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# Improving the drug delivery characteristics of graphene oxide based polymer nanocomposites through the "one-pot" synthetic approach of single-electron-transfer living radical polymerization

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ABSTRACT

Graphene oxide (GO) based polymer nanocomposites have attracted extensive research interest recently for their outstanding physicochemical properties and potential applications. However, surface modification of GO with synthetic polymers has demonstrated to be trouble for most polymerization procedures are occurred under non-aqueous solution, which will in turn lead to the restacking of GO. In this work, a facile and efficient "one-pot" strategy has been developed for surface modification of GO with synthetic polymers through single-electron-transfer living radical polymerization (SET-LRP). The GO based polymer nanocomposites were obtained via SET-LRP in aqueous solution using poly(ethylene glycol) methyl ether methacrylate (PEGMA) as the monomer and 11-bromoundecanoic acid as the initiator, which could be effectively adsorbed on GO through hydrophobic interaction. The successful preparation of GO based polymer nanocomposites was confirmed by a series of characterization techniques such as $^{1}$H nuclear magnetic resonance, Fourier transform infrared spectroscopy, thermogravimetric analysis, transmission electron microscopy and X-ray photoelectron spectroscopy. The resultant products exhibit high water disperisibility, excellent biocompatibility and high efficient drug loading capability, making these PEGylated GO nanocomposites promising candidates for biomedical applications.



## 1. Introduction

Graphene, a carbon nanomaterial, was first reported by Novoselov et al. in 2005 [1]. It is a kind of single atom thick layer of carbon materials with a large specific surface area, remarkable mechanical, electrical and optical properties, which raised increasing interest in both physics and material fields [2–6]. However, unilaminar graphene sheets tended to aggregate into three-dimensional (3D) graphite by prominent π-π interaction at high concentrations or temperature, such drawback has impacted the performance of graphene and limited its potential. Graphene oxide (GO), a quasi two-dimensional (2D) layer structure, can be regarded as graphene sheets, which connected with some hydroxyl, epoxy and carboxyl groups on its surface [7]. It can be mainly prepared through oxidizing graphite powders with some strong oxidants to get the single layer or few layer GO sheets [8]. Because the distance between GO layers is greater than that of graphene sheets and the oxygen-containing functional groups are in favor of forming hydrogen bonds in the aqueous solution. Therefore the GO sheets showed much better dispersity as compared with graphene sheets. However, such advantage is still not enough to obviously improve the performance of GO related materials. Therefore great affort has been devoted to the preparation of different GO based nanocomposites included GO composited with metal nanoparticles, semiconductor nanoparticles, metal oxide nanoparticles and polymers [9–17]. Among them, the GO based polymer nanocomposites should be the most important ones due to the combination advantages of both GO and polymers [17–29].

Previously, fabrication of GO based polymer nanocomposites through controlled living radical polymerization methods such as reversible addition fragmentation chain transfer (RAFT) polymerization, atom transfer radical polymerization (ATRP) and

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single-electrical transfer living radical polymerization (SET-LRP) has been developed [29–32]. These GO based polymer nanocomposites have demonstrated to be promising candidates for different applications [33]. For example, Rouff et al. has reported the surface modification of GO with polymers through surface-initiated ATRP. In this work, the polymerization initiator (Bromoisobutyryl bromide) should be first covalently immobilized on the surface of GO for polymer brush growth [31]. However, the water should be first removed from GO for immobilization of the initiator, that will in turn result in the restacking of GO sheets. The preparation of thermosensitive GO-polymer composites through RAFT polymerization was also demonstrated by Liu et al. [32] In Liu's work, the chain transfer agent (CTA) was first conjugated with perylene, and then the thermal response polymer brushes (PNIPAM) terminated with perylene were synthesized via RAFT polymerization. These perylene terminated polymer brushes can attact onto GO sheets through hydrophobic interaction. In our former report, a novel approach combines mussel inspired chemistry and free radical polymerization was carried out [28]. We demonstrated that GO can be functionalized with various polymers for different applications [33]. Nevertheless, most of these modification strategies are not easily to realize because immobilization of initiators and polymerization procedures are required under non-aqueous solvents. The complete removal of water from GO is a rather complex procedure and will lead to restacking of GO sheets into graphite oxides. Therefore, the development of novel, effective and simple surface modification strategies for preparation of GO based polymer nanocomposites is still highly desirable. SET-LRP is a novel emerged controlled living polymerization method with good controllability and high polymerization rate, that can be used for growth of polymer brushes under room temperature, air atmosphere and aqueous solution within short time [34–41]. More importantly, a large number of monomers such as poly(ethylene glycol) methyl ether methacrylate (PEGMA), *N*-isopropylacrylamide (NIPAM) and styrene sulfonic acid can be polymerized using SET-LRP [30,37,42,43]. These features make SET-LRP very suitable for preparation of various homopolymers or copolymers in aqueous solution, low temperature and air atmosphere.

We present a facile and effective strategy for fabrication of GO based polymer nanocomposites through "one-pot" SET-LRP in aqueous solution (Scheme 1). The water soluble and biocompatible PEGMA was selected as the monomer. 11-Bromoundecanoic acid was employed as the initiator, which initiated the polymerization of PEGMA to generate PPEGMA brushes via SET-LRP. The PPEGMA brushes can strongly attach to GO sheets in aqueous solution due to the hydrophobic interaction between GO sheets and alkyl chain of 11-Bromoundecanoic acid. The biomedical application potential of resultant products GO-PPEGMA was also examined.

## 2. Experiments

### 2.1. Materials and characterization

Graphite powders were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai, China). PEGMA (MW: 950 Da, 98%) was obtained from Aladdin (Shanghai, China). Cuprous bromide (CuBr) and tris[2-(dimethylamino) ethyl] amine ($Me_6$TREN) as a catalytic system was supplied by Heowns (Tianjin, China). Dialysis membranes (MWCO $\geq$ 3500 Da) were obtained from Viskase (America). The other chemical reagents mentioned in this experiment were got from Aladdin (Shanghai, China) of analytical grade and used directly without further purification. The synthetic materials were characterized by Fourier transform infrared (FT-IR) spectroscopy using KBr pellets. FT-IR spectra were obtained on a Nicolet 5700 FT-IR spectrometer (Thermo Nicolet Corporation) with a resolution of 4 $cm^{-1}$. The thermogravimetry (TGA) was carried out on a TA instrument Q50 with a heating rate of 10 °C $min^{-1}$ using crucibles of aluminum. Samples weighing between 10 and 20 mg were heated from 30 to 600 °C with $N_2$ as the carrier gas (40 mL $min^{-1}$). X-ray photoelectron spectroscopy (XPS) spectra were measured on a VGESCALAB 220-IXL spectrometer using an Al Kα X-ray source (1486.6 eV). Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV. The TEM specimens were obtained by placing a drop of a nanoparticle ethanol suspension on a carbon-coated copper grid. $^1$H NMR spectra were recorded on Bruker Avance-400 spectrometer with $CDCl_3$ as the solvent.

### 2.2. Preparation of GO

The GO was prepared via a modified Hummers' method [8]. Briefly, 1 g graphite powder, 0.5 g $NaNO_3$ and 6 g $KMnO_4$ were added into a 500 mL conical flask. The container was next put in an ice-water bath. Then 46 mL concentrated sulfuric acid was added into the flask slowly. After that, 92 mL deionized water was dropwise added into the flask with stirring for 30 min at 90 °C. Then, 10 mL $H_2O_2$ and 100 mL $H_2O$ was added slowly. The mixture was maintained the solution at room temperature for 30 min with ultrasonication. Finally, the mixture was centrifuged and washed with HCl (aq) for three times. And then the sediment was dialysed in deionized water for three days before GO was collected for further modification.

### 2.3. Preparation of GO-PPEGMA

The polymerization was carried out via SET-LRP using CuBr/$Me_6$TREN as catalytic/ligand system in the presence of water. Briefly, 0.5 g GO, 0.13 g 11-Bromoundecanoic acid, 5.7 g PEGMA, 50 mL $H_2O$ and 80 mg CuBr were added into a polymerization bottle. The reaction system was exhausted the air under a vacuum pump and filled with nitrogen for three times. After 10 min ultrasonic vibration the solution of 0.1 mL $Me_6$TREN in 3 mL $CH_3CN$ was added into the polymerization bottle via injection. The polymerization bottle was immersed in an oil bath at 40 °C and stirring for 2 h. Then reaction mixture was collected via repeated centrifugation and washing procedures for three times. The final products were dried in vacuum at 40 °C.

### 2.4. Biocompatibility of GO-PPEGMA

Cell viability of GO-PPEGMA on A549 cells was determined by CCK-8 assay according to our previous reports [44–49]. Briefly, cells were seeded in 96-well microplates at a density of $5 \times 10^4$ cells $mL^{-1}$ in 160 μL of respective media containing 10% FBS. After 24 h of cell attachment, the cells were incubated with 10, 20, 40, 80, 120 μg $mL^{-1}$ GO-PPEGMA for 12 and 24 h. Then nanoparticles were removed and cells were washed with PBS for three times. 10 μL of CCK-8 dye and 100 μL of DMEM cell culture media were added to each well and incubated for 2 h at 37 °C. Plates were then analyzed with a microplate reader (VictorIII, Perkin-Elmer). Measurements of dye absorbance were carried out at 450 nm, with the reference wavelength at 620 nm. The values were proportional to the number of live cells. The percent reduction of CCK-8 dye was compared to controls (cells not exposed to nanoparticles), which represented 100% WST reduction. Three replicate wells were used for each control and test concentrations per microplate, and the experiment was repeated three times. Cell survival was expressed as absorbance relative to that of untreated controls. Results are presented as mean ± standard deviation (SD)