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POSS-modified PEG Adhesives for Wound Closure*

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Abstract PEG-related adhesives are limited in clinical use because they are easy to swell and cannot support the cell growth. In this study, we produced a series of POSS-modified PEG adhesives with high adhesive strength. Introduction of inorganic hydrophobic POSS units decreased the swelling of the adhesives and enhanced cell adhesion and growth. The *in vitro* cytotoxicity and *in vivo* inflammatory response experiments clearly demonstrated that the adhesives were nontoxic and possessed excellent biocompatibility. Compared with the sutured wounds, the adhesive-treated wounds showed an accelerated healing process in wounded skin model of the Bama miniature pig, demonstrating that the POSS-modified PEG adhesive is a promising candidate for wound closure.

Keywords Adhesives; PEG; POSS; Hydrogel; Wound closure

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INTRODUCTION

In the past decades, tissue adhesives have been widely used in surgery as wound closure sealants, hemostatic agents and drug carriers to promote healing and repair[1, 2]. Tissue adhesives usually include natural adhesives and synthetic adhesives[3–5]. The natural adhesives are biocompatible, but the weak adhesive capacity, difficulty to adjust properties and the risk of transferring blood-relevant diseases severely limit their clinical applications[6–8]. Compared with natural adhesives, synthetic adhesives can precisely control their structures and easily adjust the adhesive properties for various applications. Cyanoacrylate-based adhesives, a kind of typical synthetic adhesives, have strong adhesion strength, but their biocompatibility is poor because of long-term degradation time and toxic degraded products.

Synthetic PEG-related adhesive is essentially non-immunogenic and nontoxic, which is very popular in many biomedical applications[9]. Strehin *et al.* developed a versatile pH sensitive chondroitin sulfate-PEG tissue adhesives[10]. Biocompatible PEG adhesives like Coseal and Duraseal have already been commercialized[11].

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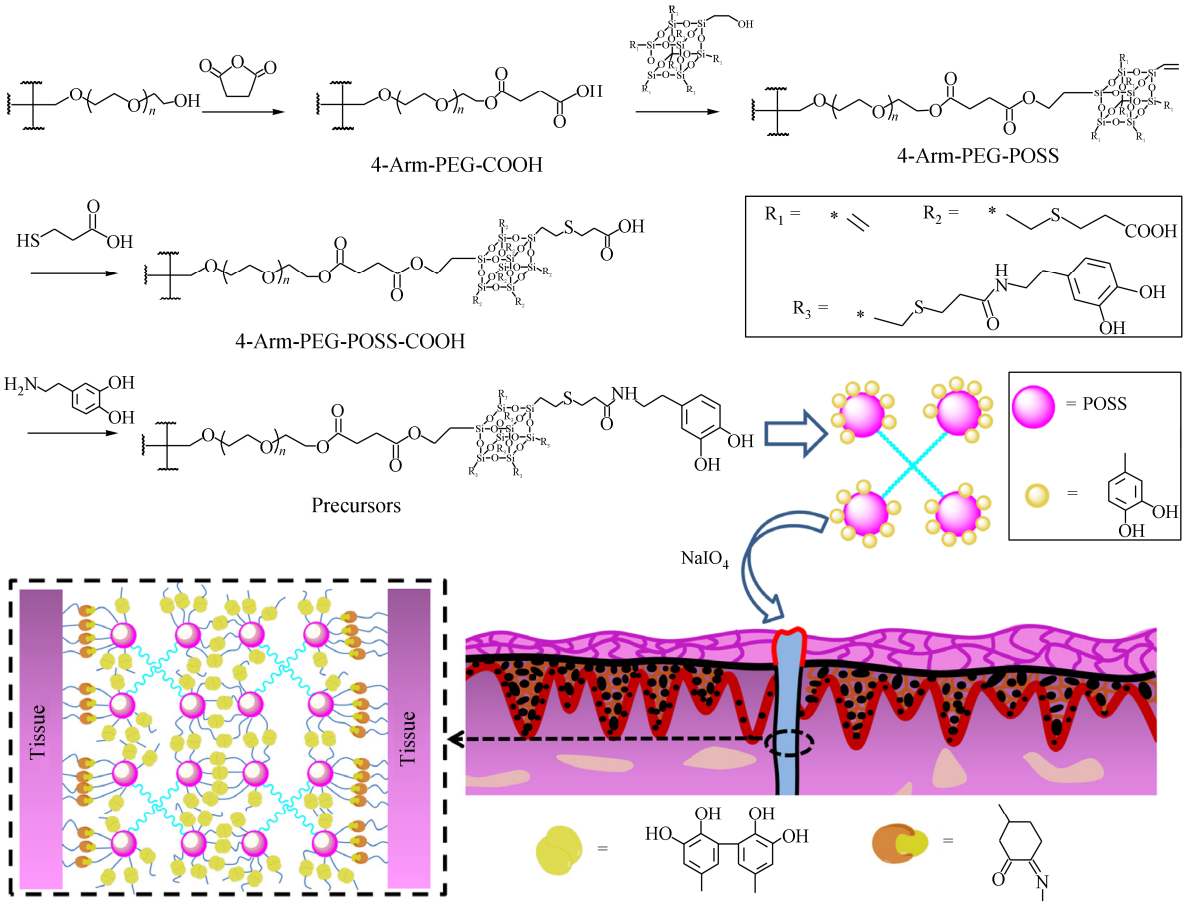
However, the PEG-related adhesives usually have weak adhesion properties and are easy to swell excessively to press surrounding tissues[12–14]. Besides, the PEG-based adhesives possess antifouling properties to prevent cell growth on their surfaces, hindering tissue ingrowth and wound healing[15–18]. To overcome the shortcomings of the existed synthetic adhesives, development of novel adhesives with strong adhesion strength and good biocompatibility is still highly desirable.

The hydrophobic T8 polyhedral oligomeric silsesquioxane (POSS) has been used as biomedical materials in applications for complicated microvessel construction and microfluidic devices, because POSS is nontoxic, biocompatible and multifunctional[19, 20]. The POSS-modified materials have been proved to be able to support cell adhesion and proliferation[21, 22]. Our group previously synthesized a septvinyl mono-hydroxyl AB_7 POSS monomer, $(Vinyl)_7$-POSS-OH, to construct G1 and G2 POSS dendrimers with 56 and 392 terminal vinyl groups by only one and three steps[23]. The 1→7 branching approach could facilely produce POSS embedded materials with huge exact end groups.

Herein, we adopted $(Vinyl)_7$-POSS-OH to modify the 4-arm-PEGs and yield 28 active vinyl groups, and then vinyl groups were further turned into catechol groups for production of POSS-modified PEG adhesives as shown in Scheme 1. The swelling and adhesion properties, biocompatibility and wound healing effect were evaluated by the *in vitro* and *in vivo* experiments.



Scheme 1 Synthetic route to the adhesive precursors and schematic of the wound closure by the adhesives (The online version is colorful.)

EXPERIMENTAL

Materials

4-Arm poly(ethylene glycol) (4-arm-PEG-OH, M_w = 10, 20 and 40 kDa, M_w/M_n = 1.03), 4-arm poly(ethylene glycol) succinimidyl (4-arm-PEG-NHS, M_w = 10, 20 and 40 kDa, M_w/M_n = 1.03) and 4-arm poly(ethylene glycol) amine (4-arm-PEG-NH_2, M_w = 10, 20 and 40 kDa, M_w/M_n = 1.03) were purchased from SINOPEG, China. Octavinyl POSS was purchased from Hybrid Plastics. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 4-dimethyl-aminopyridine (DMAP), dopamine, succinic anhydride and *N*-hydroxysuccinimide (NHS) were purchased from ENERGY CHEMICAL. All chemicals were of analytical grade and used as received.

Characterization

All NMR spectra were obtained on Bruker AV300 FT-NMR spectrometer. The field emission scanning electron microscopy (SEM) images were obtained at an acceleration voltage of 5 kV on a JSM-6700F microscope (JEOL, Japan). The rheometry tests were performed on the Thermo Haake with a plate geometry (35 mm diameter) at 25 °C. The contact angle was measured using the contact angle measurement instrument with a Sanyo camera. The shear strength was measured using the universal tensile machine (3365 Instron, USA). The histological imaging results were obtained on the Olympus microscope.

Synthesis of the Septvinyl Monohydroxyl POSS, (Vinyl)$_7$-POSS-OH

The (Vinyl)$_7$-POSS-OH was synthesized according to the method described by the previous reports[23, 24]. Briefly, trifluoromethanesulfonic acid (0.280 mL, 3.159 mmol) was slowly added to a solution of octavinyl POSS (2 g, 3.159 mmol) in 300 mL of fresh distilled CH_2Cl_2. Then, 4 h later, the solution was diluted with CH_2Cl_2 and then washed with saturated aqueous Na_2CO_3 three times. The organic layer was collected and concentrated. Then wet acetone was added into the concentrated solution and the hydrolysis process was performed for another 4 h. After removing the solvent, the final product was separated chromatographically on silica gel with CH_2Cl_2/hexane (V/V = 2/1) to afford a white solid, (Vinyl)$_7$-POSS-OH, (604 mg, 32.1%).

Synthesis of 4-Arm Poly(ethylene glycol) Carboxyl (4-Arm-PEG-COOH)

4-Arm-PEG-COOH was prepared, characterized and purified according to the reported method[23]. In brief, 4-arm-PEG-OH (1 mg, 1 equiv.), succinic anhydride (50 mg, 5 equiv.) and DMAP (61 mg, 5 equiv.) were dissolved in dry CH_2Cl_2 (40 mL). Then, the system was stirred at 37 °C for 24 h after which the mixture was directly precipitated twice in excess diethyl ether to give a white solid. The white solid was collected, dissolved in CH_2Cl_2 and washed with 1 mol/L HCl (3 × 40 mL). The organic layer was then dried partially under reduced pressure and the polymer was obtained as a white solid after drying under vacuum. Yield: 90%.

Synthesis of 4-Arm Poly(ethylene glycol) Polyhedral Oligomeric Silsesquioxanes (4-Arm-PEG-POSS)

POSS-OH (625 mg, 10 equiv.), EDCI (192 mg, 10 equiv.) and DMAP (61 mg, 5 equiv.) were dissolved in dry CH_2Cl_2 (40 mL), followed by the addition of 4-arm-PEG-COOH (1 g, 1 equiv.) under a nitrogen atmosphere. The system was stirred at 37 °C for 24 h after which the mixture was directly precipitated twice in excess diethyl ether to give a white solid. Then the white solid was dissolved in CH_2Cl_2 and washed with 1 mol/L HCl (3 × 40 mL) and brine (3 × 40 mL). The organic layer was then dried partially under reduced pressure and the polymer was obtained as a white solid after drying under vacuum. Yield: 87%.

Synthesis of Precursors of the Adhesives

A typical procedure is described below. 4-Arm-PEG-POSS (1 g, 1 equiv.), 2,2-dimethoxy-2-phenylacetophenone (5 mg) and 3-mercaptopropionic acid (246 mg, 30 equiv.) were dissolved in tetrahydrofuran and were purged with argon for 3 min. The mixture was then irradiated under a 365 nm UV lamp at room temperature for 3 h after which the mixture was directly precipitated in excess diethyl ether for three times to give a white solid (4-arm-PEG-POSS-COOH). Yield: 95%.

4-Arm-PEG-POSS-COOH (1 g, 1 equiv.), EDCI (362 mg, 30 equiv.), NHS (217 mg, 30 equiv.) were

dissolved in CH_2Cl_2 and were stirred at 37 °C for 24 h. Then, dopamine (288 mg, 30 equiv.) was added to the mixture and stirred for another 24 h. Then the mixture was washed with 1 mol/L HCl (3 × 40 mL). The organic layer was collected and precipitated twice in excess diethyl ether to give a white solid. Yield: 90%.

Preparation of the Adhesives

To prepare the adhesives, the precursor solution (300 mg/mL) and $NaIO_4$ solution (3 wt%) were mixed with equal volumes. $NaIO_4$ triggers oxidation of the precursors, leading to the crosslinking.

Rheological Studies

The Thermo Haake with a plate geometry (35 mm diameter) at 25 °C was used to perform the rheometry. The precursor solution was prepared and put on the plate with a gap distance of 1 mm. Before the tests, we performed an amplitude sweep to define the linear viscoelastic region (LVR) in which the storage modulus is independent to the strain amplitude. Then an angular frequency ω of 15 rad/s and a deformation amplitude γ_0 of 0.5% were selected to perform the rheological studies. The rheometry tests of the adhesives 1–3 were tested in the same way.

Scanning Electron Microscopy (SEM)

The fresh adhesives obtained were freeze-dried at −50 °C for 48 h. Then the dried samples were carefully stuck onto the conducting resin with double-sided adhesive and were sputter-coated with a thin layer of Pt for 180 s to make the sample conductive before testing. Field emission scanning electron microscopy (SEM) images were obtained at 5 kV accelerating voltage under high vacuum on a JSM-6700F microscope (JEOL, Japan).

Contact Angle Test

The adhesive films of 2 mm in thickness were prepared for testing. The contact angle test was performed using the contact angle measurement instrument with a Sanyo camera. The standard water volume was 2 μL. Each test was carried out for 5 times. PEG-hydrogels formed by mixing 4-arm-PEG-NHS and 4-arm-PEG-NH_2 were used as controls.

Swelling Ratio

The phosphate buffered solution (PBS) (pH = 7.4) was used in the test. The discs of the adhesives (10 mm in diameter and 5 mm in thickness) were dried first at 25 °C for 24 h in a vacuum oven to remove the water and then weighed (W_d). Then the dried samples (~1 g) were immersed into 25 mL of PBS at 37 °C. The samples were taken out and weighed at specific intervals of time and the maximal weight (W_s) was recorded. The swelling ratio was calculated as: swelling ratio (%) = $(W_s - W_d)/W_d \times 100$.

Degradation Tests

The PBS (7.4) was used in the experiment. The discs of the adhesives (10 mm in diameter and 5 mm in height) were weighed (W_0) and put into the centrifuge tube with 10 mL of PBS. At specific intervals of time, the discs were weighed (W_t) till complete degradation of polymer. The mass loss was calculated as: mass loss (%) = $(W_0 - W_t)/W_0 \times 100$.

Adhesion Strength Measurement

The adhesion tests were performed according to the previous report[16]. Briefly, strips of porcine were prepared in 30 mm × 10 mm dimension. Then, 30 μg of the precursor solution (150 mg/mL) was placed at the end of one porcine strip over an area of 10 mm × 10 mm. 30 μL of $NaIO_4$ solution (3 wt%) was placed at another porcine strip over an area of 10 mm × 10 mm. Then the $NaIO_4$ solution-coated porcine strip was set on the precursor-coated porcine strip after which the adhered porcine strips were placed in a highly humid chamber for 2 h. The shear strength was measured using the universal tensile machine (3365 Instron, USA).

Cell Viability

The extracts of the adhesives were used in the cell viability tests by quantitative MTT cytotoxicity assay. The 3T3 mouse fibroblasts were suspended in cell culture medium and seeded into 96-well microculture plates with a density of 1×10^4 cells/100μL/well and incubated for 24 h at 37 °C in a 5% CO_2 humidified incubator to obtain a

monolayer of cells. Cell medium was replaced with the adhesive extracts and further incubated for an additional time (48 or 96 h). The sample solution was removed and the cells were incubated with 50 μL of 1 mg/mL of CCK8 in acetone solution for 2 h. Finally, the absorbance of the sample solution was detected at 570 nm (reference 650 nm). The relative cell viability was calculated as the ratio between the mean absorbance value of the sample and that of cells cultured in the medium. Samples with relative cell viability less than 70% were deemed to be cytotoxic. For each sample, 7 independent cultures were prepared and cytotoxicity test was repeated 3 times for each culture.

Cell Growth on the Adhesive

Thin films of the adhesive were made and placed in the 24-well plates. 500 μL of 1×10^5 cells/mL suspension of 3T3 mouse fibroblasts were injected into the well and incubated at 37 °C and 5% CO_2. After 24 h substrates were rinsed with PBS and fresh medium to remove unattached cells. Cells on the substrates were stained with 2% FDA solution and fixed with 2.5% glutaraldehyde solution. Fluorescence images were taken with a laser confocal microscope.

In Vivo Biocompatibility

The *in vivo* biocompatibility experiments were carried out according to the previous report[15]. Briefly, discs of the adhesive 2 (10 mm in diameter and 5 mm in thickness) were disinfected by the ethanol-based sterilization and then bilaterally implanted subcutaneously in the backs of the rats along the dorsal midline. After 3, 7 and 28 days of implanting, rats were sacrificed and adhesives along with surrounding tissues were collected, after which the tissues were fixed in formalin for 3 days. Following fixation, the sample was embedded in paraffin, cut into 3−5 μm and stained with H&E. The histological imaging results were obtained by an Olympus microscope. Healthy, weight-matched Sprague-Dawley rats of two months old obtained from Beijing Vital River Laboratory Animal Technology Co., Ltd. were used in this experiment.

Wound Healing Experiments

Bama miniature pigs of 2 months were used in the experiment. Skin incisions (1 cm in length and 1 cm in depth) were created with a pair of scissors on both sides of the pig's back. The skin incisions were quickly closed by suture and the adhesives. After 28 days, the closure skin was harvested and fixed in formalin and stained with H&E and Masson's trichrome staining for histological analysis as well as for the mechanical tests.

RESULTS AND DISCUSSION

Synthesis and Characterization of the Precursors

We adopted POSS with catechol end groups to modify 4-arm-PEGs to produce the precursors of the adhesives, and the synthetic approach is summarized in Scheme 1. First the septvinyl POSS was grafted onto the 4-arm-PEGs by two esterification reactions: (a) the reaction of hydroxyl groups in PEGs and succinic anhydride to generate 4-arm-PEG-COOH, and (b) the reaction of carboxyl groups in the 4-arm-PEG-COOH and hydroxyl group in $(Vinyl)_7$-POSS-OH (Fig. S1 in supporting information, SI) to generate 4-arm-PEG-POSS. Figure S2 (in SI) shows that all four terminal hydroxyl groups of PEG_{10k} and PEG_{20k} were successfully esterified to carboxyl groups as verified by I_e/I_a to be ~1, and only ~2.3 hydroxyl groups of PEG_{40k} were turned into carboxyl groups by I_e/I_a to be ~0.58. Figure S3 (in SI) indicates all the resulting carboxyl groups could react completely with $(Vinyl)_7$-POSS-OH to yield PEG_{10k}-$POSS_4$-$Vinyl_{28}$, PEG_{20k}-$POSS_4$-$Vinyl_{28}$, and PEG_{40k}-$POSS_{2.3}$-$Vinyl_{16}$, respectively. Then the vinyl groups were further modified into catechol groups by another two steps: (c) thiol-ene addition to introduce carboxyl groups (Fig. S4 in SI), and (d) the amidation to introduce catechol groups (Fig. S5 in SI). The integral ratio of I_{p+q+r}/I_{e+h} to be ~5.2 in Fig. S5 (in SI) strongly proved that all the vinyl groups were successfully modified in the catechol groups to produce the precursors 1−3 of PEG_{10k}-$POSS_4$-$Catechol_{28}$, PEG_{20k}-$POSS_4$-$Catechol_{28}$, and PEG_{40k}-$POSS_{2.3}$-$Catechol_{16}$. The catechol groups of the precursors were 4−6.5 folds of the reported catechol-modified 4-arm-PEG adhesives, endowing them the strong adhesive strength[12, 25].

The yielded precursors were white powders (Fig. 1a). After water was added to the powders for 1 min, the precursors became soft, viscous liquids. The precursors could absorb 1 time to 10 times of water of its initial weight but did not dissolve in water even overnight. The liquid precursors were similar to viscoelastic liquids as there were no significant gel points observed in rheological tests (Fig. 1b). Dynamic-state shear further showed the continuously-decreased viscosity with the increase of shear frequency (Fig. 1c). The typical behaviour of a shear thinning polymer is very useful for the adhesives delivered by syringe-needle injection because of the increase of the shear rate at the narrow needle[26].

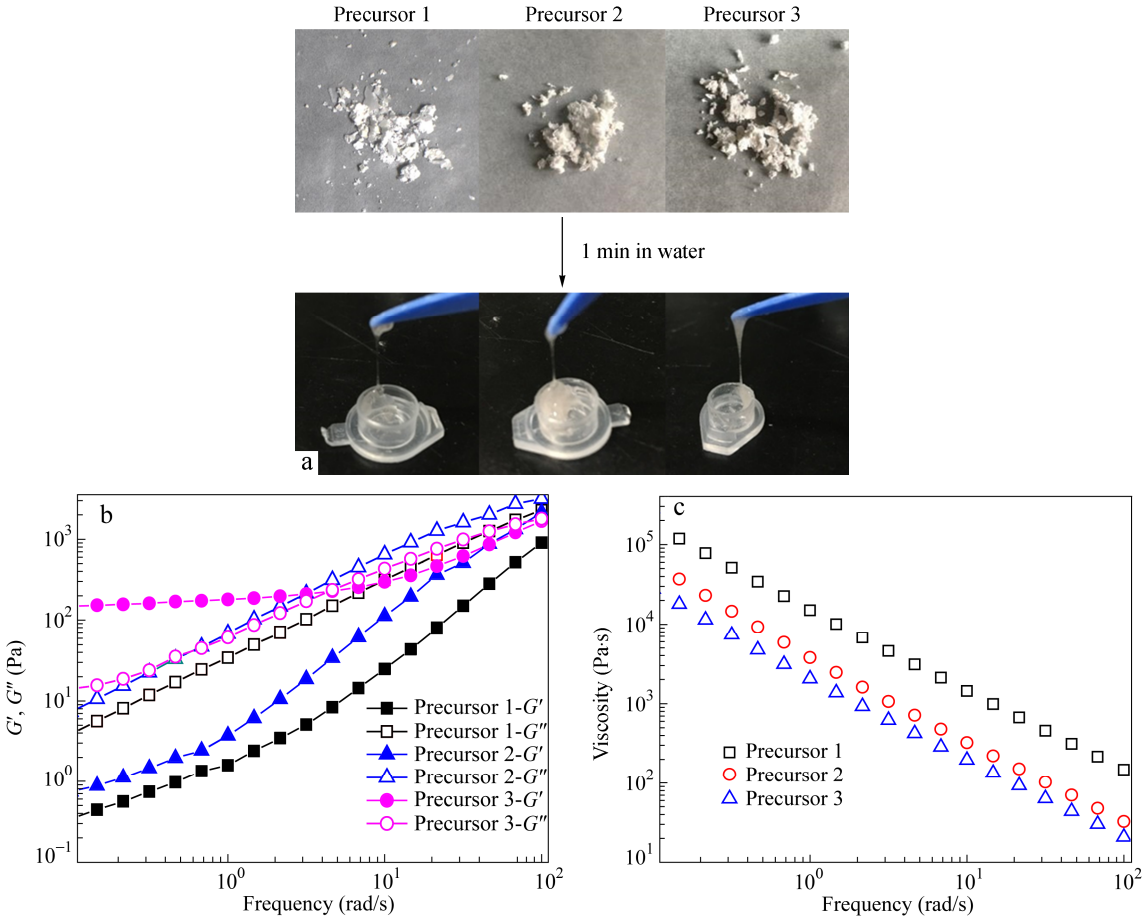


Fig. 1 (a) Property changes of the precursors in water; (b) Storage modulus (G') and loss modulus (G'') of the precursors as a function of frequency; (c) Viscosity of the precursors as a function of frequency (The online version is colorful.)

Preparation and Adhesion Strength of the Adhesives

The adhesive strength of adhesives is mainly determined by the interaction between the adhesives and the tissue, and the bulk intensity of the adhesives[26]. The catechol groups can react with the amino groups of the tissue protein, which has already been well-documented[4, 12]. Here, the bulk intensity was improved by crosslinking the precursors using $NaIO_4$ to yield the adhesives. After crosslinking, the adhesives showed a rubber-like behavior ($G' > G''$), and had a significantly increased intensity with that G' values of the adhesives 1–3 were far more than those of the precursors 1–3 (Figs. 1b and 2a). To test the adhesion strength, we applied the porcine skin as a model, which is commonly used for biomedical experiments due to its biological similarity to human dermis[27]. Figure 2(b) reflected that the adhesive strengths of the adhesives 1–3 ((30.4 ± 7.6), (36.2 ± 4.1) and (35.6 ± 7.2) kPa) were about 2–2.5 folds higher than that of the commercial fibrin glue ((16.3 ± 4.5) kPa). So the three adhesives with good adhesion strength are promising candidates for wound closure.

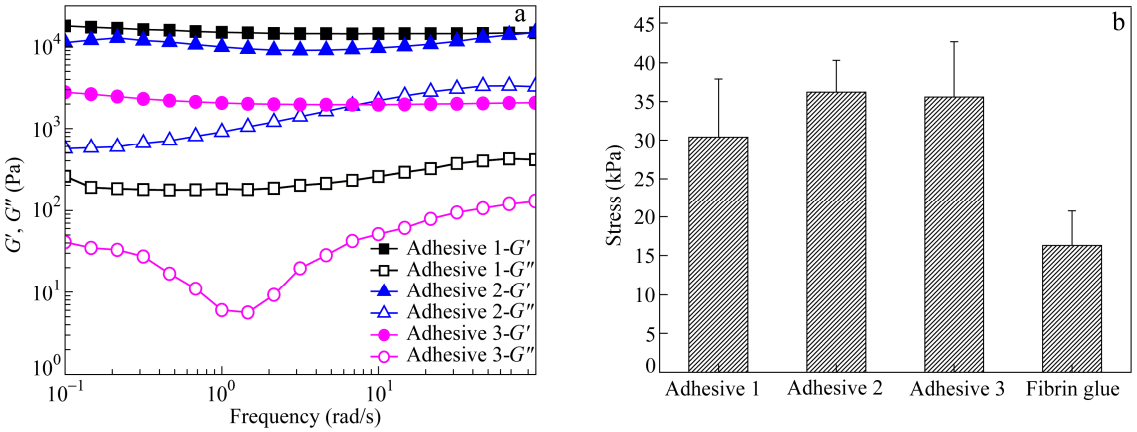


Fig. 2 (a) Elastic modulus (G') and viscous modulus (G'') of the adhesives as a function of frequency; (b) Adhesion properties of the adhesives 1–3 and the commercially available fibrin glue (The online version is colorful.)

Porous Structures of the Adhesives

Porous structures are important for wound healing since they are beneficial for nutrients transport and oxygen exchange[28–32]. The SEM images in Fig. 3 clearly disclosed the porous structure of the three adhesives. No significant differences in pore sizes were observed for the three adhesives, as indicated by that the pore sizes were (29.2 ± 6.2), (29.5 ± 4.9) and (30.2 ± 2.3) μm for the adhesives 1–3, calculated by the Image-pro Plu. The large porous structures made the adhesives promising for the wound healing.

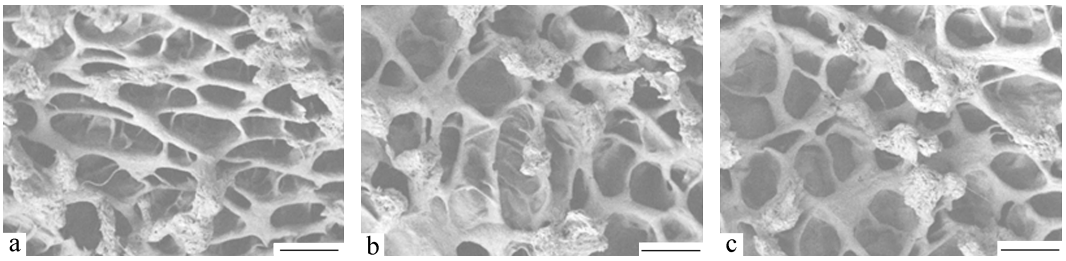


Fig. 3 SEM images of the (a) adhesive 1, (b) adhesive 2 and (c) adhesive 3 (Scale bar: 30 μm)

Swelling and Degradation Properties

Incorporation of POSS aims at decreasing the hydrophilicity of the adhesives. The contact angel to water can visually reflect the change of hydrophilicity. Figure 4(a) shows that the contact angles of the pristine 10k, 20k and 40k PEG hydrogels were (34.1 ± 4.2)°, (38.7 ± 4.4)° and (43.7 ± 3.0)°. After the POSS modification, the contact angles of the corresponding adhesives significantly increased to (69.8 ± 6.2)°, (71.8 ± 1.8)° and (84.6 ± 0.8)°, illustrating that the embedded POSS effectively reduces the hydrophilicity. Swelling ratio is another important factor to demonstrate water-absorption ability of the adhesives. Lower molecular weight PEG and more POSS contents are favourable for weaker water-absorption ability. The swelling ratios of pure PEG hydrogels were more than 1700% of the solid content[9], but decreased to 166%, 495% and 885% for the adhesives 1–3 respectively (Fig. 4b). In our experiments, the initial water contents to solid contents of the adhesives all were 567%, indicating significant shrinkage, slight shrinkage and slight swelling for the adhesives 1–3 respectively after crosslinking. Since slight shrinkage is beneficial for sealing the wound without applying too large pressure to surrounding tissues, the adhesive 2 is preferable to be used for animal testing.

Different initial molecular weights of PEGs and POSS contents can influence not only the swelling property but also the degradation time. Figure 4(c) shows that the days of complete degradation were 35, 28 and 7 for the adhesives 1–3 respectively. The fastest degradation of the adhesive 3 should be ascribed to its highest hydrophilicity and smallest crosslinking degrees resulted from the least POSS contents. The tunable degradation properties made the adhesives proper for various applications.

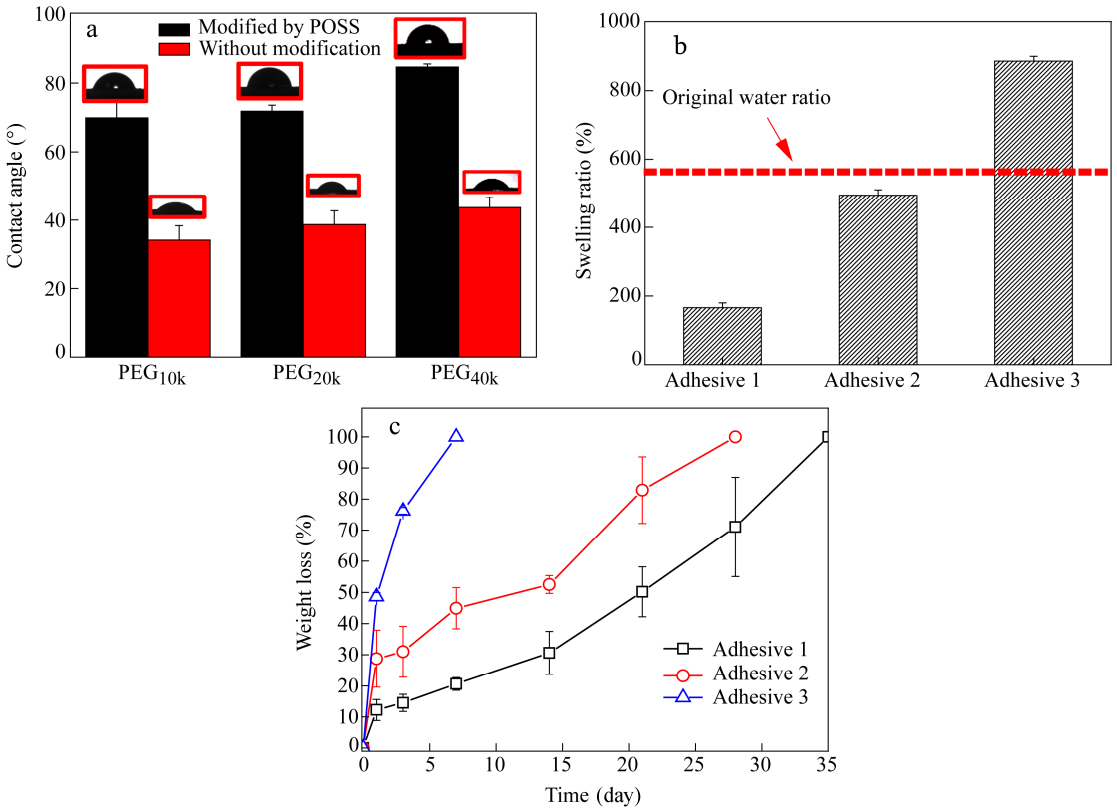


Fig. 4 (a) Contact angles of the pristine PEG hydrogels and corresponding adhesives; (b) Swelling ratios and (c) degradation properties of the adhesives (The online version is colorful.)

In Vitro Cell Viability and Proliferation

The main components of the adhesives were POSS, PEG and $NaIO_4$, all of which have been widely used in biomedical applications safely[4, 10, 12, 29, 33]. So the adhesives are supposed to be nontoxic. To further confirm this, we performed the cell viability experiments using 3T3 fibroblast cells. Figure 5(a) demonstrates that the cell viability remained over 90% even under the original adhesive extracts after incubation for 4 days, illustrating that the adhesives will not induce significant cytotoxicity and can be used in the tissues safely. The PEG-adhesives are limited in clinical use because they do not support the cell adhesion, which thus act as barriers to the wound healing[15]. Introduction of POSS could improve the cell adhesion and growth[34]. To demonstrate the POSS-modified adhesives to have good cell adhesion capacity, we adopted the adhesive 2 with suitable adhesion, swelling and degradation properties for evaluation. Many 3T3 mouse fibroblast cells were obviously observed from the SEM image in Fig. 5(b) as well as the laser confocal microscopy image in Fig. 5(c), clearly illustrating that the adhesive 2 possessed good cell adhesion capacity.

In Vivo Biocompatibility

The adhesives for wound closure need to be not only nontoxic, but also biocompatible without causing serious or persistent inflammation. Here, the adhesive 2 was implanted subcutaneously into the rat animal model for 3, 7 and 28 days to evaluate its biocompatibility. On the 3rd day, a strong local inflammatory response could be observed (Fig. 6a), but the inflammatory response dramatically decreased after 7 days (Fig. 6b) and the inflammatory was nearly invisible after 28 days (Fig. 6c), indicating that the adhesive 2 will not lead to persistent inflammation. Interestingly, a lot of fibroblasts that can up-regulate collagen production appeared around the adhesive on the 7th day (Fig. 6b), which is beneficial for wound healing. The subcutaneous implantation results strongly proved that the adhesive 2 has good biocompatibility and is able to accelerate wound healing through supporting fibroblast proliferation.

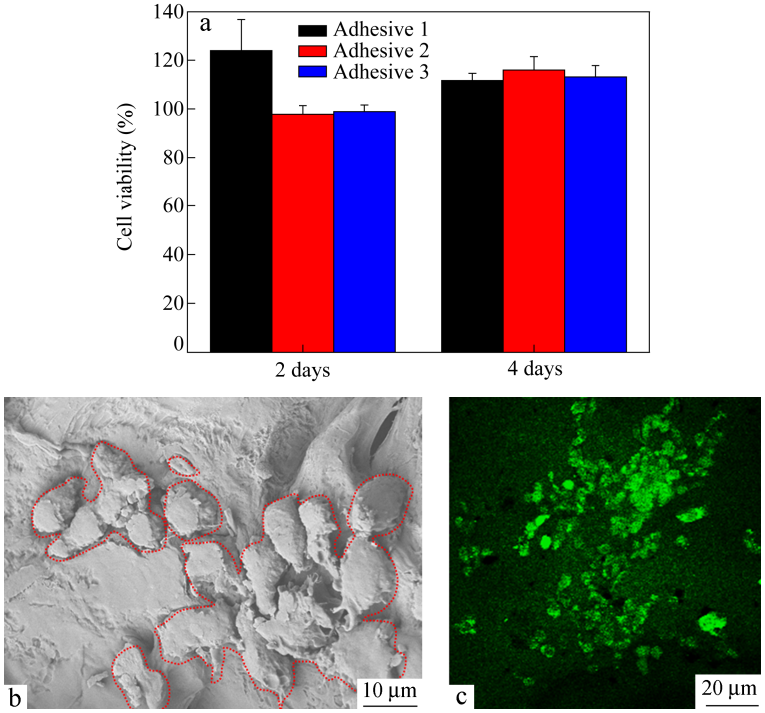


Fig. 5 (a) Cytotoxicity of the adhesives 1–3 in 3T3 mouse fibroblast cells after incubation for 2 and 4 days; (b) SEM and (c) the laser confocal microscopy images of 3T3 mouse fibroblast cells cultured on the adhesive 2 for 24 h (Cells in SEM are highlighted by the red dotted lines. The online version is colorful.)

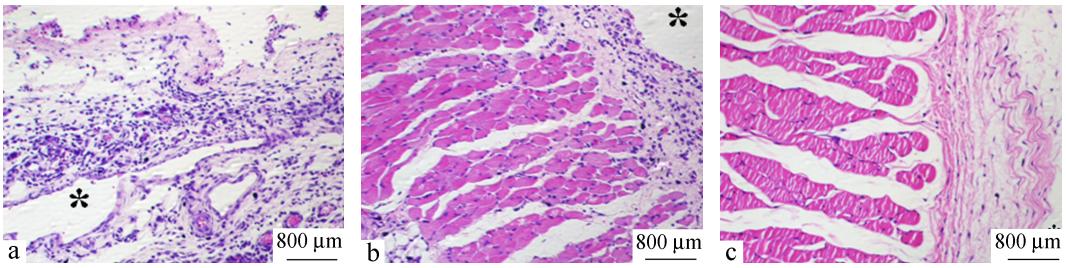


Fig. 6 H&E histological results of the adhesive 2 after implantation for (a) 3 days, (b) 7 days, and (c) 28 days (The asterisks indicate the adhesives. The online version is colorful.)

Effect on Wound Healing

The use of adhesive materials can effectively avoid the pain, lessen the performance inconvenience and accelerate the wound healing[5, 35]. Currently, most of *in vivo* wound healing experiments were carried out on small animal models like rabbits and rats[2, 4, 29]; however, these small mammals differ from humans in a number of anatomical and physiological ways. Pig skin is very similar to human skin[36], so we adopted the Bama miniature pigs of 2 months to study the wound healing effect for the adhesive 2. In our experiments, incisions of 1 cm in length and 1 cm in depth were created with a surgical scalpel on the back of the pig and then treated with the adhesive, and suture lines were used as a control. The wounds were pressed for 2 min to endow enough crosslinking degree of the adhesive. Once the pressure was released, the wounds would not open again (Fig. 7a). In this sense, the adhesive 2 can rapidly close the wounds and keep them closed. Although no significant difference was observed between the two groups of the adhesives and suture treated wounds from the visual examination after 28 days, the obvious suture holes still remained for the sutured skin (Fig. 7b). The inner observation of the slice wounds in Fig. 7(c) showed that no adhesive was observed at the location of the healed

tissue, demonstrating complete degradation of the adhesive 2. Besides, the unhealed part of the adhesive group was smaller than that of the sutured group, indicating that the adhesive could accelerate the healing process.

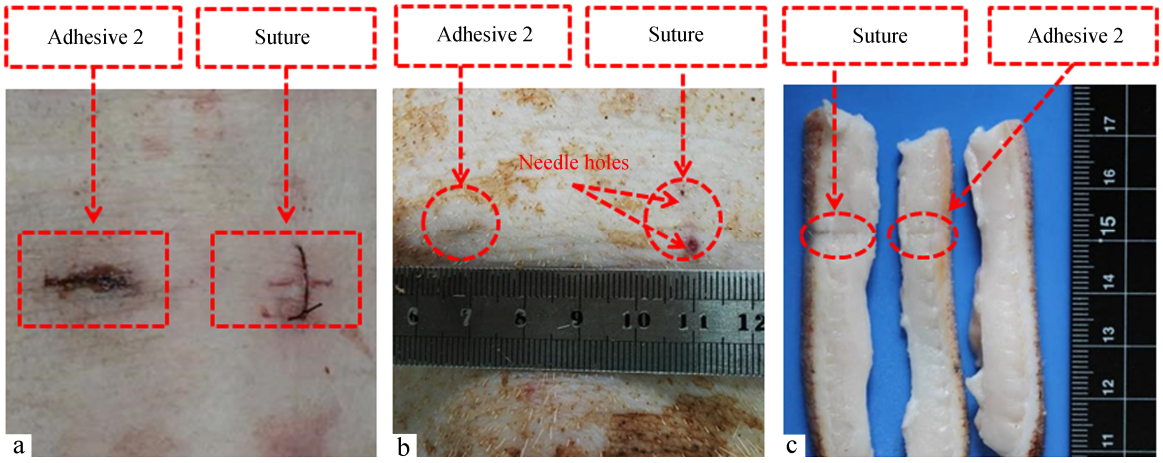


Fig. 7 Photographs of wounds treated by the adhesive 2 and suture after (a) 2 min and (b) 28-day post operation; (c) Photographs showing the inner structures of wounds treated with the adhesive 2 and suture for 28 days (The online version is colorful.)

The resulted skin samples were further harvested and treated by Mason staining. In Fig. 8(a), a newly formed dermis was clearly observed for the adhesive-treated skin. The tissue near the dermis had already been healed although there still existed some fibrosis. The wounded area for the sutured groups was larger than that for the adhesive-treated skin, including the needle hole (Fig. 8b) and the unhealed incision (Fig. 8c). The larger wound area illustrated that the suture expanded the wounds compared with the non-invasive adhesives. Although the new dermis was also observed for the sutured wounds, the tissue near the dermis was still fibrosis tissue, and no healed tissue under the dermis could be observed, demonstrating the slower healing process of the sutured wounds. The mechanical properties of the healed porcine skin were also tested for further evaluation. Figure 8(d)

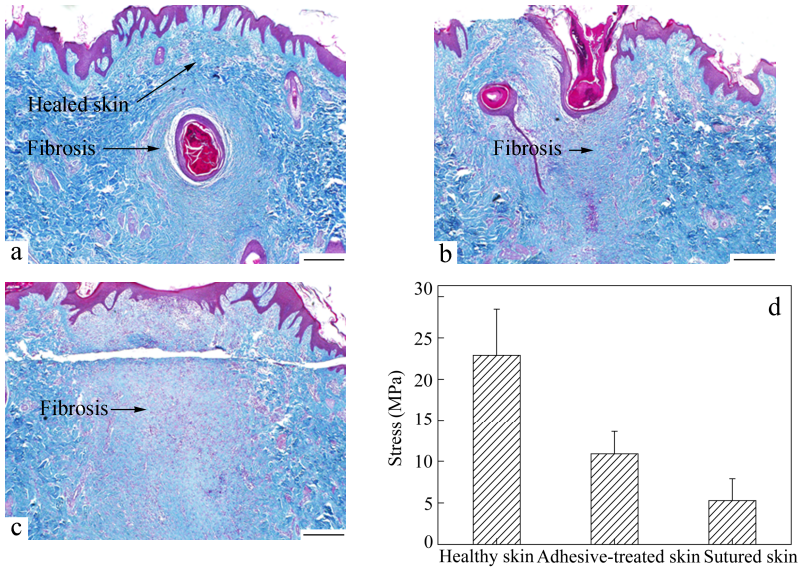


Fig. 8 (a) Mason staining of the wounds after post-treatment for 28 days with (a) adhesive 2 and (b, c) suture (b and c refer to tissue at the needle hole and the incision respectively; Scale bar: 400 μm); (d) Tensile strength of healthy skin and healed skin treated by the adhesive 2 and suture (The online version is colorful.)

shows that the tensile strength of adhesive-treated skin was (10.8 ± 2.7) MPa, two folds higher than that of suture-closed skin ((5.3 ± 2.6) MPa). These results declared that the tissue reconstruction and healing process could be accelerated by the adhesive.

CONCLUSIONS

In summary, we reported a new class of POSS-modified PEG adhesives with strong adhesion and good biocompatibility for wound healing. Incorporation of POSS decreased the swelling of the adhesives and improved the cell adhesion and growth. Evaluation of healing of the wounded pig skin proved that the adhesives could accelerate the healing process compared with the normal sutures. Our results demonstrate that the POSS-modified PEG adhesives are promising candidates for wound closure.

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