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Graphene-kaolin composite sponge for rapid and riskless hemostasis

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ABSTRACT

Kaolin is an effective and safe hemostatic agent for hemostasis. However, its ontic powder is difficult to use in actual practice. To develop a wieldy and powerful hemostat, composite strategy is usually a good choice. Herein, we developed a graphene-kaolin composite sponge (GKCS), synthesized with graphene oxide sheets, linker molecules and kaolin powders through a facile hydrothermal reaction. SEM observations support that GKCS has a porous structure, and EDS mapping further confirms that kaolin powders are embedded in graphene sheets. Once GKCS is exposed to bleeding, plasma is quickly absorbed inside the sponge, meanwhile blood cells are gathered at the interface. The gathered blood cells are in favor of accelerating clotting due to multi stimulations, including concentration, surface charge and activation of hemostatic factors, originating from both kaolin powders and graphene sponge. As a result, GKCS could stop bleeding in approximately 73 s in rabbit artery injury test. Besides, cytotoxicity and hemolysis assessments highlight that GKCS has a good biocompatibility. These remarkable properties suggest that GKCS is a potential riskless hemostatic agent for trauma treatment.

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1. Introduction

Hemorrhage is the leading cause of death in emergency and intraoperative bleeding, which results in complications such as hemorrhagic shock, infection, and organ failures [1–3]. Excessive bleeding causes nearly 40% of deaths and is the main reason of traumatic death [4,5]. Therefore, using safe and efficient hemostatic materials are important to save life. Up to now, many kinds of hemostatic materials have been developed, such as zeolite [6], porous silica [7], granulose [8] and chitosan [9]. For inorganic micro- or meso-porous materials, they promote hemostasis on the base of fast liquid absorption and the enrichment of bloods cells and platelets [10–13]. While organic glyco-based materials prefer to gather red blood cells to accelerate blood clotting by electrostatic interaction and gelation. However, most of those hemostats tend to entrap themselves in scab when exerting their performance, which will weaken hemostatic efficiency and cause unnecessary discomfort.

Recently, our group developed a cross–linked graphene sponge (CGS) acting as hemostatic material, which displays remarkable liquid adsorption capacity, thus resulting in a rapid hemostasis within 4 min [14]. Because of its good biocompatibility, this kind of graphene-based sponge is proved to be a platform to load different kinds of hemostatic materials [15–17]. Changing the cross linker from ethanediamine (EDA) to diaminopropionic acid could improve approximate half minutes for hemostatic performance [15], while the CGS combined with thrombin would stop bleeding within 100 s [16]. Recently, we used the CGS to anchor montmorillonite (MMT), the obtained graphene/MMT composite sponge (GMCS) presented remarkable characteristic, which effectively stopped bleeding in approximately 85 s in rabbit artery injury test [17]. Although GMCS eliminates the side effects of MMT, it is still a psychological disorder that the Food and Drug Administration has limited the usage of MMT as commercial hemostatic products since 2007 due to the risk of thrombosis via blood contact. Therefore, on the basis of those above-mentioned achievements and the demand of risk-free hemostasis, we try to develop a more appropriate agent with higher biosafety.

Kaolin is a natural aluminosilicate mineral [18–20]. It is well known for its remarkable ability to induce and accelerate blood clotting. Since 1950s, kaolin has been used as activating agent for clotting in medical doctor routinely performances. Up to now, kaolin still acts as ingredient for operation hemostasis [20,21]. The formed blood clots could effectively trap kaolin particles in the site of the injury, no risk of wandering their going deep into the body. In particular, in April 2008 the US naval medical research institute announced the successful introduce kaolin into ordinary gauze, which is one choice of hemostats for all branches of the US military [22]. As reported, kaolin could activate Factor XII and platelets

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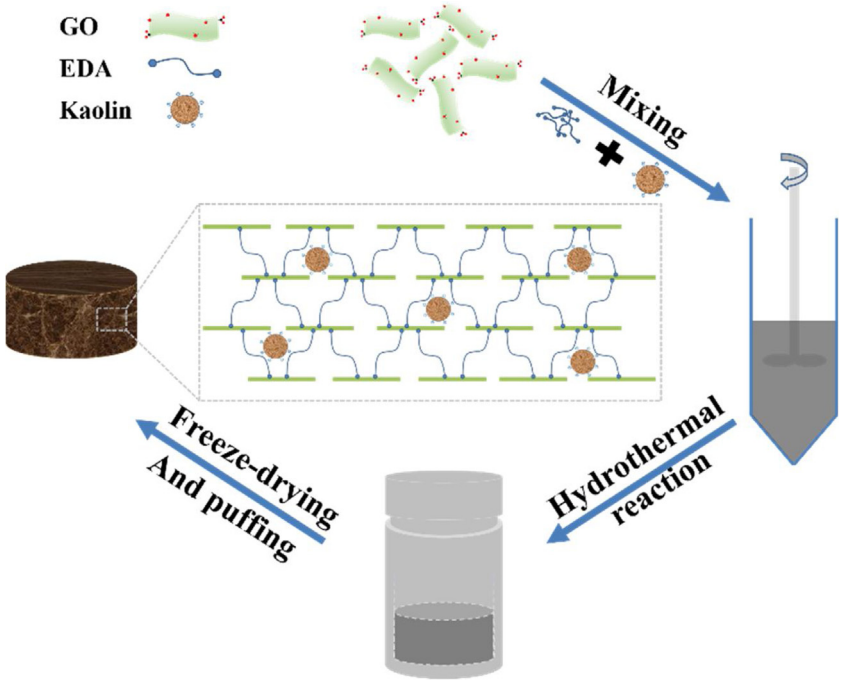

Scheme 1. Schematic representation of the preparation process of GKCS. GO sheets, EDA linkers and kaolin powders are employed to synthesize a hydrogel by a classical hydrothermal reaction. Freeze-drying and puffing are applied to the hydrogel to obtain the final composite sponge, where kaolin powders are fixed in cross-linked GO sheets.

to start the clotting cascade in vivo [20,23,24]. More importantly, kaolin has a good biocompatibility [25]. These outstanding properties highlight that kaolin is a valuable alternative substance.

Herein, we present a graphene-kaolin composite sponge (GKCS), which is synthesized by a facile hydrothermal reaction with graphene oxide (GO) sheets, EDA and kaolin powders (Scheme 1). GO and EDA mainly form the sponge framework, while kaolin powders will be embedded in to act as a new stimulation. GKCS will inherit remarkable liquid absorption capacity due to the porous structure inside, which is the key feature for this graphene-based hemostatic sponge. It can be expected that embedded kaolin into GKCS could improve its hemostatic performance especially with a risk-free way. GKCS is a new step to pursue excellence in traumatic hemostasis, on the platform of graphene-based materials.

2. Materials and methods

2.1. Materials

Graphite powders (80 mesh) were obtained from Qingdao Jinrilai Co., Ltd., Shandong, China. Sulfuric acid (H_2SO_4, 98%), sodium nitrate ($NaNO_3$, AR), potassium permanganate ($KMnO_4$, 99.9%), hydrogen peroxide (H_2O_2, 30%) and hydrochloric acid (HCl, 37%) were obtained from Sigma-Aldrich Co. The GO solution was prepared with improved Hummers' method [26], and the density of GO solution came to 7.5 mg mL^{-1}. The kaolin powders were purchased from Huawei Co., Ltd. (Beijing, China).

2.2. Preparation and characterization of GKCS

Kaolin powders (60 mg) were mixed with 60 mL of GO solution by a high-speed blender. After that, 0.9 mL of EDA was added to the mixture, new mixture needed to be mixed for the second time at the same condition. The mixed solution was sealed in a hydrothermal synthesis reaction kettle, which was heated to 96 °C and set for 6 h to get a hydrogel. The hydrogel was frozen at −4 °C for 2 h and moved into a freeze-dried machine for 2 days. Then the dry hydrogel was fed in Soxhlet extractor with ethanol for 2 days. After drying again, 5 s puffing was applied to obtain the final composite sponge. Changing the addition amount of kaolin powders from 1 mg mL^{-1} to 2, and 5 mg mL^{-1} in GO solution, different composite sponges (the ratio of kaolin/GO = 1:1, 2:1 and 5:1, w/v) were prepared with the above-mentioned method.

Scanning electron microscopy (SEM, 7800) was employed to observe the inside structure of GKCS. Energy-dispersive spectrometry (EDS, Hitachi S-4700) was employed to analyze the surface element content of GKCS. Fourier transform infrared (FT-IR) spectra of pure GO, kaolin and GKCS were recorded over a wave number range of 4000–990 cm^{-1}. Thermogravimetric analysis (TGA, Mettler Toledo TGA/DSC1/1100SF) was used to analyze the kaolin powders content of the GKCS. Zeta potential (Malvern NanoSizer ZS 2000) was employed to assess the negative potential value of GKCS and kaolin powders. Brunauer–Emmet–Teller (BET) surface area measurements were determined by the nitrogen gas adsorption method by using a Micromeritics ASAP 2460 2.02 analyzer at liquid nitrogen temperature.

The liquid absorption of GKCS was assessed by utilizing a CGS control. The absorption capability was measured by weighting GKCS on the condition of absorbing liquid or not. In addition, the absorption rate was scaled by recording the time that a liquid drop got into materials.

2.3. Assessment of the hemostatic performance

The hemostatic performance of GKCS was evaluated with the rabbit femoral artery injury model. NEW Zealand rabbits (weight 2.0–2.5 kg, n = 3) were obtained from Beijing Fuhao Experimental Animal Breeding Center (Beijing, China). Experimental animal treatment was carried out as reported [16]. After the femoral artery was transected, the blood loss at first 30 s was recorded to make sure all of experimental animal in same condition. Then, a piece of GKCS (4 cm diameter, 2 cm thickness) was slight compressed on the wound. The GKCS was slightly uplifted every 10 s to observe if the gap stop bleeding or not. When the gap stopped bleeding, the time and blood loss was recorded. After that, sufficient physiolog-

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