Graphene Oxide-Silica Composite Fillers into the Experimental Dental Adhesives for Potential Therapy

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The aim of this study was to investigate the benefits of incorporation of graphene oxide-silica (GO@SiO$_2$) on the degree of conversion and bond strength of an experimental dental adhesive. The GO@SiO$_2$ nanocomposites were prepared and characterized by using FTIR, Raman and TEM. After that, GO@SiO$_2$ was added into an experimental dental bonding system as novel nanofiller, and the effect of the modification on the dispersion stability of the GO@SiO$_2$ nanocomposites in the experimental adhesive was studied. In addition, the degree of conversion was characterized by real-time FTIR, and the light conversion kinetic curves were calculated. Furthermore, the bond strength of the experimental adhesive to dental restorative resin was investigated. The result showed that the GO@SiO$_2$ nanocomposites dispersed well in the experimental adhesive, and the introduction of GO@SiO$_2$ improved effectively the degree of conversion of the dental adhesive after curing. In addition, the experimental adhesive filled with GO@SiO$_2$ nanocomposites showed not only similar bond strength to a commercial adhesive, but also enhanced dramatically compressive strength as well. Furthermore, the obtained experimental dental adhesives can increase reactive oxygen species level in cells through photothermal conversion to be used in potential therapy.

**Keywords** graphene oxide-silica, degree of conversion, bonding strength, reactive oxygen species

**Introduction**

In recent years, inorganic filler/resin composites have attracted considerable interest in the field of dental restorative materials. The combined advantages of inorganic filler and polymer usually afford polymer composites with unique performances. Among them, SiO$_2$ with various size and structure has been widely used to strengthen different composites. The wear behavior of the resin composites was effectively improved by introduction of bimodal silica nanostructures including silica nanoparticles and nanoclusters as co-fillers. For example, the resin composites have higher light transmission and adequate mechanical properties than ordinary resins with the addition of monodispersed SiO$_2$ microspheres. In addition, the incorporation of the modified nanoclay provided a dental bond system with higher shear bond strength.

Generally, silane coupling agent was used to improve the interface reaction between SiO$_2$ nanoparticles and polymer. However, recently, GO served as an unconventional coupling agent of the silica filler and was found to enhance effectively the interfacial interaction of the epoxy/SiO$_2$-GO composites. Graphene oxide (GO) nanosheets are heavily oxygenated graphene with a great deal of epoxy, hydroxyl, and carboxyl functional groups on its basal planes. These functional groups make them more compatible with organic polymers and perform unique properties in many fields. Nonetheless, more unique and superior properties of GO for material applications continue to be recognized or discovered. For example, the previous report explored that the novel role of GO has the ability to generate reactive oxygen species (ROS) as potential co-therapeutics for a bioactive molecule to induce cell death. In this work, the GO-SiO$_2$ composite filler was fabricated and then introduced into a experimental dental adhesive, in which the GO-SiO$_2$ composite can not only enhance their mechanical properties but only mediate cell ROS for potential therapy. The aim of this study was to evaluate its potential application as novel reinforcement fillers for dental adhesives.

**Experimental**

**Materials**

2,2-Bis[4-(2-hydroxy-3-methylacryloxypropoxy)-phenyl] propane (Bis-GMA), triethylene glycol dimethacrylate (TEGMA), 2-(dimethylamino)ethyl methacrylate (DAMAEMA) and camphorquione (CQ) were purchased from Sigma Aldrich. Hydroxy ethyl methacrylate (HEMA) was produced by Tokyo Chemical Industry. Tetraethyl orthosilicate (TEOS), 3-(aminopropyl)triethoxysilane (APTES), ammonium hydroxide (25%-28%) and ethyl alcohol were purchased from Sinopharm Chemical Reagent. These reagents were all analytical grade. Ortho Solo adhesive was produced by Ormco, America. Z350XT resin was produced by 3M ESPE, America.

**Methods**

The nano SiO$_2$ spheres with a narrow size distribution were prepared by Stöber method, which comprised the base-catalyzed hydrolysis of TEOS in water-ethanol mixtures. In a typical process, 1.5 mL TEOS was added into a mixture of 50 mL ethanol, 1 mL deionized water and 1.5 mL aqueous ammonia. The mixture was stirred and kept at 40 °C for 3 h before 1 mL more TEOS was added and reacted for another 3 h. The nano SiO$_2$ spheres were finally collected by repeatedly centrifuging and washing with ethanol and then water to get rid of unreacted TEOS. After that, the nano SiO$_2$ spheres were freeze dried at ~80 °C to remove the water on their surface.

Then, the surface modification of SiO$_2$ with APTES coupling agent was carried out by the following procedures: The silica spheres redispersed in methylbenzene (1 g/120 mL) by sonication were mixed with 4 mL APTES, stirred at 80 °C for 24 h, and then collected by centrifuging and washing as the method stated before.
Finally, the GO@SiO₂ nanocomposite was fabricated simply by mixing the aqueous solutions of modified SiO₂ (20 mg/mL) and commercial GO (0.2 mg/mL, provided by XFNANO in Nanjing, China) in a volume ratio of 10:1. These aqueous solutions were dispersed under mild magnetic stirring and sonication, respectively. The sediments were collected and washed with water for several times to remove the unbound GO, and then freeze-dried under vacuum.

Characterization

The morphology of the modified SiO₂ spheres was investigated with a JEOL 2100F High Resolution Transmission Electron Microscopy (HRTEM) at an accelerator voltage of 200 kV. The GO@SiO₂ spheres with a content of 1 wt% was dispersed in ethanol, dropped onto the copper mesh and then dried before HRTEM.

The structure of the initial SiO₂ nanoparticles was compared with those APTES or GO modified ones, using a Nicolet 6700 FTIR spectrometer. The spectra were measured with an attenuated total reflectance accessory (ATR). Each spectrum was acquired in transmittance mode on a diamond substrate by the accumulation of 32 scans with a resolution of 4 cm⁻¹ and a spectral range of 4000–500 cm⁻¹.

The Raman measurement was performed by a laser confocal micro-Raman spectrometer (Renishaw in-Via Reflex, US) using 532 nm excitation wavelength and 10%×50 mW power. The fluorescence spectra of the GO solution (0.01 g/mL) were recorded with a fluorescence spectrophotometer (F-7000, HITACHI, Japan). The spectra were respectively collected at 380, 400, 420 and 440 nm excitation, with an emission range of 380–600 nm every 1 nm. The excitation and emission slits were both set to 2.5 nm. The scan speed was 1200 nm/min.

Stability of the adhesive

The adhesive with 1 wt% of GO@SiO₂ spheres was stored in darkness at 4 °C and were photographed at 0, 8, 24 h and 5 d to describe the dispersion stability of the modified SiO₂ in the adhesive system.

Measurement of degree of conversion

The light conversion kinetic of the experimental dental adhesives, at ambient temperature, was investigated by real-time FTIR using a Thermo Scientific iS10 FTIR spectrometer at a resolution of 4 cm⁻¹, before which the tested adhesives were cast on the infrared transparent silicon chips and then covered with a mylar film. A conventional LED light curing unit (400–500 nm, 1000–1200 mW/cm²) was used to cure the adhesives at 1608 cm⁻¹ and the untreated DMEM as the control group.

Measurement of ROS

Intracellular reactive oxygen species (ROS) generation of healthy human dental pulp cells was measured by 2',7'-dichlorofluorescin diacetate (DCFH-DA). After cellular uptake of DCFH-DA, it was cleaved by cellular esterases to 2',7'-dichlorofluorescin (DCF), and the intracellular ROS would cause the oxidation of DCFH to the fluorescent product of 2',7'-dichlorofluorescin (DCF). Cells plated on 6-well cell culture plates were maintained, and then DMEM was replaced with the medium containing the obtained experimental dental adhesives. The cells was then fixed with 4% paraformaldehyde for 10 min, washed with PBS, and then stained with DCFH-DA (10 μM) in serum-free culture medium. The medium was removed, and cells were washed three times with PBS. The DCF fluorescence intensity was measured using fluorescence microscopy excited by blue light and was also detected by a flow cytometer with an excitation wavelength of 488 nm after cells should be digested with trypsin enzyme first and washed three times with PBS through a centrifuge (1000 rpm, 3 min, 4 °C).

Cytotoxicity experiment

The cytotoxic effect of the adhesives with or without fillers was determined with the CCK-8 assay. The adhesives disks with a diameter of 10±1 mm and a thickness of 1±0.1 mm were prepared by filling the adhesives into a silica rubber mold and light curing for 1 min. After that, the disks were immersed in 75% alcohol for 30 min, washed with PBS, and then soaked in 5mL DMEM (containing 10% FBS, 100 /mL penicillin and 100 μg/mL streptomycin) in a sterile environment at 37 °C for 4 d. The extract liquids were collected and filtered using a syringe-driven filter to ensure no bacteria. Then the sterilized extract liquids (diluted with DMEM as 1:0, 1:5 and 1:10) were set as the groups, and the untreated DMEM as the control group.

Healthy human dental pulp cells (HDPC) were regularly cultured and passed in DMEM medium at 37 °C and 5% CO₂. The cells suspension (5×10⁵ cells/mL) was seeded in a 96-well plate (200 μL medium per well) and cultured for 48 h to make the cells well attached and proliferated. Then the medium was substituted with the above experimental groups and control group extract liquid. After 24 h, the cells morphology was observed by an inverted microscopy (Leica DMI 4000B, Germany). Then 100 μL CCK-8 solution (10% in volume) was added into each well and the cells were incubated for another 2 h. Cell viability was measured with the MB-40 ELISA microplate reader by recording the absorbance at 450 nm. The number of the survival cells was calculated as the ratio of the mean absorbance of experimental groups to the mean absorbance of control group.

Results and Discussion

To prepare GO@SiO₂, the SiO₂ spherical particles were firstly reacted with APTES to modify the SiO₂ surface with NH₂ groups. This made the SiO₂ surface positively charged in aqueous solution. While GO nanosheets contained a large number of hydroxyl and carboxylic groups on the surface, GO@SiO₂ could thus be obtained by mixing the negatively charged GO nanosheets and positively charged APTES@SiO₂ particles in an aqueous solution, which im-
mobilized GO onto the SiO$_2$ surface through electrostatic assembly mechanism. The SiO$_2$ nanoparticles had a diameter of about 70 nm with a sphere morphology and smooth surface (Figure 1a). As shown in Figure 1b, ultrathin GO (blue arrow) intimately wrapped the SiO$_2$ nanoparticles (red arrow). The typical HRTEM images of GO@SiO$_2$ composite filler (Figure 1c) also confirmed that the flexible and ultrathin GO sheets had indeed successfully wrapped around the SiO$_2$ nanoparticles. As shown in Figure 1d, no obvious aggregation was observed in the GO@SiO$_2$ composite filler.

![Figure 1](image)

**Figure 1** TEM images of the (a) raw SiO$_2$, and (b) created GO@SiO$_2$ hybrid, scale bar 100 nm, (c) HRTEM images of GO@SiO$_2$ (scale bar 5 nm), (d) dispersion of GO@SiO$_2$ in the light-cured experimental dental adhesives at 0, 8, 24 h and 5 d.

The structure of GO@SiO$_2$ was characterized by FTIR and Raman. As shown in Figure 2a, the main peaks of SiO$_2$ spectra curve at 797, 1050, 1626 cm$^{-1}$ and the broad band around 3350 cm$^{-1}$ were identified as symmetric vibrations of Si-O-Si, asymmetric vibrations of Si-O-Si, bending vibration of O–H and stretching vibration of OH, respectively. After surface modification by APTES, the broad band at 3350 cm$^{-1}$ became weak, which indicated the decrease of hydroxyl on SiO$_2$ surface. Furthermore, new characteristic peaks around 1500 cm$^{-1}$ belonging to N–H bending vibration were observed. Several minor bands at around 2800 to 3000 cm$^{-1}$ were also detected in the spectra of APTES@SiO$_2$, which were attributed to the N–H stretching vibration. As GO has a large amount of OH groups, the broad band around 3350 cm$^{-1}$ of GO@SiO$_2$ was higher than that of APTES@SiO$_2$. In addition, Raman spectroscopy, which was utilized as a powerful tool for the characterization of graphene and its derivatives, was employed to further identify the GO@SiO$_2$. As shown in Figure 2b, we could see two intensive peaks at 1355 and 1598 cm$^{-1}$ on both GO and GO@SiO$_2$ curves. They were referred to the D band, resulting from a disordered sp$^3$ carbon structure, and the G band representing sp$^2$ ordered crystalline graphite-like structures, respectively. Interestingly, a little increased ratio of (D)/(G) was found on the curve of GO@SiO$_2$ compared to GO. It had been reported that the increase of (D)/(G) ratio reflected the increase of disorder present within the materials. Thus the enhanced ratio for GO@SiO$_2$ proved that GO was assembled onto SiO$_2$, rather than a kind of mechanical mixture.

![Figure 2](image)

**Figure 2** FTIR spectra curves (a) of pristine SiO$_2$, APTES@SiO$_2$, GO@SiO$_2$, and GO; Raman spectra (b) of the GO@SiO$_2$ and GO.

The GO@SiO$_2$ composite was then added into the experimental dental adhesive. The adhesive was prepared mainly composing of Bis-GMA, TEGDMA and HEMA. CQ/DMAEMA was used as the co-initiator of the dental adhesives. GO@SiO$_2$ composite fillers with the content of 1 wt% were added into the dental adhesive by stirring and sonication. After that, the dental adhesive was stored in darkness at 4 °C and was photographed at 0, 8, 24 h and 5 d, respectively. Either at 8 or 24 h, no significant sedimentation was observed. Only a small amount of precipitation was found after 5 d. Therefore, the GO@SiO$_2$ composite fillers had preliminary dispersion stability in the experimental dental adhesives. The light conversion kinetic of the experimental dental adhesive was investigated by the real-time FTIR. Representative real-time spectra of the pristine experimental dental adhesive and adhesives filled with 1 wt% APTES@SiO$_2$ and 1 wt% GO@SiO$_2$ were recorded during photopolymerization, as shown in Figure 3. It was clearly discerned that the absorbance of C=O at 1637 cm$^{-1}$ decreased with increasing the polymerization time, indicating the polymerization of the monomers in the dental adhesives. In addition, the DC of the adhesive filled with 1 wt% GO@SiO$_2$ reached 52.1%, which was almost two times higher than the DC of pristine adhesive of 26.6%. This result indicated that DC of the experimental adhesive was distinctly enhanced with the addition of GO@SiO$_2$.

![Figure 3](image)

**Figure 3** The time-resolved FT-IR spectrum of the experimental dental adhesives: (a) no GO@SiO$_2$, (b) 1 wt% APTES@SiO$_2$, (c) 1 wt% GO@SiO$_2$ and (d) their light conversion kinetic curves.

The enhancement on DC of the GO@SiO$_2$ filled adhesive was attributed to two reasons. Firstly, the GO nanosheets used in this study showed photoluminescent (PL) peaks at 413, 438, 465, and 491 nm when excited respectively at 360, 380, 400 and 420 nm (in Figure 4), which showed a similar property to the graphene quantum dots (GQDs). Zhu et al. synthesized kinds of strongly fluorescent GQDs containing many chemical groups such as OH, epoxy/ether, C=O and -CO-NH$\_2$. When GQDs were excited at wavelengths from 400 to 540 nm, their PL peak shifted from 515 to 570 nm. Considering the CQ/DMAEMA co-initiator was reported to be excited at the wave-length of 400–500 nm, the PL light from GO enhanced the intensity of the curing light in the experimental adhesive when it was exposed under the LED light curing unit. Thus more free radicals were generated in the GO@SiO$_2$ filled adhesive, which resulted in higher polymerization rate and degree of conversion. Secondly, the adhesive got higher viscosity as the reaction progress, which led to the “gel” effect (“Trommsdorf” effect). Polymerization rate was increased...
at high viscosities due to a reduction in chain termination accompanying the decreased mobility of the polymer radicals. Actually, when the adhesive was exposed under the LED light curing unit, amine radicals were formed in the experimental adhesive and could be enriched around GO sheets through physical or chemical adsorptions. Therefore, GO could enhance the degree of conversion by absorption of the radicals and decreasing their mobility.

Figure 4 The excitation-dependent PL behavior of GO nanosheets.

A universal mechanical machine was used to test the microtensile bond strength and the compressive strength of the experimental dental adhesives. Microtensile bond test has now been accepted as a reliable and facile method in measuring the bond strength of dental adhesives. In order to overcome the drawback of the traditional testing method which needed additional adhesives to set the resin sticks on the testing platform, a special self-made clamp was designed. Figure 5 showed the means and standard deviations of the bond or compressive strength of adhesive with 1 wt% GO@SiO$_2$ and a commercial Ortho Solo adhesive (Ormco, America). The adhesive filled with GO@SiO$_2$ had bond strength of 20.9 MPa, which was similar to the Ortho Solo adhesives, about 21.03 MPa. While the compressive strength of the adhesives filled with GO@SiO$_2$ reached 219.3 MPa, it was much higher than the 150.8 MPa of the commercial adhesive.

Figure 5 Bonding and compressive strength of the adhesive without fillers and with 1 wt% APTES@SiO$_2$ and GO@SiO$_2$ and a commercial adhesive.

As we well known, ROS may serve as good candidates for combination therapy with a bioactive molecule. Furthermore, various ROS inducing agents like apigenin and emordin have been reported to sensitize cancer cells to conventional anti-cancer agents like paclitaxel, cisplatin, doxorubicin and arsenic trioxide. Additionally, the hyperthermia treatments (43–45 °C) cause long term cell inactivation due to the increment of the intracellular density of reactive oxygen species, which can cause oxidative damage to proteins, lipids and nucleic acids. Furthermore, GO has the ability to generate ROS. Therefore, the photothermal conversion performance of 1 wt% GO@SiO$_2$ suspension, experimental dental adhesives with 1 wt% GO@SiO$_2$ and pure water with different time was examined using the irradiation of 980 nm laser with a power density of 2 W/cm$^2$. As shown in Figure 6a, it is found that 1 wt% GO@SiO$_2$ suspension can be heated by up to 54.3 °C in the period of 240 s, demonstrating that the GO@SiO$_2$ composite can rapidly and efficiently convert 980 nm laser energy into thermal energy, compared with the control experiment of pure water that is only increased by less than 5 °C. Moreover, the obtained experimental dental adhesives with 1 wt% GO@SiO$_2$ can increase the temperature of pure water from 24.9 to 40.3 °C in the same irradiation time of 240 s, which reveals that the obtained experimental dental adhesives possess comparable optical absorption characteristic and the photothermal conversion performance. Furthermore, ROS in cells were measured by 2',7'-dichlorofluorescein diacetate (DCFH-DA). There is almost little 2',7'-dichlorofluorescein (DCF) fluorescence in the controlled group after 240 s irradiation (Figure 6b), which implies that the ROS level in cells cultured without addition is very low. However, green cells from DCF fluorescence can be seen clearly in the fluorescent microscopic image with the addition of 1 wt% GO@SiO$_2$ to dental adhesives (Figure 6c). The results show that the obtained experimental dental adhesives can be used in potential therapy because of ROS through photothermal conversion.

Figure 6 (a) Temperature elevation of 1 wt% GO@SiO$_2$ suspension, experimental dental adhesives with 1 wt% GO@SiO$_2$ and pure water with different time using the irradiation of 980 nm laser with a power density of 2 W/cm$^2$, (b–c) the fluorescent microscopic images of cellular ROS production after 240 s irradiation.

The cytotoxicity to the HDPCs of the dental adhesives was evaluated by CCK-8 test, as shown in Figure 7. The results demonstrated that the cells proliferated better with dilution of the extract liquid and the increasing of DC, and that the experimental adhesives showed slighter cytotoxicity than the commercial Ortho Solo adhesive.

Conclusions

In conclusion, this research provided evidence that GO coating on silica particle had preliminary dispersion stability in the experimental dental adhesives. The GO@SiO$_2$ nanocomposite filler largely
Figure 7 The cell viability of the adhesive without fillers and with 1 wt% APTES@SiO$_2$ and GO@SiO$_2$, and a commercial adhesive.

enhanced the degree of conversion of the dental adhesives. Additionally, the dental adhesives filled with GO@SiO$_2$ had a similar bond strength to commercial adhesive and a significantly higher compressive strength than the commercial adhesive. Furthermore, the GO-SiO$_2$ composite in the experimental dental adhesive can mediate cell ROS for potential therapy. The concept of using GO@SiO$_2$ nano-composite as novel filler provided a powerful way to control composites interfacial structure and properties.

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