTM E2180-07 (2012). 0.08 mL of inoculated molten agar slurry with *Streptococcus mutans* was placed onto the disc-shaped samples (approximately 10^6 CFU of bacteria, 14 mm diameter, n = 3). Then the samples were incubated in an anaerobic incubator at 37 °C for 24 h. The agar slurry inoculum was eluted using dey/engley (D/E) neutralizing broth and surviving *Streptococcus mutans* was recovered. Serial dilutions were made with D/E broth and then each suspension was placed on tryptic soy agar (TSA) to incubate for 48 h. Bacterial colonies were finally counted and recorded.

The morphology of *Streptococcus mutans* on the surface of DRCs was observed through staining bacteria with LIVE/DEAD® BacLight™ Bacterial Viability Kit. Five groups of samples (disc-shaped, 14 mm diameter) were sterilized with ethylene oxide and transferred to a 24-well plate. The bacteria solution (10^6 CFU/mL) was inoculated into the wells with 1 mL/well. The wells were then placed in the anaerobic incubator for 24 h. Then the samples were gently rinsed twice with phosphate buffer saline to remove non-adherent bacteria. 500 μL of bacterial dye was added and incubated for 15 min in the dark according to the instructions. The bacterial morphology on the surface of samples was observed using a fluorescence microscope (Olympus BX53, Japan).

2.4.3. Analysis of fractured surface

The morphology of fractured surface after flexural test and Zn content in DRCs were examined using FE-SEM (S-4800, Hitachi, Japan) equipped with an energy dispersive X-ray spectroscopy (EDS, Quantax 400, Bruker, Germany).

3. Results

3.1. Characterization of prepared CNC/ZnO nanohybrids

Fig. 1a is the SEM image of original MCC, which is of different shapes and sizes with micron level in length and width. After treated by mixed acid consisting of HCl and citric acid, the MCC is separated into smaller CNC with functional group −COOH, which can further absorb Zn^{2+} to obtain CNC/ZnO nanohybrids. Fig. 1b shows the morphology of CNC/ZnO nanohybrids, where ZnO nanoparticle is deposited onto the surface of CNC. There is no obvious agglomeration between ZnO nanoparticle, indicating its dispersion on the CNC is good.

Fig. 1c shows the crystalline structure of MCC and CNC/ZnO nanohybrids. The MCC is attributed to cellulose I according to peaks at 2θ = 14.9°, 16.4°, 22.7°, and 34.5°, corresponding to crystallographic plane ($1\bar{1}0$), (110), (200), and (004), respectively [22]. The new peaks at 2θ = 31.9°, 34.6°, 36.3°, 47.6°, 56.7°, 62.9°, 68.0°, and 69.0° conform to the crystalline structure of ZnO, corresponding to crystallographic plane (100), (002), (101), (102), (110), (103), (112), and (201),

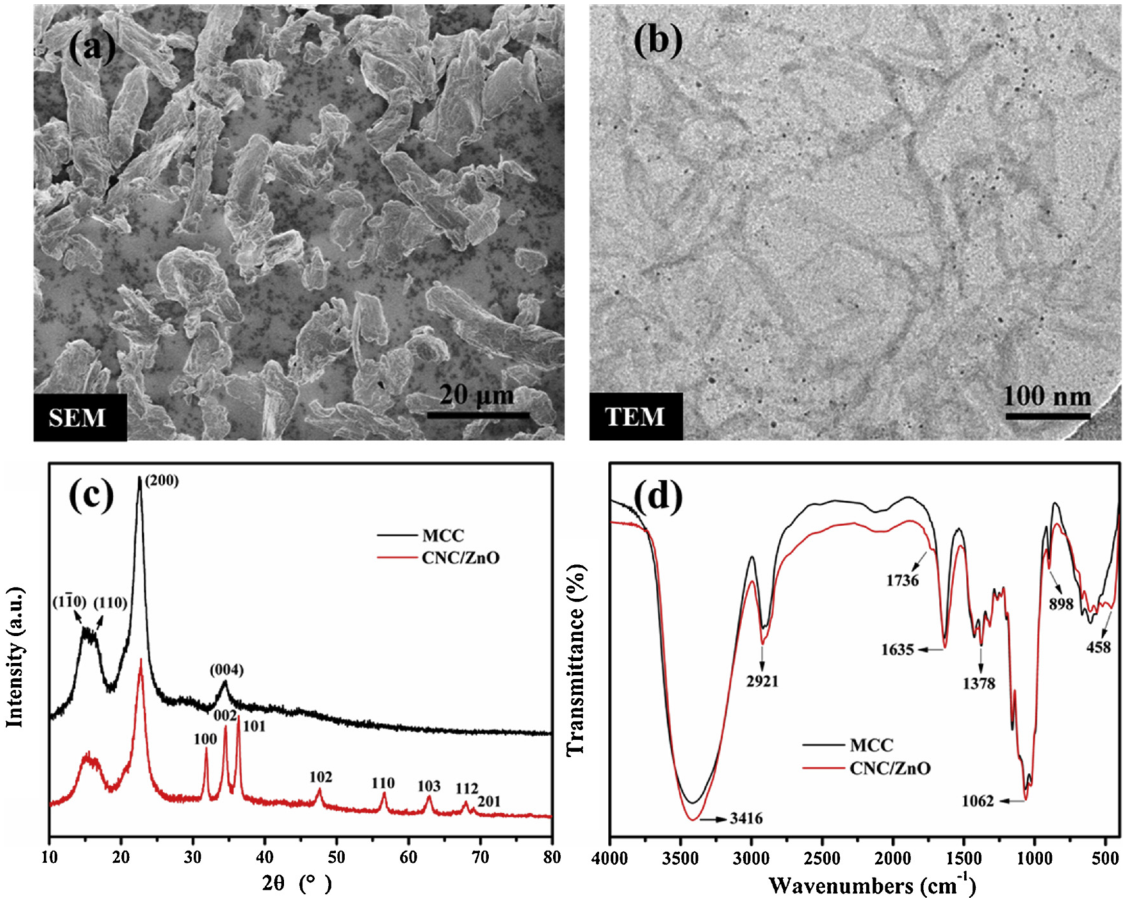


Fig. 1. The morphology (a: MCC, b: CNC/ZnO), XRD (c), and FT-IR (d) spectrum of MCC and CNC/ZnO nanohybrids.

respectively [23]. Fig. 1d shows FT-IR spectrum of MCC and CNC/ZnO nanohybrids. The band at 3416 cm^{-1} is associated with the stretching vibration of O—H. The bands at 2921, 1378, and 898 cm^{-1} can be attributed to the stretching, deformation, and rocking vibrations of C—H, respectively [24–26]. The band at 1635 cm^{-1} results from the bending mode of water absorbed by cellulose [24]. The band at 1062 cm^{-1} is due to the stretching of C—O [25]. Compared with MCC, CNC/ZnO appears new peaks at 1736 cm^{-1} and 458 cm^{-1}, which are due to the stretching vibrations of C═O and Zn—O, respectively [27]. The XRD and FT-IR results further confirm that the CNC/ZnO nanohybrids were successfully prepared.

3.2. Mechanical and antibacterial properties of dental resin composites

The mechanical properties of DRCs are shown in Fig. 2. DRCs containing 2 wt.% CNC/ZnO nanohybrids possess compressive strength of 371.0 ± 6.6 MPa and flexural modulus of 8.3 ± 0.1 GPa, higher than the control group without CNC/ZnO nanohybrids which possess compressive strength of 344.3 ± 10.7 MPa and flexural modulus of 8.0 ± 0.1 GPa. There is no significantly statistical difference ($P > 0.05$) on the flexural strength and Vickers microhardness between the two groups. However, the further increase of CNC/ZnO content can lead to the decrease of mechanical properties except the flexural modulus.

The morphology of stained *Streptococcus mutans* is shown in Fig. 3(a–e). The green indicates the live bacteria and the red indicates the dead bacteria. The DRCs without CNC/ZnO nanohybrids have almost no antibacterial activity and there is much live bacteria on the surface (Fig. 3a). The addition of CNC/ZnO nanohybrids significantly improves the antibacterial properties of DRCs and a 78% reduction in bacterial number is obtained when only 2% CNC/ZnO nanohybrids are used (Fig. 3f). With the increase of CNC/ZnO content, the rate of dead bacteria enhances and the adhesion of bacteria on the surface of DRCs decreases (Fig. 3a–e).

3.3. Surface analysis of fractured dental resin composites

The representatively fractured surface of DRCs is analysed. The spherical micro- and nano-SiO_2 are observed clearly from SEM images, which are enveloped by the resin well. It is difficult to find the CNC/ZnO nanohybrids due to its small size and low content (Fig. 4(a–c)). The DRCs containing 0 wt.% and 2 wt.% CNC/ZnO nanohybrids have roughly fractured surface (Fig. 4a and b), which is helpful for absorbing more energy during fracture. However, there are some cavities inside the DRCs containing 8 wt.% CNC/ZnO nanohybrids (Fig. 4c). These cavities could become mechanical defects and cause the fracture of DRCs easily, confirmed by the results of mechanical properties before. The results of EDS show the content of Zn in the DRCs. The DRCs without CNC/ZnO nanohybrids have no presence of Zn (Fig. 4d), showing inferior antibacterial properties. The DRCs containing CNC/ZnO nanohybrids are detected the Zn element and the content of Zn is the highest (0.88 wt.%) in the DRCs containing 8 wt.% CNC/ZnO nanohybrids (Fig. 4f), according with the results of antibacterial properties before.

4. Discussion

The MCC contains crystalline and amorphous regions. The difference between the two regions is the arrangement of cellulose chain. The cellulose chain in crystalline region is highly ordered while disordered in amorphous region. The crystalline region can be extracted through proper methods such as mechanical, chemical or enzymatic treatments, resulting in CNC [20,21]. In this study, the MCC is treated by the mixed

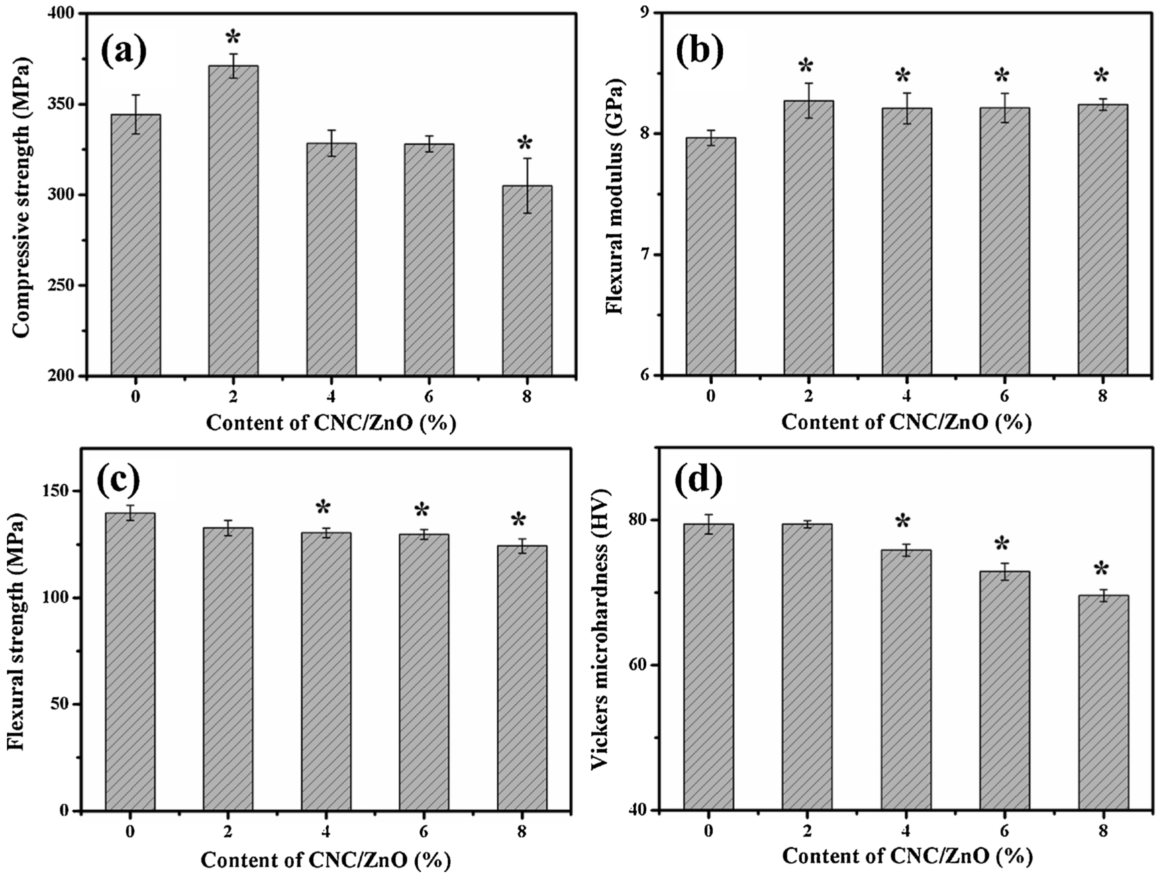


Fig. 2. The compressive strength (a), flexural modulus (b), flexural strength (c), and Vickers microhardness (d) of dental resin composites containing different amounts of CNC/ZnO nanohybrids. * indicates $P < 0.05$ and there is significantly statistical difference compared with the control group without CNC/ZnO nanohybrids.

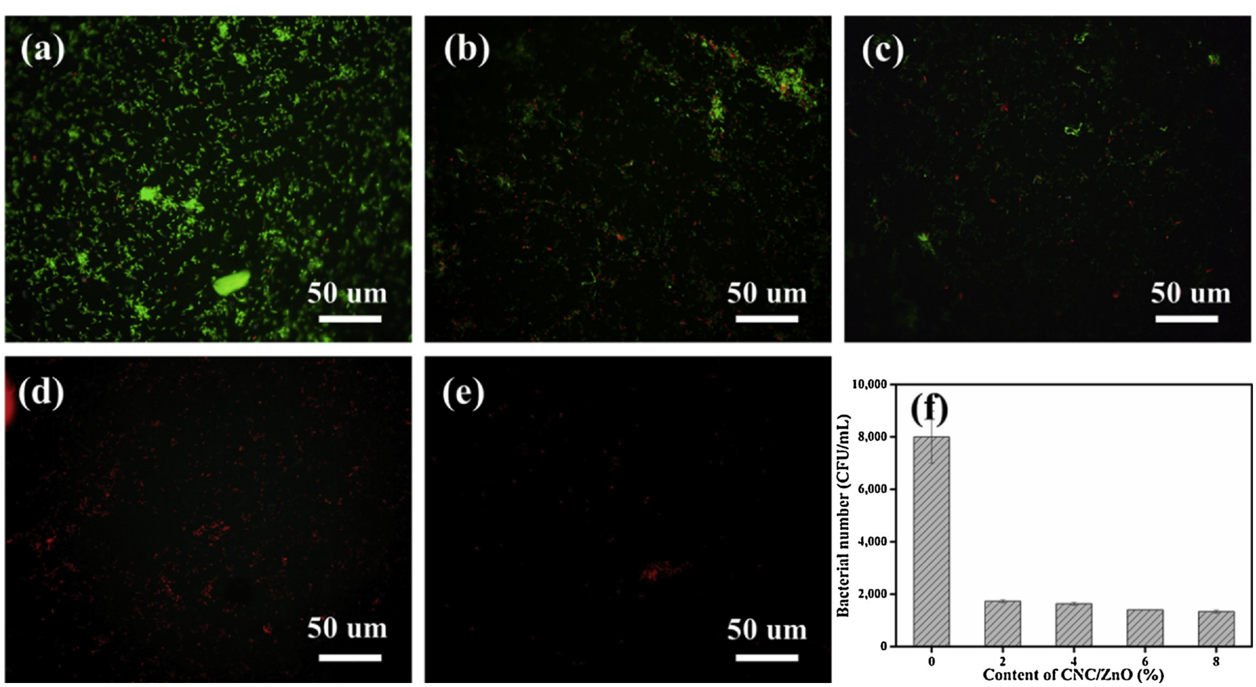


Fig. 3. The morphology of stained *Streptococcus mutans* on the surface of dental resin composites containing 0 wt.% (a), 2 wt.% (b), 4 wt.% (c), 6 wt.% (d), and 8 wt.% (e) CNC/ZnO nanohybrids. The number of *Streptococcus mutans* after incubated for a certain time (f) (For interpretation of the references to colour in the figure text, the reader is referred to the web version of this article).

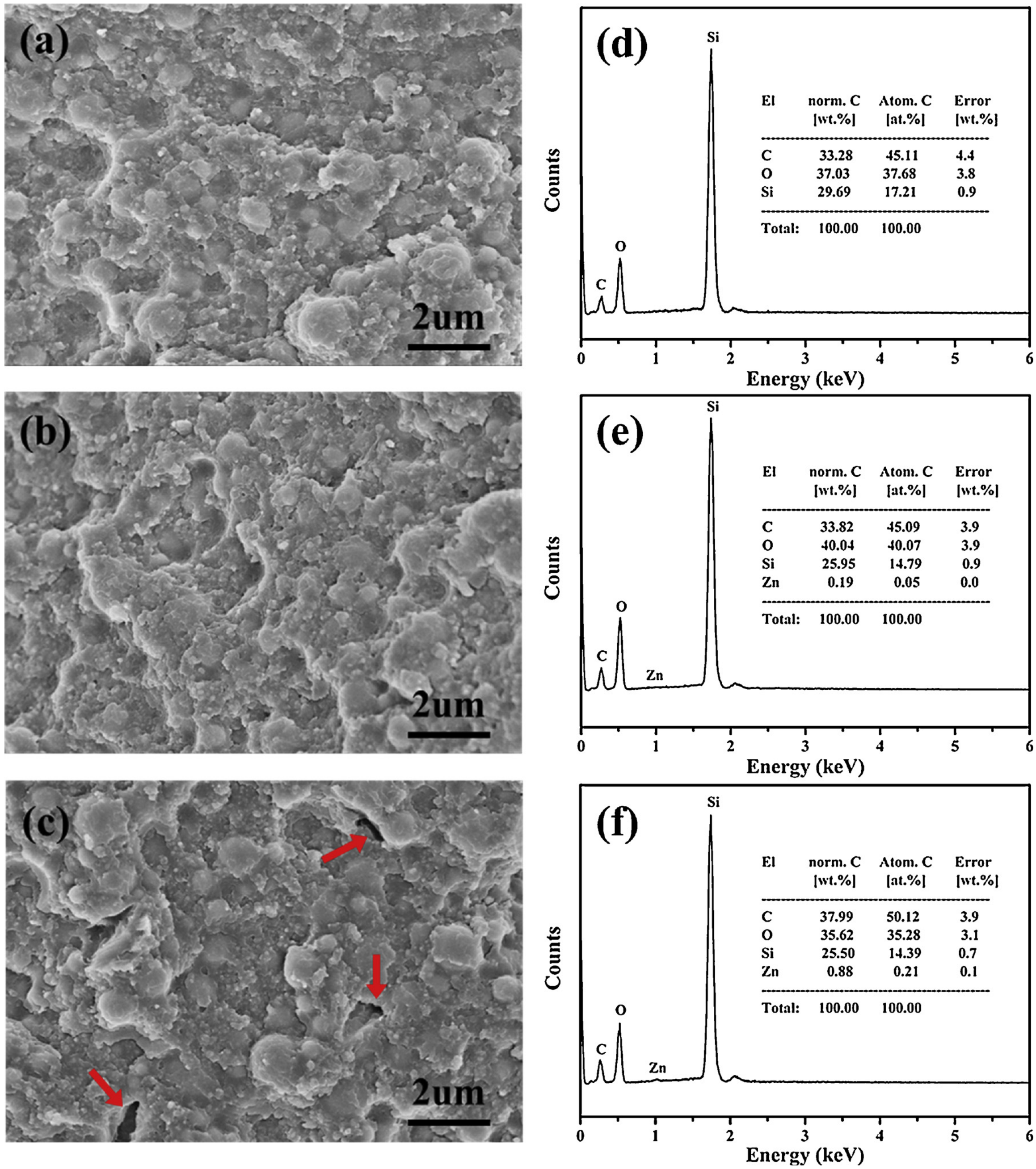
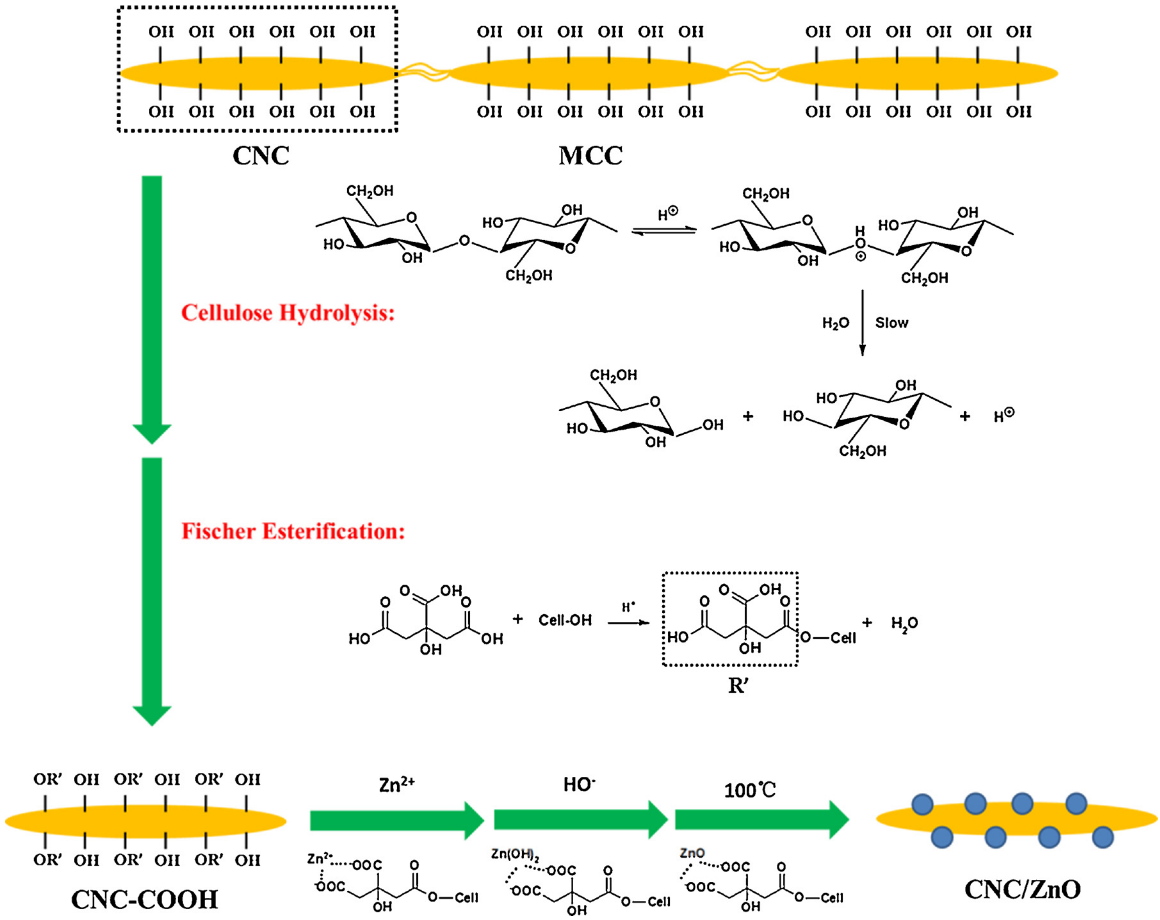


Fig. 4. SEM and EDS analysis of fractured dental resin composites containing 0 wt.% (a,d), 2 wt.% (b,e), and 8 wt.% (c,f) CNC/ZnO nanohybrids, and red arrows indicate cavities (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

acid consisting of HCl and citric acid. After the amorphous region of MCC is hydrolysed, the CNC will be extracted. Meanwhile, Fischer esterification occurs between −COOH from citric acid and −OH from cellulose chain, and the residual unreacted −COOH of citric acid is brought onto CNC, which can adsorb Zn^{2+} through electrostatic interaction. When the HO^- is added, $Zn(OH)_2$ is formed and deposited onto the surface of CNC. The CNC/ZnO nanohybrids are finally obtained through transforming $Zn(OH)_2$ into ZnO under heating. The preparation route of CNC/ZnO nanohybrids is shown in Scheme 1.

The obtained CNC/ZnO nanohybrids are utilized to strengthen DRCs. Mechanical properties are one of the important indicators for clinical application of DRCs. The occurrence of bulk fracture can be decreased when the restorative materials possess satisfactory mechanical properties [28,29]. In this study, small amounts of CNC/ZnO nanohybrids improve the mechanical properties of DRCs. With the amounts of CNC/ZnO nanohybrids further increase, the mechanical properties except the flexural modulus decrease. It could be explained by the fact that CNC is an excellent reinforcing agent to the resin matrix only when its amount reaches a proper value [30,31]. A previous research has reported that small amounts of CNC significantly reinforced the dental glass ionomer cement but the excessive addition of CNC could cause agglomeration and then decreased the mechanical properties of dental materials [17].

It is meaningful to endow DRCs excellent antibacterial properties. In clinical practice, minimally invasive treatment is usually adopted, with a purpose of saving affected tissues as much as possible. However, it also results in the difficulty of removing caries completely during restorations, which will possibly reserve much cariogenic bacteria [12]. Besides, there is an interfacial gap between DRCs and affected tissues due to polymerization shrinkage, providing survival space for bacteria.



Scheme 1. The preparation route of CNC/ZnO nanohybrids.

To overcome this problem, antibacterial DRCs are developed through introducing CNC/ZnO nanohybrids. *Streptococcus mutans* was chosen to determine the antibacterial properties of DRCs, which has been considered as the main cariogenic bacteria among over 700 bacterial species in oral cavity [7,32]. The addition of CNC/ZnO nanohybrids significantly improves the antibacterial properties of DRCs, which is hopeful to address the secondary caries. The antibacterial mechanism of ZnO nanoparticle is not completely clarified [33]. One mechanism proposed to explain the antibacterial activity of ZnO nanoparticle is that under ultraviolet light, it can generate active oxygen species such as H_2O_2 to inhibit the growth of bacteria [16,34]. However, in practical application, it is almost impossible that the restorative materials in oral cavity are exposed to the ultraviolet light. Antibacterial activity of ZnO nanoparticle in the dark has been detected. It can be explained that Zn^{2+} with positive charge can interact with the bacterial cell membrane with negative charge and then kill bacteria [33].

Current research mainly focuses on the mechanical and antibacterial properties of DRCs. Considering the complexity of oral environment, more research is needed in future, such as the long-term service behaviour of DRCs, the biosafety to the human body, and so on.

5. Conclusion

Strong antibacterial DRCs have been developed through the introduction of CNC/ZnO nanohybrids. Small amounts of CNC/ZnO nanohybrids can significantly inhibit the growth and the adhesion of bacteria on the surface of DRCs, and doesn't compromise the mechanical properties of DRCs. The excess use of CNC/ZnO nanohybrids could result in the decrease of mechanical properties except flexural modulus, due to the agglomeration of nanohybrids. This study could be promising to overcome the secondary caries and bulk fracture through adding small amounts of CNC/ZnO nanohybrids into DRCs.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This work is financially supported by National Key Research and Development Program of China (2016YFA0201702/2016YFA0201700), National Natural Science Foundation of China (NO. 51733002), Program for Changjiang Scholars and Innovative Research Team in University (IRT 16R13), and Shanghai Pujiang Program (18PJ1400300).

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