Research Article

Multiclawed SiO₂ Nano-Antibacterial Agent Based on Charge Inversed Ce6 Ionic Liquid Polymers for Combating Oral Biofilm Infection

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Received 10 August 2021; Accepted 20 November 2021; Published 12 January 2022

1. Introduction

Oral biofilm infection is most important pathogenic factor of dental caries [1, 2]. Thus, eliminating biofilm on the tooth surface is a primary strategy to prevent and treat dental caries [3]. However, with the protection, bacteria in the biofilm is difficult to eradicate by common strategy of mechanical cleaning combined antibiotics. In this background, it is urgently to develop new treatment against oral biofilm infection. One promising therapy is PACT [4]. Compared with traditional treatment, PACT could efficiently control of bacteria and bacterial biofilm infection. However, owing to rapid clearance by saliva and barrier of biofilm, the photosensitizers are not concentrated in the infection site, and the efficacy of PACT against oral biofilm infections is limited [5]. Faced with the dilemma, the concentration of photosensitizer in the site of oral biofilm is the key to improve the PACT efficiency.

An understanding of oral biofilms matrix could offer opportunities to exploit photosensitizer delivery systems [6]. Because oral biofilm develop when microbes accumulate and form structured communities encapsulated within an extracellular matrix such as exopolysaccharides (EPS) [7, 8], the sugars are fermented by bacteria within the EPS matrix, then created highly acidic microenvironments and negative charge. The pH values often reach pH~4.5 or even lower in oral biofilm and particularly after exposure to sucrose, starch, and other cariogenic food products [9]. So,
A photosensitizer delivery system that could respond to lower pH microenvironments is an effective method to improve delivery efficiency. Furthermore, many researches on cationic polymers [10], especially on the charge-reversal polymers, indicated that positively charged polymers could combine with extracellular polymeric substances (EPS) [11] and increase concentration of photosensitizer in biofilm. However, due to the dense and thick structure of biofilm, the photosensitizers difficultly penetrated into biofilm; then, photochemical reaction initiated by photosensitizer occurs mainly in the outermost layers of biofilm. The PACT efficiency was not significantly improved.

To overcome these challenges, polyionic liquid that composed of polycation and anion is introduced in previous studies [12, 13]. Inspired by octopus claws, the polyionic liquid photosensitizer nanoparticle (SiO$_2$-PCe$_6$-IL) like arms of octopus was prepared in this work. In acid microenvironment of oral biofilm, the SiO$_2$-PCe$_6$-IL could change to nano-claws SiO$_2$-PIL$^+$ and firmly combine to negatively charged EPS to overcome the saliva cleaning. Then, the dodecyl on the SiO$_2$-PIL$^+$ could pierce through the biofilm and break down the barrier of biofilm. Finally, the photosensitizer was highly concentrated in oral biofilm, and the biofilm infection was eliminated. The high binding energy between positively charged SiO$_2$-P$_{C66.IL}$ and oral biofilm, excellent breaking ability of polydodecyl, and effective enrichment of photosensitizer were the key factors to effectively eliminate oral biofilm. The mechanism of SiO$_2$-P$_{C66.IL}$ against oral biofilm is showed in Figure 1.

**2. Materials and Methods**

**2.1. Materials.** Ce6 was purchased from Frontier Scientific. KOH, methanol, methanol, absolute ethanol, cyclohexane, ammonia solution, hexanol, trimethylamine, Triton x-100, and 1,3-diphenylisobenzofuran (DPBF) were purchased from Sinopharm Chemical Reagent Co., Ltd. Artificial saliva was purchased from Beijing Regan Biotechnology Co., Ltd. Tetraethyl orthosilicate (TEOS), 3-aminopropyl triethoxysilane (APTES), CuCl, 2-bromoisobutyryl bromide, and N,N,N,N′,N″-pentamethyldiethylenetriamine were purchased from Aladdin. Streptococcus mutans (S. mutans, ATCC 700610) was purchased from ATCC. Brain Heart Infusion Broth (BHIB) was purchased from Beijing Land Bridge Technology Co., Ltd. The live/dead Baclight bacterial viability kit (L7012) was purchased from Invitrogen. Hydroxyapatite tablets were purchased from National Bio-medical Materials Engineering Technology Research Center (China). Alexa Fluor 647 was purchased from Thermo Fisher Scientific.

**2.2. The Synthesis and Characterization of Multiclawed SiO$_2$-P$_{C66.IL}$.** The preparation of SiO$_2$-Br was similar with previous research [14], except the 2.4 mL of triethylamine and 2-bromoisobutyryl bromide (1.2 mL) were added to prepare SiO$_2$-Br. The multiclawed SiO$_2$-P$_{C66.IL}$ was prepared by ATRP. Briefly, 10 mg Ce6-IL and SiO$_2$-Br dispersed into a mixture solution of ethanol and distilled water (5:1, V:V) for stirring 10 min at 800 rpm. 200 μL of PMDETA and 30 mg of CuCl were quickly transferred into the flask for reaction 8 h at 35°C. The SiO$_2$-P$_{C66.IL}$ was washed with ethanol, distilled water.

The morphology of SiO$_2$-P$_{C66.IL}$ was examined by TEM and SEM. The change of SiO$_2$-P$_{C66.IL}$ zeta potentials in pH 4.5 and 7.4 was measured by a Delsa Nano C particle analyzer (Beckman Coulter Ireland Inc.).

The UV absorption of 5.0 mg·mL$^{-1}$SiO$_2$-P$_{C66.IL}$ was measured by UV-vis (MAPADA). The Ce6 loading efficiency ($L$) was calculated as formula:

\[
L = \frac{C \times V}{W} \times 100\%.
\]

$L$ was SiO$_2$-P$_{C66.IL}$ loading efficiency; $C$ was the concentration of Ce6 (mg mL$^{-1}$); $V$ was solution volume (mL); $W$ was the weight of SiO$_2$-P$_{C66.IL}$ (mg).
Figure 2: Continued.
The Ce6 released in acidic microenvironment of oral biofilm (pH 4.5) was quantified by UV-vis. Briefly, 10 mg multiclawed SiO$_2$-P$_{Ce6}$-IL was placed in pH 4.5 solution 10 min and separated by centrifugation. The concentration of Ce6 in supernatant was examined by UV-vis.

DPBF was used to measure the generation of $^{1}$O$_2$ [15]. Briefly, 2.0 mL DMSO solution containing SiO$_2$-P$_{Ce6}$-IL (equalled 100 μM Ce6) and 100 μM DPBF was irradiated by 660 nm light with a power density of 0.5 W cm$^{-2}$. The absorbance of DPBF at about 410 nm was taken to record at 1 and 2 min.

2.3. Binding Ability of SiO$_2$-P$_{Ce6}$-IL to Oral Biofilm. Hydroxyapatite tablets (6.0 mm in diameter, 1.5 mm in thickness) were washed twice with PBS and incubated with artificial saliva to obtain saliva-coated hydroxyapatite. The S. mutans biofilm was formed on hydroxyapatite surfaces in BHIB medium which contained S. mutans (10$^6$) and 2% sucrose (w/v) for incubated 72 h at 37°C. The binding capacity of SiO$_2$-P$_{Ce6}$-IL to the hydroxyapatite and S. mutans biofilm was measured by UV-vis. The 0.1 mM multiclawed SiO$_2$-P$_{Ce6}$-IL was incubated with hydroxyapatite and biofilm in pH 4.5 and 7.4 solutions for 10 min at 37°C, and then, the concentration of SiO$_2$-P$_{Ce6}$-IL was measured before and after adsorption to calculated binding capacity.

In order to examine the binding ability of SiO$_2$-P$_{Ce6}$-IL to oral biofilm, the interaction between SiO$_2$-P$_{Ce6}$-IL and S. mutans biofilm was measured by AFM. The procedure was as follows: the AFM tip (NP-O10, Bruker) contacted with epoxy. After waiting for 10 min, 1 μL SiO$_2$-P$_{Ce6}$-IL (0.1 mM) was put on the tip and heated to completely cure epoxy. Then, the AFM tip was put in ultrapure water and ultrasonicated for 30 s to get rid of unattached SiO$_2$-P$_{Ce6}$-IL. The SEM was used to check the AFM tip modified with SiO$_2$-P$_{Ce6}$-IL.

2.4. Photosensitizer Concentration in Biofilm. The S. mutans biofilm was stained with Alexa Fluor 647. Briefly, 1 μM Alexa Fluor 647 was added to the S. mutans biofilms for 6 h. 20 μL of SiO$_2$-P$_{Ce6}$-IL or Ce6 (120 μM) was added onto the S. mutans biofilm interaction for 30 min, and then, wash with PBS 3 times to remove unconjugated SiO$_2$-P$_{Ce6}$-IL or Ce6. The laser scanning confocal microscopy (LSCM, Leica TCS SP8 STED 3X Super-resolution Confocal Microscope, Germany) was used to examine the concentration of Ce6 in biofilm.

2.5. Antibiofilm Activity. The S. mutans biofilm was treated with PBS, SiO$_2$-P$_{Ce6}$-IL, and Ce6. The biofilm incubated with BacLight live/dead dye in the dark after illumination for 15 min to observe dead/live bacteria. The CLSM images were taken to analyze the live and dead bacteria.

2.6. In Vivo Efficacy. Animal experiments were performed on a well-established model of dental caries disease as described in previous literatures [16]. Briefly, rats with two weeks old were purchased from animal center of the Air Force Medical University and screened for infection with S. mutans. Any rats infected with S. mutans prior to inoculation were removed. The animals were infected orally using an actively growing culture of S. mutans by oral swabbing three times a day for 2 weeks. Infected animals were randomly placed into three treatment groups of $n=5$, and their teeth treated topically once daily. The treatment groups included (1) PBS, (2) SiO$_2$-P$_{Ce6}$-IL (amount to 0.1 mM Ce6) using a 660 nm LED light (0.5 W/cm$^2$) for 15 min, and (3)
Figure 3: Continued.
free Ce6 (0.1 mM Ce6) using a 660 nm LED light (0.5 W/cm²) for 15 min. Each group was provided the National Institutes of Health cariogenic diet 2000 and 5% sucrose water ad libitum. The experiment proceeded for 2 weeks; all animals were weighed weekly. At the end of the experimental period, animals were sacrificed, and the teeth were observed by SEM. Finally, the heart, liver, spleen, lung, and kidney were harvested for histological sections (H&E staining analysis on a Leica SP8 microscope).

2.7. Cell Viability Assays. The cell viability of SiO₂-P₇₆₆-IL was evaluated by CCK-8 assays. L929 fibroblast cells were used as model cells and seeded into 96-well plates (6000 cells per well) with 180 μL of DMEM culturing medium in each well for 24 h. SiO₂-P₇₆₆-IL solution with concentrations from 0.2974, 0.5587, and 1.1173 mM was added to the cells and irradiated by LED light (0.5 W/cm²) for 15 min. After being incubated for 48 h, 200 μL of MTT solution (0.5 μg/mL) was added to each well and cultured for another 2 h. 200 μL DMSO was added and shook for 10 min to dissolve the crystal. Then, the absorbance was recorded at 490 nm by a microplate reader (model 550, BioRad).

2.8. Hemolysis Assay. The red blood cells washed with PBS until the supernatant was pellucid and was diluted to 2 vol% by PBS. The Ce6 and SiO₂-P₇₆₆-IL (0.1 mM) were immersed into 2 vol% red blood cell solutions (5 mL for each tube) and incubated at 37°C for 3 h, respectively. Then, the samples were centrifuged at 1500 rpm for 10 min, and the OD values were recorded at 545 nm. The red blood cells treated with water as the positive control, while the red blood cells treated with PBS as negative control. The hemolysis rate was determined by the equation (2):

\[
\text{Hemolysis rate} = \frac{\text{OD}_{\text{positive}} - \text{OD}_{\text{negative control}}}{\text{OD}_{\text{positive}} - \text{OD}_{\text{negative control}}} \times 100\%.
\]

Besides hemolysis rate, the major organs including the hearts, livers, spleens, lungs, and kidneys were collected and stained with H&E for further evaluation of biocompatibility as previously reported [17].

3. Results and Discussion

3.1. Characterization of SiO₂-P₇₆₆-IL. In order to strong interaction, the 8.92% Br of ATRP grafted on SiO₂ (Figure 2(d)). As showed in Figure 2(a), the size of SiO₂-P₇₆₆-IL was about 70 nm, and the surface was more rough after initiated by CuCl. Element analysis displayed that N elements of P₇₆₆-IL were on the SiO₂. The location of Si
and N elements was further analyzed by the Spherical Aberration Corrected Transmission Electron Microscope (ACTEM) analysis software. The analysis results showed that the N element was on the surface of Si (Figure 2(b)). These results indicated that the P Ce6-IL was successful grafted on the surface of SiO₂.

Because ¹⁰² was a major factor in photodynamic therapy [18], the ¹⁰² production of SiO₂-P Ce6-IL was examined.

Figure 4: (a) (A) S. mutans biofilm; (B) S. mutans biofilm treated with Ce6; (C) S. mutans biofilm treated with SiO₂-P Ce6-IL; (b) live (green) and dead (red) results; (A) control group; (B) treated with Ce6; (C) treated with SiO₂-P Ce6-IL; (c) (A–C) the morphology of S. mutans biofilm; (D, E) the morphology of S. mutans biofilm treated with Ce6; (F, G) the morphology of S. mutans biofilm treated with SiO₂-P Ce6-IL; (H) the morphology of S. mutans biofilm combined with SiO₂-P Ce6-IL; (I) the pores in the EPS.
by DPBF. For the reaction of DPBF with $^{1}\text{O}_2$, decreased the absorption of DPBF at 410 nm, the consumption rate of DPBF corresponds to the $^{1}\text{O}_2$ production. Compared to the reduced absorbance of DPBF treated by Ce6 (from 3.15 to 1.75)\(^{14}\), the absorbance of DPBF treated by SiO$_2$-P$_{Ce6}$-IL reduced from 2.69 to 0.24, and the consumption of DPBF was 2.45 (Figure 2(c)). The SiO$_2$-P$_{Ce6}$-IL had higher $^{1}\text{O}_2$. More $^{1}\text{O}_2$ production indicated that SiO$_2$-P$_{Ce6}$-IL had strong oxidation capacity and high PACT efficacy.

3.2. Binding Ability of SiO$_2$-P$_{Ce6}$-IL with Oral Biofilm. The Streptococcus mutans (S. mutans) is one of the primary pathogenic bacteria that cause caries. In this work, S. mutans biofilm as model was used to study antibacterial ability of SiO$_2$-P$_{Ce6}$-IL. To mimic the bacterial biofilm on the teeth, bacteria were grown for 72 h on hydroxyapatite disks. Due to acid microenvironment of S. mutans biofilm, the Ce6 was protonated and released; then, SiO$_2$-P$_{Ce6}$-IL changed to positive charged SiO$_2$-P$_{IL}^+$. The biofilm had anions such as carboxyl, phosphoryl, and glycerate at the proteins or polysaccharides would produce negatively charge\(^{19}\). The electrostatic interactions would occur between SiO$_2$-P$_{IL}^+$ and S. mutans biofilm. In order to detect interaction strength, the AFM was used to detect the interaction between SiO$_2$-P$_{IL}^+$ and S. mutans biofilm. As showed in Figure 3(a), the SiO$_2$-P$_{Ce6}$-IL has been successfully modified on the AFM probe. The interaction between SiO$_2$-P$_{Ce6}$-IL with S. mutans biofilm was 954.02 nN which contributed by imidazolium cation and dodecyl in the SiO$_2$-P$_{IL}^+$. However, the interaction of Ce6 with S. mutans biofilm was only 23.35 nN, and this weak force was difficult to resist saliva cleaning. This strong interaction was also proved by SEM. As showed in Figure 4(c), the SiO$_2$-P$_{IL}^+$ like multiclawed octopus and could firmly adsorb on the S. mutans biofilm (EPS). Along with massive positive charges of SiO$_2$-P$_{IL}^+$, the surface potential of S. mutans biofilm changed from -117 to 35 mV, and the adhesion of S. mutans biofilm was decreased from -76 nN to -25 nN. However, the adhesion of S. mutans biofilm treated by Ce6 alone was -45 nN. Due to the strong adhesion, the oral biofilm infection was difficult to eradicate. So, the decreased adhesion of SiO$_2$-P$_{Ce6}$-IL will be beneficial to eliminating biofilm infection.

3.3. Antibacterial Activity In Vitro. As a result of strong interaction, the SiO$_2$-P$_{IL}^+$ combined with biofilm firmly and the problem of saliva cleaning was solved. But the barrier of biofilm also severely restricted the PACT efficacy against oral biofilm. As showed in Figure 4(a), the blue was S. mutans biofilm, and the red Ce6 was difficult to enter the biofilm (Figure 4(a)). Limited by lifetime and diffusion distance of $^{1}\text{O}_2$\(^{20}\), the Ce6 was difficult to damage protected bacteria outside biofilm. As showed in Figure 4(b), green represented live bacteria, and red represented dead bacteria. Most bacteria were alive after treated by Ce6 alone. So it is very important to destroy the dense structure of biofilm to improve the Ce6 concentration in biofilm. Compared to Ce6, SiO$_2$-P$_{Ce6}$-IL had hydrophobic dodecyl chain which like suckers on the arm of octopus and could destroy the structure of biofilm. In order to examine the membrane breaking effect of SiO$_2$-P$_{Ce6}$-IL, the morphology of S. mutans biofilm was characterized by SEM. As showed in Figure 4(c), the pores were created in the S. mutans biofilm. Once the biofilm was broken, the Ce6 was highly concentrated in biofilm (Figure 4(a)). After illumination for 15 min, most of S. mutans in the biofilm were killed by SiO$_2$-P$_{Ce6}$-IL. (Figure 4(c)). The SiO$_2$-P$_{Ce6}$-IL greatly

![Figure 5: Tooth surface morphology with the treatment of Ce6 and SiO$_2$-P$_{Ce6}$-IL.](image-url)
improved the PACT efficacy and could effectively eliminate of S. mutans biofilm.

3.4. *In Vivo Antibiofilm Assessment.* The in vitro results revealed that multiclawed SiO$_2$-P$_{Ce6-IL}$ had excellent efficacy against S. mutans biofilms. To further verify these conclusions, the in vivo experiments were designed. The infected mice were divided into three groups: treated with PBS, Ce6 with illumination for 15 min, and SiO$_2$-P$_{Ce6-IL}$ with illumination for 15 min. The therapeutic effects of SiO$_2$-P$_{Ce6-IL}$ were evaluated by SEM. As showed in Figure 5, the treatment with SiO$_2$-P$_{Ce6-IL}$ was very effective in preventing the development of dental caries and completely blocked extensive enamel damage. In contrast, treatment with Ce6 alone was no significant effect and resulted in enamel loss and damage, then led to dental caries.

3.5. *Biocompatibility Evaluation.* Although SiO$_2$-P$_{Ce6-IL}$ could effective combine with oral biofilm and almost impossible to transport into the stomach from the mouth, it was important to evaluate their biocompatibility. So the cytotoxicity, hemolysis rate, and the histological section of main organs including the heart, liver, spleen and lung, and kidney were examined. The results show that no abnormal effects or damages were observed in these organs (Figure 6), and the body weights of rats treated with SiO$_2$-P$_{Ce6-IL}$ were similarly to healthy rats. The hemolysis rate and cytotoxicity were 4.2% (limit of clinical hemolysis rate < 5%) [21] and above 90% within therapeutic concentration (Figure 6). The SiO$_2$-P$_{Ce6-IL}$ was a potential safe material for clinical applications in oral biofilm infection.

4. Conclusions

In this work, the SiO$_2$-P$_{Ce6-IL}$ with charge reversal and high binding ability was prepared. The potential measurements showed that SiO$_2$-P$_{Ce6-IL}$ could turn into positive and combine with EPS firmly in the acidic microenvironment of oral biofilm. The morphology of S. mutans biofilm results showed that SiO$_2$-P$_{Ce6-IL}$ could combine with EPS and destroy the structure of biofilm. The laser scanning confocal microscopy results found that the concentration of Ce6 in S. mutans biofilm was greatly improved, and most of bacteria in biofilm were killed. In vivo experiments showed that the SiO$_2$-P$_{Ce6-IL}$ was a highly desirable property for oral biofilm infection and had high quality in the prevention of dental caries. Most importantly, SiO$_2$-P$_{Ce6-IL}$ had good biocompatibility in therapeutic effective concentrations.

**Data Availability**

The experimental data used to support the findings of this study are included within the article.

**Conflicts of Interest**

The authors declare that there is no conflict of interest regarding the publication of this paper.

**Authors’ Contributions**

Ziyi Jiao and Yonggang Teng contributed equally to this work.

**Acknowledgments**

This work was supported by the National Natural Science Foundation of China (Grant Nos. 31771087 and 32171388), the Innovation Capability Support Plan of Shaanxi Province (No. 2020TD-041), and the Shaanxi Natural Science (Nos. 2021JM-238 and 2021JQ-334).

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