Self-Hydrophobization in a Dynamic Hydrogel for Creating Nonspecific Repeatable Underwater Adhesion

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Adhesive hydrogels are widely applied for biological and medical purposes; however, they are generally unable to adhere to tissues under wet/underwater conditions. Herein, described is a class of novel dynamic hydrogels that shows repeatable and long-term stable underwater adhesion to various substrates including wet biological tissues. The hydrogels have Fe$^{3+}$-induced hydrophobic surfaces, which are dynamic and can undergo a self-hydrophobization process to achieve strong underwater adhesion to a diverse range of dried/wet substrates without the need for additional processes or reagents. It is also demonstrated that the hydrogels can directly adhere to biological tissues in the presence of under sweat, blood, or body fluid exposure, and that the adhesion is compatible with in vivo dynamic movements. This study provides a novel strategy for fabricating underwater adhesive hydrogels for many applications, such as soft robots, wearable devices, tissue adhesives, and wound dressings.

1. Introduction

Hydrogels are widely used biomaterials with attractive features, including high water content, high deformability, structural similarity to biological tissues, and potential functionalization. In many applications, such as underwater soft robots, implantable devices in human body, wound dressing, tissue engineering, and drug delivery systems, hydrogels are required to adhere firmly to substrate surfaces in both dried and wet environments. To this end, adhesive hydrogels have been designed and developed and in general the reported materials stick effectively to dry substrates in air. However, it is challenging to achieve robust adhesion underwater with these adhesive hydrogels owing to hydration overlayers that prevent on their surfaces in underwater/wet conditions. The hydration overlayer either prevents the formation of molecular bridges between the adhesive and applied surfaces, or induces swelling stress that leads to the failure of adhesion. To overcome these challenges, underwater adhesive hydrogels based on proteins, synthetic polymers, and biomolecules have recently been developed recently. These materials can undergo in situ gelation/crosslinking reactions at the interfaces, or form specific interactions with some functional substrates, to generate strong underwater adhesion. Such underwater adhesion requires either long gelling time or complex premodification processes, and moreover, is generally irreversible, which limits immediate practical applications of the hydrogels in many fields. Therefore, it remains desirable to develop an adhesive hydrogel with strong, reversible, and nonspecific adhesion that performs well in wet and even underwater conditions.

Herein, we report a class of dynamic hydrophobic hydrogels that offer repeatable, long-term stable underwater adhesion to various substrates, including wet biological tissues. The hydrogels consist of a crosslinked copolymer of hydrophilic acrylamide and hydrophobic stearyl methacrylate (C$_{18}$), sodium dodecyl sulfate (SDS), and Fe$^{3+}$ ions (Figure 1a). They were prepared via a facile micellar copolymerization of both monomers in the presence of a small amount of chemical crosslinker (N,N'-methylenebisacrylamide, MBAA), followed by immersion in FeCl$_3$ solution and a water-washing treatment (see the Experimental Section for details and Scheme S1, Supporting Information). The hydrogels before and after immersion in Fe$^{3+}$ solution are denoted as PAM-C-M and Fe-PAM-C-M, respectively. In the hydrogels, the covalent linkage made from MBAA was designed to provide a permanent polymer network while the hydrophobic alkyl chains of the C$_{18}$ units aggregate in SDS (or ferric dodecyl sulfate (FDS)) micelles to form dynamic hydrophobic associations. We found that the dynamic crosslinked PAM-C-M hydrogels are able to self-adjust their interfacial molecular components to form Fe-PAM-C-M hydrogel with a hydrophobic surface following a two-step Fe$^{3+}$ solution-immersion and water-washing process (the hydrophobization process in Figure 1a). This hydrophobic surface favors the formation of a water-resistant molecular bridge between the hydrogel surface and hydrophobic domains on the substrates, while the nature of self-hydrophobization would enable the growth of hydrophobic...
interactions to further repel water molecules away from the interface, which endows the hydrogels with outstanding underwater adhesion behavior (Figure 1b). Using a simple comparison demonstration, we showed that the obtained Fe-PAM-C-M hydrogel could readily adhere to substrates underwater and remain in place (Figure 1c, Video S1, Supporting Information). The adhesion was strong enough to withstand water blasting for at least 10 s (Figure 1d, Video S2, Supporting Information). In contrast, the PAM-C-M hydrogel was slippery and nonsticky underwater (Figure 1c, Video S3, Supporting Information).

2. Results and Discussion

We first studied the Fe$^{3+}$-induced hydrophobization process on the hydrogel surfaces. Figure 2a shows the water contact angle

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**Figure 1.** Underwater adhesive hydrogels. a) Schematic illustration of the fabrication of the underwater adhesive hydrogels. The hydrogel (PAM-C-M) made from MBAA-crosslinked poly(acrylamide-co-C$_{18}$) was immersed in an aqueous Fe$^{3+}$ solution, followed by a water-washing process to obtain a hydrogel (Fe-PAM-C-M) with a hydrophobic surface. DI water was used and MBAA is N,N'-methylenebisacrylamide. b) Schematic illustration of the self-hydrophobization process for the formation of firm underwater adhesion between the hydrogel and substrate. When the hydrogel is compressed to achieve contact with the substrate underwater, the hydrophobic interactions form and grow at the interface, and repel water away from the interface. c) Demonstration of underwater adhesion. The as-prepared hydrophilic PAM-C-M hydrogel was nonadhesive and slipped away from the metal block surface underwater, while the hydrophobic Fe-PAM-C-M hydrogel firmly adhered to the metal block surface and was able to lift the block (200 g) up underwater. d) Photograph showing that the adhesion between the hydrogel and substrate is strong enough to resist water blasting for 10 s.
The (WCA) of the hydrogels after immersion in FeCl₃ solution for different times. The surfaces of the PAM-C-M hydrogels were hydrophilic showing an average WCA of 22°, due to the hydrophilic nature of the polyacrylamide segments. In this case, the hydrophobic C₁₈ units were stabilized in SDS micelles. After immersion in Fe³⁺ solution (0.12 M), the WCA of the hydrogel surfaces increased and reached to a maximum value of 115° for an immersion time of 80 min. This hydrophobization process was attributed to the Fe³⁺ ion-induced reconfiguration of the C₁₈-loaded SDS micelles. It is known that SDS micelles would reassemble into large structures when exposed to high ionic strength solutions. We also performed a molecular dynamics calculation to investigate the structures of SDS micelles in the presence of Fe³⁺ ions, and the results show that the Fe³⁺ ions induce larger SDS micelles (Figure S1, Supporting Information). We also performed a molecular dynamics calculation to investigate the structures of SDS micelles in the presence of Fe³⁺ ions, and the results show that the Fe³⁺ ions induce larger SDS micelles (Figure S1, Supporting Information). We therefore expected that a bilayer of the surfactants (SDS/FDS) and C₁₈ units was formed on the interface between the hydrogel surface and FeCl₃ solution during immersion (Figure 1a). This hypothesis was supported by the observation of SDS crystallization (fully ordered SDS bilayer structure formation) which occurred at the interface over extended Fe³⁺ solution immersion (>1 day, Figure S2, Supporting Information). The fresh surfaces of the Fe³⁺-immersed hydrogels became slightly hydrophobic with a WCA of 51° since the sulfate group of SDS was exposed to air in this state (Figure S3, Supporting Information). After water-washing treatment to remove the surfactant molecules on top layer, exposed alkyl chains of surfactant and C₁₈ units in the bottom layer made the surface more hydrophobic (Figure 1a and Figure S3, Supporting Information). The presentation of the alkyl chains was confirmed by the Fourier-transform infrared spectroscopy (FT-IR) spectra measurement in which the two characteristic peaks (2850 and 2916 cm⁻¹) of long aliphatic carbon tails appear on the surface of Fe-PAM-C-M hydrogel (Figure 2b). The hydrophobization only occurred on the interface, which was proved by the hydrophilic feature of the inner surface of the Fe-PAM-C-M hydrogel (exposed cross-section after cutting), which had the WCA < 10° (Figure S4, Supporting Information). We also found that further increasing the immersion time led to a decrease in WCA. This was attributed to the diluting effect of SDS molecules in the hydrogel during immersion.

In our systems, three kinds of compositions, i.e., C₁₈ units, SDS, and Fe³⁺ ions, are essential for the hydrophobization. Fe³⁺ solution triggered the formation of a hydrophobic surface while the C₁₈ units stabilized the SDS-based hydrophobic layer. To confirm this, three control hydrogels were prepared (experimental details in Supporting Information), including 1) SDS-free hydrogel with only C₁₈, 2) C₁₈-free hydrogel with only SDS micelles, and 3) covalently crosslinked hydrogel without hydrophobic C₁₈ units or SDS. After the same treatment in Fe³⁺ solution and washing with water, these three control samples showed hydrophilic surfaces with WCAs of 39°, 11.5°, and 5°, respectively (Figure S5a, Supporting Information). As the hydrogels were too slippery to be fixed on the jig, we could not bond the hydrogels to the substrate and therefore, could not get reliable bonding strength. We further evaluated the stability of the Fe³⁺ ions in both Fe-PAM-C-M and these control hydrogels and found that Fe³⁺ ions could be
removed by a water-immersion treatment for control samples but not for Fe-PAM-C-M hydrogels (Figure S5b, Supporting Information). These results supported the hypothesis of hierarchical interactions (the C$_{18}$ units stabilized the surfactants which bound the Fe$^{3+}$ ions).

With these hydrophobic Fe-PAM-C-M hydrogels in our hands, we quantitatively evaluated their underwater adhesion behaviors by a tensile-adhesion test using polypropylene (PP) films as the substrate (Scheme S2, Supporting Information). Figure 2c shows the underwater adhesive strength of different Fe-PAM-C-M hydrogels obtained after different periods of immersion time in Fe$^{3+}$ solution. The adhesion strength increased with the immersion time, achieved a maximum value at 80 min, and then decreased because of the reduced hydrophobic effects, which agrees with the change in hydrophobicity of the hydrogel surface. Such consistency in underwater adhesion and surface hydrophobicity indicated a direct correlation between them. Therefore, the adhesion strength can be tracked by monitoring the WCA of the hydrogels. Based on these results, the adhesive Fe-PAM-C-M hydrogels with 80 min Fe$^{3+}$ immersion were selected for subsequent studies.

Figure 2d,e shows the underwater adhesion of the Fe-PAM-C-M hydrogel with increasing preload and contact time, respectively. When it is reasonable to note that the adhesion strength increases with preloading, it is interesting to find that the strength increased with increasing contact time. This self-strengthening process implied a self-hydrophobization process in which water molecules at the hydrogel–substrate interface were continuously repelled after contacting until an entire hydrophobic interface formed (Figure 1b). Furthermore, since the hydrophobic interface was made from both surfactants and C$_{18}$ units, the fraction of C$_{18}$ units in the hydrogels was expected to play a significant role in enhancing the underwater adhesion. This hypothesis was confirmed by the observation of increasing underwater adhesion strength of the hydrogel with increasing C$_{18}$ fraction (Figure 2f). With further increase in the C$_{18}$ fraction 40 wt%, the adhesive strength decreased, which might be the result of weaker dynamic behavior in the highly crosslinked state.

The underwater adhesion of hydrophobic Fe-PAM-C-M hydrogel is nonspecific to the substrates. This was demonstrated using synthetic polymers, metals, and glasses, as well as a natural stone as versatile substrates (Figure S6, Supporting Information). Figure 3a shows the quantitative adhesion strength of the Fe-PAM-C-M hydrogel to glass, titanium (Ti), polyethylene (PE), and PP in both air and water conditions. The underwater adhesion behavior of the Fe-PAM-C-M hydrogels was further quantified by the adhesion energy using peel testing (Figure S7, Supporting Information). The hydrogel showed higher adhesion to hydrophobic substrates (PE and PP) than hydrophilic ones (glass and Ti) in the underwater conditions, while the opposite behavior was observed in the air.

Figure 3. Underwater adhesion performance of Fe-PAM-C-M. a) The adhesion strengths of Fe-PAM-C-M to different substrates in air and underwater conditions. b) Underwater adhesion strength of Fe-PAM-C-M after different attachment--detachment cycles. The testing substrate was PP film. The preload was 25 kPa and the contact time was 120 s. c) The WCAs and underwater adhesion strengths of Fe-PAM-C-M after different storage times in air. d) Underwater stability of the adhesion strength measured after immersing the hydrogel-joined substrates in water for 7 days. The insert shows that the hydrogel was adhered to the glass after a 7 day immersion in water. Abbreviations: PE: polyethylene; PP: polypropylene, Ti: Titanium. Error bars show the standard deviation; sample number $n= 3$ in (a), (c), and (d).
The results indicated that the adhesion strength was depended on the surface chemistry of the testing substrates in different conditions. Unlike most adhesive hydrogels on which water molecules act as a sliding lubricant, the Fe-PAM-C-M hydrogel prefers an aqueous environment for adhesion since the expulsion of water is an energy-favored process during formation of the hydrophobic interface. Additionally, the environment-dependent adhesion of the hydrogel implied that the Fe-PAM-C-M hydrogel was able to self-adjust its surficial groups to achieve nonspecific interactions with the adherents with different surface properties, which is due to the existence of a dynamic hydrophobic layer (comprised of C18 stabilized hydrophobic surfactants) on the surface of the hydrogels. For a hydrophobic adherent, the hydrophobic layer consisting of the surfactants (SDS/FDS) and C18 units was directly adhered to the adherent via hydrophobic interactions (Figure S8, Supporting Information). For a hydrophilic adherent, we hypothesized that the surfactants (SDS/FDS) from the hydrogels attached to the hydrophilic surfaces at first and converted the surface properties to hydrophobic to achieve adhesion (Figure S8, Supporting Information). To confirm this self-regulation process, we measured the WCA of the substrates and hydrogel samples before and after adhesion.\textsuperscript{35} As anticipated, the hydrophobic PE substrate becomes hydrophilic with a WCA of \(\approx 30^\circ\) after detaching from the hydrogel, while the Fe-PAM-C-M hydrogel retained hydrophobicity with the WCA of \(\approx 100^\circ\). The hydrophilic glass became slightly hydrophobic with a WCA of \(\approx 55^\circ\) (intact glass: \(\approx 16^\circ\)) after detaching from the hydrogel, while the detached Fe-PAM-C-M hydrogel was shifted toward hydrophilicity with a WCA of 82° from 115° (Figure S9, Supporting Information). The diverse adhesion properties of the hydrogels therefore enable a variety of promising applications in different fields.

Furthermore, the Fe-PAM-C-M hydrogel adhesion is highly repeatable. As shown in Figure 3b, the hydrogel retained its strong underwater adhesion even after more than 50 adhesion–detachment cycles with the testing substrates. These results indicated that Fe-PAM-C-M hydrogel has potential for use in some practical applications that require adhered surfaces are easily separable for recycling or repair, such as material separation and recycling systems, biomedical holding equipment for reversible transfer of soft and fragile biological tissues, and the repair of joints.

The Fe-PAM-C-M hydrogel retained its underwater adhesion even after long-term storage. This was confirmed by sealing the Fe-PAM-C-M hydrogel samples in petri dishes and then measuring their WCA and underwater adhesion strength at predetermined time intervals. As shown in Figure 3c, the contact angle of the hydrogel surface slightly decreases but remains > 90° after 15 days of storage. In addition, the hydrogels were still sticky and showed an adhesion strength (29 kPa) underwater. The slight decrease in adhesion strength might be attributed to the decreased hydrophobicity of the hydrogels as a consequence of the formation of a bilayer. After the samples were stored in a sealed condition, water molecules inevitably evaporated from the hydrogel to increase the environmental humidity and therefore, SDS reassembled to form bilayer structure to reduce the hydrophobicity. This stability favors its use in practical applications and its commercialization.

In addition, the Fe-PAM-C-M hydrogel exhibited the excellent stable adhesion in an underwater environment. Note that the traditional adhesive hydrogels will delaminate from substrates after long-time water immersion as the inevitable swelling increases stress, which significantly thus hinders their applications as long-term adhesives. However, our hydrogels maintained their adhesive states (joined with PP films and glass slides) in water for more than 7 days (tested time) without any detachment (the sticking sample does not detach under water blasting, Figure S10, Supporting Information). We then clamped the samples in a mechanical test machine to investigate the tensile strength and measured the force to pull apart the sample pairs. The maximum adhesion strength on the PP substrates was 30 kPa, while that on glass slides even increased to 75 ± 10 kPa (Figure 3d). The stability of underwater adhesion was owing to the self-hydrophobic effect from the hydrogel surfaces and the nonswellability of the hydrogels (Figure S11, Supporting Information). In contrast to its swellable precursor (PAM-C-M hydrogel), the Fe-PAM-C-M hydrogel was almost nonswellable owing to the synergistic crosslinking interactions formed by Fe\textsuperscript{3+}, surfactants, and the hydrophobic C18 units. The increase in underwater adhesion in an employed state was also attributed to the same self-adaptability of the dynamic molecules at the interface. In the employed state, the self-hydrophobic effect at the adhered interface created a water-resistant environment, and thus the molecules at the interface would reassemble to minimize the interfacial energy, resulting in an increase in the interfacial interactions and then enhancing the adhesion between the glass slide and hydrogel surfaces.

The Fe-PAM-C-M hydrogel also shows strong adhesion to biological tissues that are composed of abundant hydrophobic proteins. As shown in Figure 4a, b, the Fe-PAM-C-M hydrogel directly adhered to the forehead skin of one of author after prespring as a result of exercise (Video S4, Supporting Information), as well as wet porcine muscle. This ready adhesion allows the hydrogel to be applied in a facile manner, which would avoid the need for tedious processes to be carried out by the clinicians. We then evaluated the tissue-adhesive strength of the Fe-PAM-C-M hydrogel by using wet porcine skin and bone surfaces as the representative biological tissues. The Fe-PAM-M-C hydrogel exhibited high tissue adhesive strength on both wet porcine skin and bone surfaces immediately after adhesion (Figure 4c), which was comparable to that obtained by other commercially available bioadhesives or sealants such as Quixil (24.6 kPa), Beriplast (24.2 kPa), Tachosil (59.6 kPa), and Tisseel (77.5 kPa).\textsuperscript{36} Note that some adhesives have poor adhesion, especially in wet condition, and falls off quickly, such as polyethylene glycol (PEG)-based adhesive (ReSure, Ocular Therapeutix Inc., USA).\textsuperscript{37} We listed the properties of several typical adhesives in Table S1 in the Supporting Information to clarify the comparisons of our adhesive hydrogel with commercially available adhesives. The adhesive strength of the hydrogel increases after 1 day of adhesion, which might be attributed to the self-adaptability of the dynamic adhesive surface of the hydrogel. In addition, the hydrogel showed stable adhesion to the bone tissues after immersing the hydrogel-joined bone tissues in water for 7 days with adhesion strength of 50 kPa.
We also tested the adhesion ability of the hydrogel in vivo, where the adhesion is often more complicated by exposure to blood or other body fluids as well as in dynamic movements. Figure 4d shows the representative photos of a Fe-PAM-C-M hydrogel adhered to a beating porcine heart covered with fresh blood and the subsequent peeling off. The Fe-PAM-C-M hydrogel showed strong adhesion on the dynamic heart surface (Video S5, Supporting Information), and was able to accommodate movement of the beating heart while keeping firm adhesion due to high excellent mechanical properties of the hydrogel. Tensile tests indicate that the Fe-PAM-M-C hydrogel displays a maximum tensile strain of 2000%, tensile strength of 15 kPa, and fracture energy of 4000 J m$^{-2}$ (Figure S12, Supporting Information). These mechanical performances cannot be achieved among existing tissue adhesives. For example, the fibrin- and collagen-based adhesives
(Tissel and Bioglué) have relatively low mechanical strength,[18] while the PEG-based adhesives (COSEAL) are formed with a brittle matrix.[20] In contrast, our adhesive hydrogel was stretchable and met the mechanical requirements when applied as adhesive bandages.

The hydrogel was also used as a sealant to close defects in the liver, heart, or stomach of a rabbit owing to its excellent bio-adhesion (Figure 4e,f and Figure S13 and Video S6, Supporting Information). The hydrogel was compliant and conformal closely to the geometry of the organs. When the heart and stomach were being injected with phosphate-buffered saline (PBS), the hydrogel was expanded with the deformation, and no leakage was observed in either cases. The burst pressure tests were further used to investigate the capacity of the Fe-PAM-M-C hydrogel adhering on tissue walls with a defect to resist bursting pressure (Scheme S3, Supporting Information). The sample was first adhered on the wet surface of porcine myocardium tissue with a 2 mm diameter hole in a chamber linked to a syringe pump and filled with PBS. PBS was then pumped to exert pressure on the hydrogel-sealed hole. The measured burst pressure of Fe-PAM-B-C hydrogel was up to 400 mm Hg (Figure S14, Supporting Information), which was higher than the normal arterial blood pressure in humans (80–120 mmHg) and the performance of commercially available surgical sealants.[20,30] Furthermore, the in vivo biocompatibility and local tissue interactions of the hydrogel were evaluated by subcutaneous implantation in subcutaneous pockets of rats dorsal (Figure S15a, Supporting Information). After 1 and 2 weeks of post-implantation and the histological assessment, it was found that the degree of inflammatory reaction produced by our hydrogels decreased after 2 weeks of implantation (Figure S15b,c, Supporting Information), and the hydrogel integrated well with the surrounding tissues as a seamless interface was formed between the hydrogels and tissues after 2 weeks of implantation (Figure 4g). These results indicated that our hydrogels might be more convenient for surgical applications than previous adhesive hydrogels that involve in situ gelation and extra reagents.[19,25,29]

3. Conclusions

In summary, we have demonstrated a class of underwater adhesive hydrogels, which show strong, long-term stable, and reversible underwater adhesion to various substrates including living tissues. The formation of such underwater adhesion was based on the novel self-hydrophobization process. Because of the superior performance and facile fabrication, we envision their promising applications in the gluing of tissues and attaching devices in vivo, tissue repair, attaining hemostasis.

4. Experimental Section

Materials: Acrylamide (AAm), initiator ammonium persulfate (APS), the accelerator N,N,N',N'-tetramethylethylenediamine (TEMED), MBA, SDS, sodium chloride (NaCl), stearyl methacrylate (C18), and iron(III) chloride hexahydrate (FeCl3·6H2O) were purchased from Sigma-Aldrich and used directly. Other solvents were used as obtained, unless otherwise specified. Deionized (DI) water was used in all the experiments.

Preparation of Prehydrogel (PAM-M-C): In a typical example, SDS (2.12 g) was first dissolved in NaCl solution (30 mL of 0.8 wt%) at 50 °C to form SDS/NaCl micelles. Hydrophobic monomer (0.26 g) was added to this solution, which was then stirred at 50 °C for 1 h to incorporate C18 into the micelles. AA monomers (1.5 g) were then dissolved in the mixture. After the mixture was degassed with nitrogen for 10 min, MBA (0.003 g), APS (0.08 g), and TEMED (10 μL) were added. The mixture was stirred vigorously for 30 s, then transferred to a nitrogen-purged mold, and sealed for polymerization at room temperature for 1 h to yield the as-prepared hydrogel samples, which were denoted PAM-C-M hydrogel. The hydrogel samples were cut using a scalpel to give dimensions of 10 mm × 10 mm × 2 mm before further treatment.

Preparation of the Adhesive Hydrogel: The adhesive hydrogels were obtained through a Fe3+-induced hydrophobization process (Scheme S1, Supporting Information). Briefly, the as-prepared PAM-C-M hydrogel samples were immersed in FeCl3 solution (0.12 μL). After a set period of time, the hydrogels were removed from the solution, rinsed with adequate DI water to remove unbonded residuals, and then water was further removed using paper. The adhesive hydrogel obtained was denoted as Fe-PAM-C-M. Unless otherwise noted, the adhesive gel was prepared through above methods and proportions. Details of the hydrogel synthesis process and preparation of control samples are described in the Supporting Information.

WCA Tests: All WCAs were measured on an OCA20 Contact Angle Measuring System (Dataphysics instruments GMBH, Germany). The tests were conducted at room temperature and the volume of water droplet was 5 μL. At least three different spots on the same sample were measured to give a mean value.

FT-IR Spectra: An FT-IR (Bruker VERTEX 70v spectrometers, Bruker Corporation, USA) was used to characterize the chemical structure of the hydrogel before and after immersion in Fe3+ solution.

Adhesion Tests: The underwater adhesion strength of the hydrogels was measured by using a universal testing machine (TA Electroforce 3200 system) equipped with a 200 N load cell. Hydrogel samples with the same dimensions (thickness of 2 mm and area of 10 mm × 10 mm) were used. Tensile adhesion testing was performed to measure the adhesive strength of the hydrogels to different substrates (Scheme S2, Supporting Information). Specifically, the crosshead speed was set to 1 mm s⁻¹ in the tensile mode to obtain the load force-displacement curve. To provide a wet environment, the water was dropped at the interface between the hydrogel and target substrates. To investigate the effects of contact time and preload on the adhesion strength, the applied load was set to 5, 12.5, 25, 37.5, 50 kPa with a contact time of 120 s, or the contact time was varied from 0 to 240 s with a preload of 5 kPa. PP films were used as a representative substrate. After being compressed with the preload, the two surfaces were separated and the interfacial adhesion strength was determined based on the adhesion force curve. The adhesion strength was calculated from the maximum debonding force to the projected surface area of the sample. To investigate the nonspecific adhesion of the hydrogels, different substrates, including glass, PE, PP, and Ti, representing hydrophilic, hydrophobic, and metal materials were used. For the adhesion test, the applied load was set as 25 kPa and the contact time between two surfaces was 120 s. Adhesion-strip cyclic tests were also conducted to evaluate the multiple-time adhesion strength of the hydrogels.

Long-Term Storage Stability: To test the long-term stability, the Fe-PAM-C-M hydrogel samples were placed into a sealed petri dish at room temperature (25 °C) for 15 days. The contact angle and adhesiveness of the samples were then measured at predetermined intervals.

Underwater Adhesion Stability: To test the underwater adhesion stability, the Fe-PAM-C-M hydrogel-joined glass slides and PP films were immersed into DI water for 7 days. The adhesion strength after 7 days of immersion was measured.

Mechanical Tests: The tensile tests were performed on a universal tensile tester (ZWICK 1446, Germany) with a 200 N load cell. The rectangular PAM-C-M and Fe-PAM-C-M hydrogels were used for the tests. The thickness and width of the specimen were 2 and 15 mm,

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respectively. The samples were fixed between the double-sided tapes to fasten the grips. The gauge length between the clamps was 20 mm. Samples were stretched at a rate of 100 mm min$^{-1}$ until breaking. The fracture energy was determined using the classical single edge notch test. The measurement of each sample was repeated at least five times.

In Vitro Tissue Adhesion Tests: The in vitro adhesion of the Fe-PAM-C-M hydrogel was tested on porcine skin and bone tissues. The fresh porcine skin and bone tissues were purchased from a local grocery store. The porcine skin and bone were first cut to a standard size (10 mm $\times$ 10 mm $\times$ 2 mm) and then washed to remove the surface fat. They were then immersed in DI water at 37 °C for 2 h. After the pretreatment, the Fe-PAM-C-M hydrogels were adhered on the surfaces of the skin and bone. Then the two substrates were pressed together for 120 s with a small preload (5 kPa) and the adhesion strength was measured with tensile-adhesion tests.

In Vivo Tissue Adhesion Tests: Female Yorkshire swine with a bodyweight of 60–75 kg was used. After been anesthetized by intramuscular injection of tiletamine + zolazepam (50 mg mL$^{-1}$), and intubated with a cuffed endotracheal tube and ventilated with a volume control ventilator (Hallowell EMC Model 2000, Hallowell EMC, Pittsfield, MA) at a rate of 10–20 breaths per minute. Anesthesia was maintained with isoflurane (1–2%). Fentanyl and buprenorphine were used for analgesia, and a maintenance IV infusion of 150–300 mL h$^{-1}$ was administered. The chest cavity was accessed via midline sternotomy and the pericardium was opened to expose the heart surface. The Fe-PAM-C-M hydrogel was applied to the beating heart surface of the left ventricle and held in place. Then the hydrogel was peeled from the surface of the heart while video recording.

Burst Pressure Test: The performance of this hydrogel was evaluated by means of the maximum pressure withstand by the hydrogel when sealing a perforation of 2 mm in diameter on a fresh tissue. The testing rig provided a perfect sealing (tested by inflating a latex film up to 100 mbar) once the tissue was clamped and an exposed tissue area was of 20 mm in diameter (Scheme S3, Supporting Information). A piece of 4 $\times$ 4 cm myocardium tissue with 3–5 mm thickness was explanted from fresh porcine heart purchased from a local store. A 2 mm incision was made on the myocardium tissue with a tissue punch and the surface was kept wet (Scheme S3a, Supporting Information). Then, the hydrogel with a diameter of 10 mm and thickness of 2 mm was adhered on the puncture site. The myocardium tissue was fixed to a homemade rig provided a perfect sealing (tested by inflating a latex film up to 100 mbar) when the hydrogel was peeled from the surface of the heart while video recording.

Subcutaneous Implantation: Four female Sprague–Dawley rats (175–200 g) were used in vivo biocompatibility studies. Two subcutaneous pockets per animal were created by blunt preparation (Figure S15a, Supporting Information). The hydrogels were implanted into the dorsal subcutaneous pockets under sterile conditions. Then the skin incisions were closed, and the animals were returned to their cages after recovery from anesthesia. At designated time intervals (1 and 2 weeks), the rats were killed and the samples were collected and processed for histology and eosin staining. The histological sections were imaged with a BA200 Digital microscope. The degree of inflammation was assessed by two experienced pathologists, which can be divided into four evaluation levels (1 = normal, 2 = mild, 3 = moderate, 4 = severe). All animal procedures were performed in accordance with protocols approved by the laboratory animal administration rules of China. Informed consent was obtained from the volunteer for their participation in the human experiments in this study.

Statistical Analysis: The data were analyzed by one-way analysis of variance followed by the Tukey multiple-comparison post hoc test to determine significant differences between test groups. The level of statistical significance was set to $p < 0.05$. The error bars represented the standard deviation.

Supporting Information
Supporting Information is available from the Wiley Online Library or from the author.

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Conflict of Interest
The authors declare no conflict of interest.

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[1] J. Li, D. J. Mooney, Nat. Rev. Mater. 2016, 1, 16071.
[2] D. Seliktar, Science 2012, 336, 1124.
[3] J. L. Drury, D. J. Mooney, Biomaterials 2003, 24, 4337.
[4] Y. S. Zhang, A. Khademhosseini, Science 2017, 356, eaaf3627.
[5] H. Yuk, S. Lin, C. Ma, M. Takkaffoli, N. X. Fang, X. Zhao, Nat. Commun. 2017, 8, 14230.
[6] D.-H. Kim, N. Lu, R. Ma, Y.-S. Kim, R.-H. Kim, S. Wang, J. Wu, S. M. Won, H. Tao, A. Islam, Science 2011, 333, 633.
[7] I. R. Minev, P. Musienko, A. Hirsch, Q. Barraud, N. Wenger, E. M. Moraud, J. Gandar, M. Capogrosso, T. Milekovic, L. Asboth, Science 2015, 357, 159.
[8] R. Feiner, L. Engel, S. Fleischer, M. Malki, I. Gal, A. Shapira, Y. Shacham-Diamand, T. Dvir, Nat. Mater. 2016, 15, 679.
[9] C. Ghobrial, K. Charoen, E. K. Rodriguez, A. Nazarian, M. W. Grinstaff, Angew. Chem., Int. Ed. 2013, 52, 14070.
[10] M. W. Grinstaff, Biomaterials 2007, 28, 5205.
[11] C. Ghobrial, M. Grinstaff, Chem. Soc. Rev. 2015, 44, 1820.
[12] J. Shin, J. S. Lee, C. Lee, H. J. Park, K. Yang, Y. Jin, J. H. Ryu, K. S. Hong, S. H. Moon, H. M. Chung, Adv. Funct. Mater. 2015, 25, 3814.
[13] A. Amjadi, S. Sheykhansari, B. J. Nelson, M. Sitti, Adv. Mater. 2018, 30, 1704530.
[14] H. Yi, M. Seong, K. Sun, I. Hwang, K. Lee, C. Cha, T. I. Kim, H. E. Jeong, Adv. Funct. Mater. 2018, 28, 1706498.
[15] A. Y. Stark, I. Badge, N. A. Wucinich, T. W. Sullivan, P. H. Niewiarowski, A. Dhojiojwala, Proc. Natl. Acad. Sci. U. S. A. 2013, 110, 6340.
[16] D. Gan, W. Xing, L. Jiang, J. Fang, C. Zhao, F. Ren, L. Fang, K. Wang, X. Lu, Nat. Commun. 2019, 10, 1487.
[17] X. Liu, Q. Zhang, L. Duan, G. Gao, Adv. Funct. Mater. 2019, 29, 1900450.
[18] J. Yang, R. Bai, Z. Suo, Adv. Mater. 2018, 30, 1800671.
[19] P. Rao, T. L. Sun, L. Chen, R. Takahashi, G. Shinozuka, H. Guo, D. R. King, T. Kurokawa, J. P. Gong, Adv. Mater. 2018, 30, 1801884.
[20] N. Annabi, Y.-N. Zhang, A. Assmann, E. S. Sani, G. Cheng, A. D. Lasaletta, A. Vegh, B. Dehghani, G. U. Ruiz-Esparza, X. Wang, Sci. Transl. Med. 2017, 9, eaai7466.
[21] M. A. Gonzalez, J. R. Simon, A. Ghoochian, Z. Scholl, S. Lin, M. Rubinstein, P. Marszalek, A. Chilkoti, G. P. López, X. Zhao, Adv. Mater. 2017, 29, 1604743.
[22] Y. Bu, L. Zhang, G. Sun, F. Sun, J. Liu, F. Yang, P. Tang, D. Wu, Adv. Mater. 2019, 31, 1901580.
[23] Q. Zhao, D. W. Lee, B. K. Ahn, S. Seo, Y. Kaufman, J. N. Israelachvili, J. H. Waite, Nat. Mater. 2016, 15, 407.
[24] J. Li, A. Celiz, J. Yang, Q. Yang, I. Warmala, W. Whyte, B. Seo, N. Vasilyev, J. Vlassak, Z. Suo, Science 2017, 357, 378.
[25] Y. Zhao, Y. Wu, L. Wang, M. Zhang, X. Chen, M. Liu, J. Fan, J. Liu, F. Zhou, Z. Wang, Nat. Commun. 2017, 8, 2218.
[26] T. Kakuta, Y. Takashima, T. Sano, T. Nakamura, Y. Kobayashi, H. Yamaguchi, A. Harada, Macromolecules 2015, 48, 732.
[27] A. H. Hofman, I. A. van Hees, J. Yang, M. Kamperman, Adv. Mater. 2018, 30, 1704640.
[28] J. H. Ryu, S. Hong, H. Lee, Acta Biomater. 2015, 27, 101.
[29] B. Soltania, D. Sameoto, ACS Appl. Mater. Interfaces 2014, 6, 21995.
[30] J. Yu, Y. Kan, M. Rapp, E. Danner, W. Wei, S. Das, D. R. Miller, Y. Chen, J. H. Waite, J. N. Israelachvili, Proc. Natl. Acad. Sci. U. S. A. 2013, 110, 15680.
[31] C. Su, H. Wang, Cryst. Res. Technol. 2012, 47, 896.
[32] J. Gao, W. Ge, J. Li, Sci. China, Ser. B: Chem. 2005, 48, 470.
[33] L. Smith, R. Hammond, K. Roberts, D. Machin, G. McLeod, J. Mol. Struct. 2000, 554, 173.
[34] P.-G. De Gennes, Rev Mod. Phys. 1985, 57, 827.
[35] Z. Zhao, C. Li, Z. Dong, Y. Yang, L. Zhang, S. Zhuo, X. Zhou, Y. Xu, L. Jiang, M. Liu, Adv. Funct. Mater. 2019, 29, 1807858.
[36] W. D. Spotnitz, ISRN Surg. 2014, 2014, 203943.
[37] H. C. Park, R. Champakalakshmi, P. P. Panengad, M. Raghunath, J. S. Mehta, Expert Rev. Ophthamol. 2011, 6, 631.
[38] L. Sanders, R. Stone, K. Webb, T. Mefford, J. Nagatomi, J. Biomed. Mater. Res., Part A 2015, 103, 861.
[39] P. K. Campbell, S. L. Bennett, A. Driscoll, A. Sawhney, Evaluation of Absorbable Surgical Sealants: In Vitro Testing, Confluent Surgical, Inc., Waltham, MA 2005.