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Letter

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Strong and Degradable Adhesion of Hydrogels

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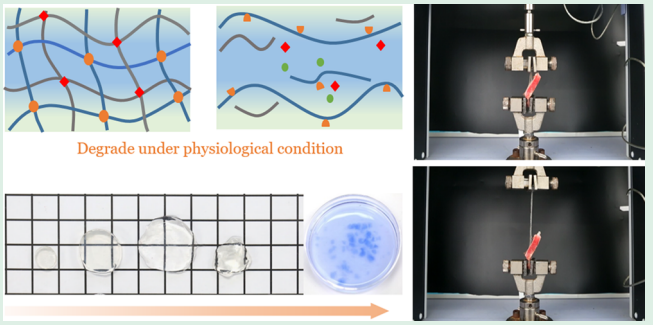
ABSTRACT: Adhesives potentially offer convenient means to close wounds, but existing adhesives do not fulfill many common requirements. Here we demonstrate an approach to develop hydrogel adhesives that are strong initially, remain soft when adhered to soft tissues, and degrade over time. We demonstrate the approach by using a hydrogel that dissipates a large amount of energy during separation, forms strong and interlinks with the soft tissues, and degrades by breaking cross-links. The hydrogel achieves initial adhesion energies of 300−700 J/m^2 when adhered to different tissues, can bear huge pressure, and completely degrades in 5 weeks under simulated physiological conditions.



KEYWORDS: *tough hydrogel, degradable hydrogel, tissue adhesive, topological adhesion*

INTRODUCTION

Compared to sutures and staples, adhesives may offer convenient means to close wounds, blocking any leak of liquid and gas.[1,2] Commercial adhesives, however, do not fulfill many basic requirements for wound closure. Cyanoacrylate adhesives are strong but are cytotoxic and form a glassy phase that constrains the dynamic movements of soft tissues.[3,4] Fibrin, polyethylene glycol, as well as other natural and synthetic hydrogels, have long been developed as adhesives for wound closure because of their biocompatibility, but they have weak adhesion and are unsuitable by themselves for load bearing applications such as sealing lungs and hearts.[5,6] Another essential requirement is that adhesives should degrade as wounds heal.[7−9] Permanent adhesives may cause infection, and their surgical removal may cause secondary injury.[1,6] Despite the clear need, strong and biodegradable adhesives do not exist.[4]

An opportunity has just emerged. The last few years have witnessed disruptive advances in the development of strong hydrogel adhesion. Demonstrated approaches include modification by functional groups,[10,11] modification by initiators,[12,13] diluted cyanoacrylate,[14] bridging polymers,[15] and topological adhesion.[16,17] These approaches strongly adhere hydrogels to various materials (e.g., elastomers, plastics, glasses, and metals), in various manufacturing processes (e.g., attach, coat, and print), for medical and engineering applications.[18] Some of these approaches strongly adhere hydrogels and soft tissues without hardening.[15−17,19] It is urgent to develop strong hydrogel−tissue adhesion further to meet essential requirements for wound closure. In particular, here we focus on developing hydrogel adhesives that both strongly adhere to tissues initially and degrade over time under physiological conditions.

By strong adhesion we mean that the adhesion energy is comparable to the fracture energy of at least one of the adherends. For example, if a tissue is tougher than a hydrogel, their adhesion is said to be strong if the adhesion energy is comparable to the fracture energy of the hydrogel. A covalently cross-linked hydrogel (e.g., polyacrylamide) has a fracture energy on the order of 100 J/m^2, and tough hydrogels have fracture energy above 1000 J/m^2.[20] By contrast, hydrogel adhesives relying on weak physical interactions have adhesion energy about 0.1−10 J/m^2.[6,15] To adhere a hydrogel and a soft tissue strongly but without hardening, the polymer network of the hydrogel and that of the soft tissue must form strong and sparse interlinks, with the strength and density of the interlinks being comparable to those of the cross-links in the hydrogel or the tissue. The adhesion energy is high because the separation dissipates energy by breaking not only the interlinks, but also sacrificial bonds in the bulk of the hydrogel and/or the tissue.

Here we describe an approach to develop strong and degradable hydrogel adhesives to close wounds in soft tissues. The approach fulfills three requirements: (1) the hydrogel dissipates a large amount of energy during separation, (2) the hydrogel degrades under physiological conditions, and (3) the polymer network of the hydrogel and that of a soft tissue form strong and sparse interlinks. We characterize the kinetics of the strong and degradable hydrogel. The hydrogel adhesives achieve adhesion energy above 700 J/m^2 and completely

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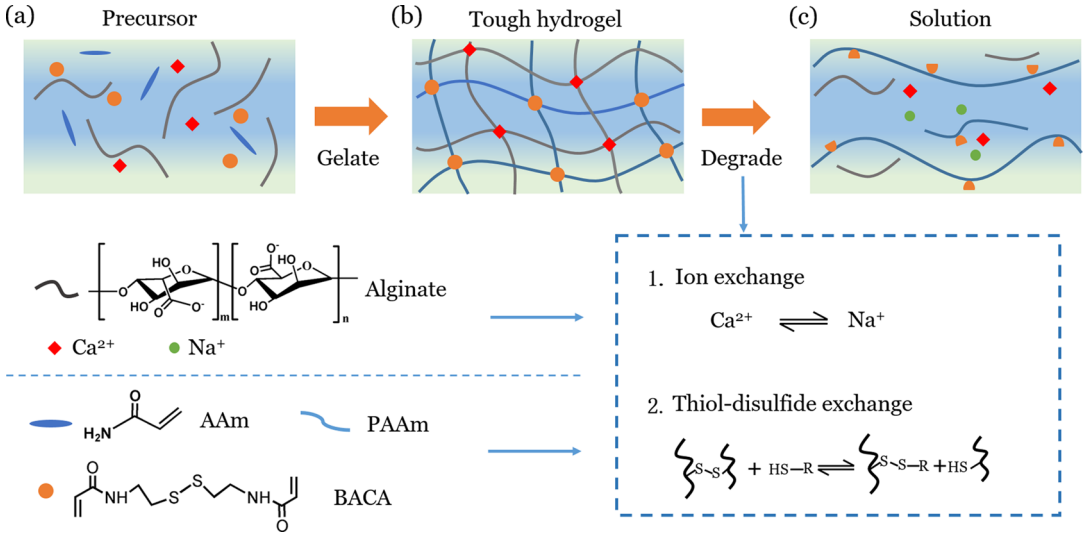

Figure 1. Synthesis and degradation of the hydrogel. (a) The precursor of the hydrogel contains the acrylamide monomers, BACA cross-linkers, alginate chains, and calcium ions. (b) The precursor forms a hydrogel with two interpenetrating polymer networks: the alginate network cross-linked by calcium and the polyacrylamide network cross-linked by disulfide bonds. (c) Under physiological conditions, the hydrogel degrades as the alginate network dissociates by ion exchange and the polyacrylamide network dissociates by thiol−disulfide exchange reaction.

degrade in 5 weeks under physiological conditions. The hydrogel adhesives can bear the pressure of a lung and liver.

EXPERIMENTAL SECTION

Materials: Acrylamide (AAm; Aladdin A108467), sodium alginate (Aladdin S100126), *N*,*N*′-bis(acryloyl)cystamine (BACA, Alfa Aesar 044132), ammonium persulfate (APS, Aladdin A112449), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TEMED, Sigma-Aldrich 411019), calcium sulfate ($CaSO_4$, Aladdin A105242), Methyl blue (MACKLIN M812703), L-cysteine (MACKLIN L804954), phosphate-buffered saline (PBS, Biosharp BL601A, pH ∼ 7.2); *N*,*N*′-methylenebis-(acrylamide) (MBAA, Aladdin M128783); chitosan (Sigma-Aldrich, Medium Viscosity 448877), 1-ethyl-3-(3-(dimethylamino)propyl) carbodiimide hydrochloride (EDC, Aladdin E106172), *N*-hydroxysulfosuccinimide sodium salt (sulfo-NHS, Aladdin H109337), 4-morpholineethanesulfonic acid (MES hydrate; Aladdin M163014). All reagents were used as purchased without further purification.

Preparation of Hydrogel. The hydrogel was prepared by free radical polymerization. The mixture of 30 g of deionized water, 3.6 g of AAm monomers, and 0.6 g of sodium alginate chains was stirred overnight on a magnetic stirrer until the sodium alginate was completely dissolved. Then 0.0132 g of the BACA cross-linker was added to the solution, which was stirred again overnight on the magnetic stirrer. This solution was drawn into a syringe. Meanwhile, a mixture of 0.0578 g of APS, 1057 μL of calcium sulfate turbid liquid ($CaSO_4$, 0.1135 g/mL), and 38 μL of TEMED was drawn into another syringe. We connected the two syringes with a Luer lock and mixed all solutions by pushing the two syringes back and forth quickly to form a homogeneous precursor. The hydrogel precursor was injected into an acrylic mold, thickness 2 mm, sandwiched by two glass plates and stored in an oven at 50 °C for 1 h. Then we took the mold out and stored it at room temperature overnight to complete polymerization. As comparison, the nondegradable hydrogel was fabricated in the same way by adding 0.0078 g of MBAA instead of BACA.

Preparation of Chitosan Solution. We dissolved 0.976 g of MES hydrate into 50 g of deionized water and tuned the pH to ∼4.5 by dropping 0.1 w/w NaOH solution. Then we added 1 g of chitosan powder and stirred the mixture overnight on a magnetic stirrer. A uniform thick liquid with a little sediment was formed. The chitosan solution was kept stirring and used in 2 days.

Compression Test. The precursors of the hydrogels were drawn into a 10 mL syringe to form hydrogels, which were then cut into 20 mm lengths. All these specimens are pillars, height 20 mm and diameter 19.20 mm, in the as-prepared state. We submerged the pillars in four fluids: deionized water, 1 mM L-cysteine aqueous, PBS), and a mixture of PBS and 1 mM cysteine. Then we compressed the pillars to a quarter of their initial heights. The weight ratio of the hydrogels to the fluids was kept at 1:20. They were stored at 37 °C in an incubator. The test was performed on a test machine (SMADAZU AGS-X) with a 500 N loading cell. The loading speed was 30 mm/min.

Hydrogel−Hydrogel Adhesion. We put a piece of the hydrogel in an acrylic mold, spread chitosan solution uniformly on its surface, and placed another piece of the hydrogel on the top. Then we covered the mold with an acrylic sheet and clamped the setup with foldback clips to apply a 5% compression strain to the hydrogels. The compression mold can apply a constant compression strain by tuning its height. For instance, we designed the height of the mold to be 3.8 mm and the two gels had a total thickness of 4 mm; thus we got a 5% compression strain to the hydrogels. The dosage of chitosan solution on the hydrogel is ∼1.8 $\mu L/mm^2$, and the redundant solution was extruded out. The compression was kept for 1 h. The hydrogel specimens for adhesion tests had a size of 70 × 15 × 2 mm^3.

Hydrogel−Tissue Adhesion. We purchased the porcine tissues from a local grocery and washed them with the PBS. The bonding procedure for the hydrogel-tissue adhesion is similar to that of hydrogel−hydrogel adhesion, except we added 12 g/L of EDC and 12 g/L of sulfo-NHS to the chitosan solution. We compressed the tough hydrogel on the tissue with a pressure of 1.63 kPa by weights for 30 min in a humidity chamber.

Peel Test. For the hydrogel−hydrogel peel test, we glued PET films on the top and bottom faces of the hydrogels using 406 Superglue (Loctite) to constrain the stretch of the peel arm. For the hydrogel−skin and hydrogel−cartilage peel tests, we glued PET films on the hydrogel side, but left the skin surface bare, since the skin and cartilage are stiff enough to resist the stretch during peel. For the hydrogel−stomach, hydrogel−liver, and hydrogel−lung peel tests, both the hydrogel and tissues are constrained by the PET films. The peel test was performed on a tensile test machine (SMADAZU AGS-X) with a 50 N loading cell and 30 mm/min in speed.

Bulge Test. The bulge test was conducted for the hydrogel (thickness, 2 mm) adhered on a lung (Figure 4d). We drilled a hole, diameter 5 mm, on the lung and used chitosan and EDC/NHS to adhere the hydrogel, diameter 20 mm, on the top. The pressure was applied by pumping the PBS from the bottom using a syringe pump

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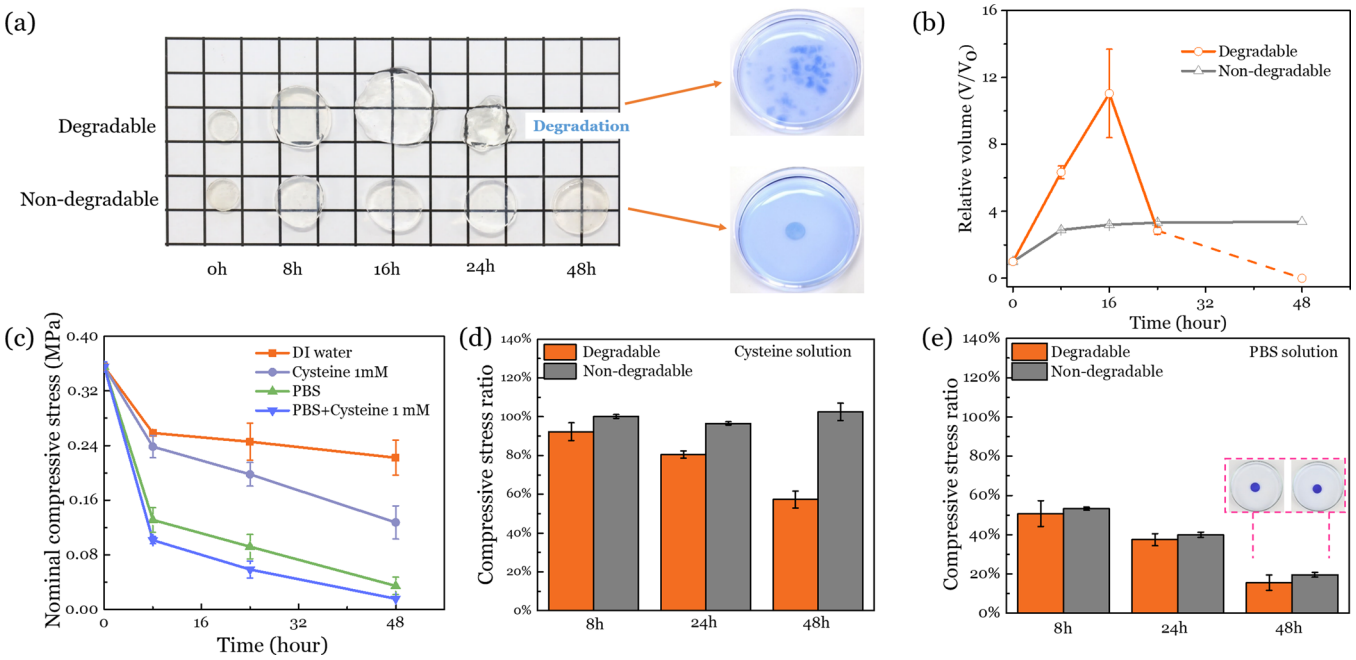

Figure 2. Behavior of two hydrogels in four fluids. (a) In a solution of PBS and 1 mM cysteine, a disk of the degradable hydrogel fully dissolves within 48 h, but a disk of the nondegradable hydrogel remains a solid. (b) The kernel volume changes with time of the degradable and nondegradable hydrogels. (c) Pillars of the degradable hydrogels are compressed to a quarter of their initial heights while submerged in four fluids: deionized water, an aqueous solution of 1 mM cysteine, PBS, and a mixture of PBS and 1 mM cysteine. The nominal stress (i.e., the compressive force divided by the area of as-prepared hydrogel prior to the immersion in a fluid) deceases over time. The effect of the cysteine solution (d) and the PBS solution (e) on the stress of the degradable and nondegradable hydrogel is graphed. The stresses of the hydrogels in the deionized water are used as the baselines to calculate the ratios.

(Longer Pump) at a rate of 20 mm/min. The pressure was recorded with time by a pressure gauge (Asmik)

RESULTS AND DISCUSSION

We demonstrate our general approach using a hydrogel developed by us and others in recent years (Figure 1). The hydrogel consists of two polymer networks: an alginate network cross-linked by ionic bonds (calcium), and a polyacrylamide network cross-linked by covalent bonds.[20] The two networks interpenetrate in topological entanglement. The ionic cross-links are weaker than the covalent cross-links. The topology of the networks, as well as the different strengths in the cross-links, makes the hydrogel exceptionally tough. Before a crack breaks the polyacrylamide chains on the crack plane, the topologically entangled networks transmit high stress from the crack front into the hydrogel, unzip the ionic cross-links in a large volume off the crack plane, and dissipate a large amount of energy.[20] From *in vitro* cytotoxicity assay and *in vivo* implantation, it is found that the alginate−PAAm hydrogel is generally noncytotoxic and causes minimal inflammation *in vivo*.[21] Its degradation under physiological conditions has also been studied. When better biocompatibility is required, the covalent PAAm network in this work can be replaced by other more biocompatible polymers, such as polyethylene glycol (PEG).[22] The human body has widely distributed Na^+ and cysteine.[23] Under physiological conditions, the alginate network dissociates as the ionic cross-linker Ca^{2+} exchanges with Na^+.[24] The polyacrylamide network remains intact when the cross-linker is *N,N′*-methylenebis(acrylamide) (MBAA)[21] but dissociates when the cross-linker is *N,N′*-bis(acryloyl)cystamine (BACA) as the disulfide cross-links undergo the thiol−disulfide exchange reaction.[25] Thus, under physiological conditions, the alginate−polyacrylamide hydrogel with the bis-acrylamide cross-links is a nondegradable hydrogel, whereas the alginate−polyacrylamide hydrogel with the disulfide cross-links is a degradable hydrogel.[25] We use the latter to demonstrate a strong and degradable adhesive.

We prepare a mixture of the phosphate-buffered saline (PBS) and cysteine as a simulated body fluid. The PBS contains 163 mM Na^+. We cut a disk of the degradable hydrogel, height 2 mm and diameter 10 mm, and submerge it in a mixture of the PBS and 1 mM cysteine. The disk dissolves in 48 h at 37 °C (Figure 2a). As a comparison, the nondegradable hydrogel swells in the simulated body fluid but remains a solid. Figure 2b shows the volume change with time for both degradable and nondegradable hydrogels. To mimic the normal concentration of cysteine in the human blood, we prepare a simulated body fluid with PBS and 20 μM cysteine.[26] With regular renewal of the simulated body fluid, the degradable hydrogel completely dissolves at 37 °C in 5 weeks.

We further characterize the kinetics of degradation by a mechanical test (Figure 2c). We prepare pillars of both types of hydrogels, diameter 19.2 mm and height 20 mm. These pillars are larger than the disks to slow down degradation to allow enough time for measurements with narrow statistical scatter. We immerse the pillars in four fluids: deionized water, an aqueous solution of 1 mM cysteine, PBS, and a mixture of the PBS and 1 mM cysteine. Right after the immersion, we compress each pillar to a quarter of its initial height and record the force as a function of time. We define the nominal stress as the force at a given time divided by the cross-sectional area of the as-prepared pillar before the immersion. In the deionized water, degradation is negligible, and the stress decreases due to

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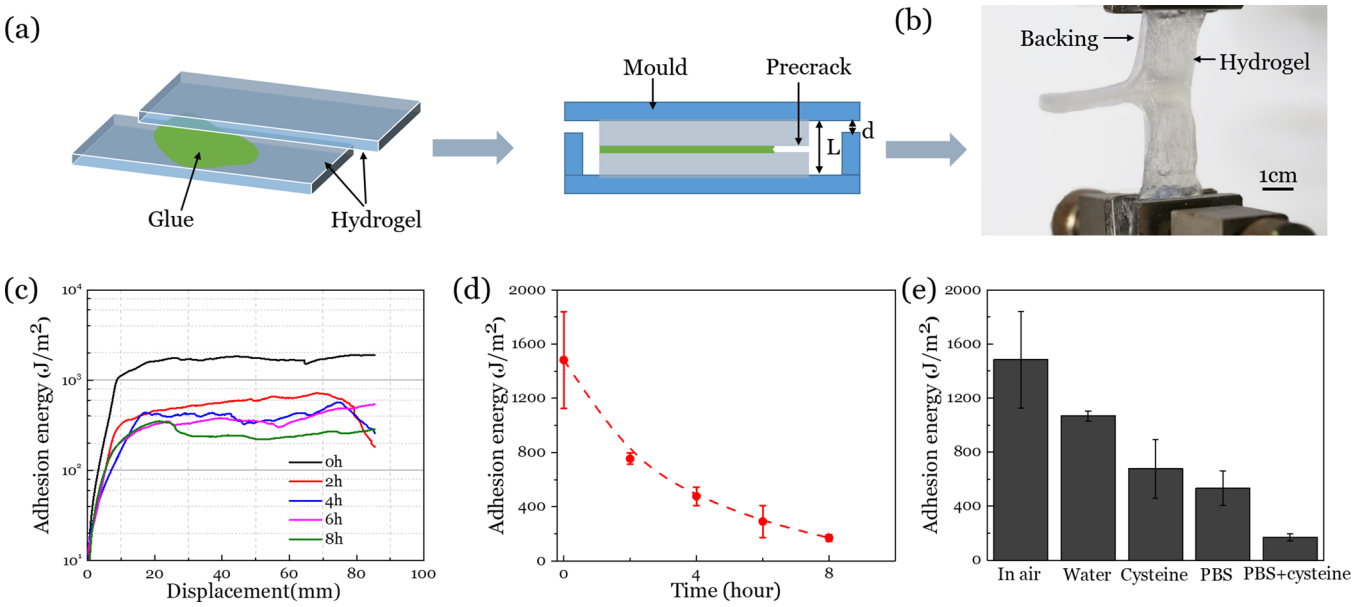

Figure 3. Topological adhesion of two pieces of the degradable hydrogel. (a) Aqueous solution of chitosan spread on the surface of one piece of the hydrogel, the other piece of the hydrogel placed on top, and the bilayer compressed with a strain of d/L = 5%. (b) Peel test. (c) Force–displacement curves for the adhered hydrogels immersed in the mixture of the PBS and 1 mM cysteine. (d) Adhesion energy declining over time. (e) Adhesion energy for the hydrogels kept in air and immersed in different solutions for 8 h.

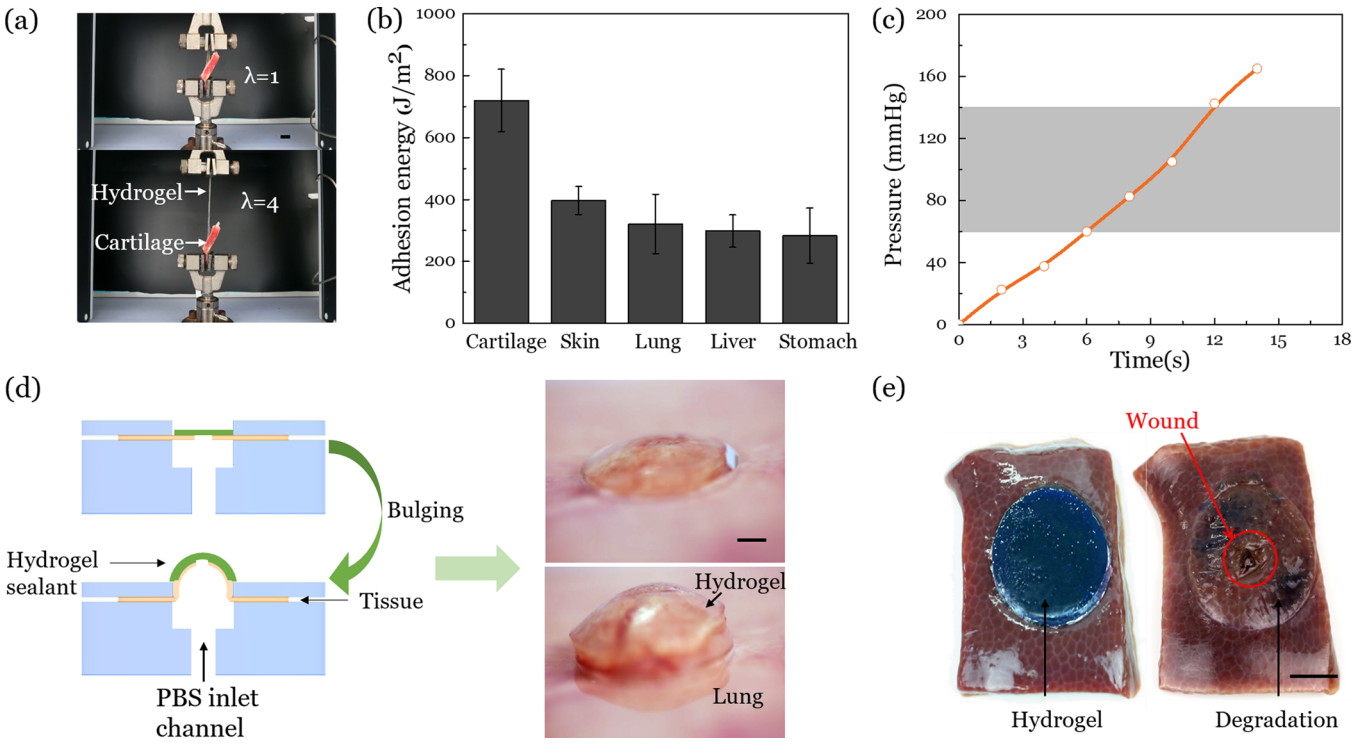

Figure 4. Strong and degradable hydrogels adhered to soft porcine tissues. (a) The hydrogel sustains a large stretch when adhered to cartilage (λ = 4). (b) Adhesion energy between the hydrogel and several tissues. (c) The hydrogel sustains a high pressure when sealing a lung. The pressure–time curve for the bulge experiment shows the hydrogel can endure the normal range of pressure (shaded). (d) Schematic of the set up for the bulge test. The hydrogel adheres to a drilled lung and bulges under the pressure of the PBS. (e) A dyed hydrogel seals a hole on a liver and degrades completely overnight in the mixture of the PBS and 1 mM cysteine.

swelling. In the cysteine solution, the stress decreases with an additional cause: the thiol–disulfide exchange reaction. In the PBS, the stress rapidly declines due to ion exchange. In the mixture of the PBS and 1 mM cysteine, the stress decreases even more due to the concomitant ion exchange and thiol–disulfide exchange.

We compare the degradable and nondegradable hydrogels, both immersed in the cysteine solution (Figure 2d). To exclude the swelling effect, we take the ratio of the stress in the cysteine solution to the stress in the deionized water. The ratio declines with time for the degradable hydrogel but remains the same for the nondegradable hydrogel. We also compress the

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two hydrogels immersed in the PBS and find that the stress ratios decline for both hydrogels (Figure 2e). These data illustrate the kinetics of the dissociation of the calcium-cross-linked alginate network and disulfide-cross-linked polyacrylamide network. The bis-acrylamide-cross-linked polyacrylamide network is stable in the simulated body fluid.

Hydrogels mimic soft tissues in many ways and are more readily characterized than most tissues. It has become common to use hydrogels as tissue mimics in the development of adhesives for soft tissues. To confirm that the degradable hydrogel does form strong adhesion, we first adhere two pieces of the hydrogel using topological adhesion. This method of adhesion enables strong and stretchable adhesion without requiring the adherends themselves to have any functional groups for strong interlinks.[17] The hydrogel is cured in a solution of pH ∼ 7. We spread an aqueous solution of chitosan of pH ∼ 4.5 on the surface of one piece of the hydrogel, place the other piece of the hydrogel on top, and compress the bilayer with a strain of d/L = 5% (Figure 3a). As chitosan chains diffuse into the two hydrogels in contact, the higher pH in the hydrogels causes the chitosan chains to form a network *in situ*, in topological entanglement with the existing polymer networks in the two hydrogels. We submerge the adhered hydrogels into various solutions for various times and then take them out to measure the adhesion energy by the peel test (Figure 3b). Let F be the peel force and b be the width of the hydrogel; the ratio $2F/b$ is recorded as a function of the peel displacement (Figure 3c). The plateau gives the adhesion energy. The adhesion energy is 1483 ± 365 J/m^2 when the hydrogels are just adhered but decreases to 165 ± 25 J/m^2 after they are submerged in the mixture of PBS and 1 mM cysteine for 8 h (Figure 3d). We then immerse the adhered hydrogels in deionized water, an aqueous solution of 1 mM cysteine, PBS, and a mixture of PBS and 1 mM cysteine for 8 h. To guarantee the integrity of the hydrogel sample for the peeling test, here we choose 8 h as the appropriate soaking time. The deionized water reduces the adhesion energy to ∼1067 ± 37 J/m^2, whereas various solutions reduce the adhesion much more substantially (Figure 3e). The various amounts of reduction illustrate the kinetics of degradation and the relative importance of the alginate and polyacrylamide networks. In every case, the bilayer peels inside a hydrogel, not on the interface between the two pieces of the hydrogel. The adhesion energy declines due to the degradation of the hydrogel degradation rather than the degradation of the chitosan network. When we use chitosan to adhere two pieces of the nondegradable hydrogel, the bilayer remains solid even after 5 months in various fluids used here.

We next adhere the hydrogel to several soft porcine tissues (cartilage, skin, lung, liver, and stomach). Here we illustrate the use of another recent method of strong hydrogel adhesion, which is based on the topological adhesion, using chitosan solutions and two coupling agents: 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) and *N*-hydroxysulfosuccinimide (NHS).[25] The positively charged amines on the chitosan chains can react with the carboxylic groups in the hydrogel and the tissues to form amide interlinks. The adhesive endures a stretch more than 4 when adhered to cartilage (Figure 4a). We measure an adhesion energy of 720 ± 101 J/m^2 for cartilage and about 300 J/m^2 for other tissues (Figure 4b). The measured adhesion energies are much higher than energies of all commercially used adhesives for soft tissues, such as the fibrin glue TISSEEL (Baxter), polyethylene glycol–based adhesives COSEAL (Baxter), and DURASEAL (Confluent Surgical), which show an adhesion energy on the order of 10 J/m^2.[27,28] The hydrogel endures a high pressure >160 mmHg when adhered to a lung (Figure 4c,d), which is much higher than the breathing pressure (∼1−2 mmHg) and blood pressure (∼1−24 mmHg) in lung,[5] and is even higher than normal blood pressure (<140 mmHg).[29] Prolonged air and blood leak is the most common complication in lung surgery.[30] The strong and degradable hydrogel adhesive has the potential to serve as a sealant to block the leak of air and blood during and after surgery. We also confirm the degradability of the hydrogel adhered on a soft tissue. We drill a hole on a liver and then seal the hole with a hydrogel disk. Then we submerge the patched part in a mixture of PBS and 5 mM cysteine solution at 37 °C. The hydrogel degrades overnight, with a little hydrogel residual around the hole (Figure 4e). The gel is dyed by methyl blue for visual clarity.

CONCLUSIONS

In summary, we have described an approach to develop strong and biodegradable adhesion. We demonstrate this approach using a specific hydrogel and two specific methods of strong adhesion. But the principle of the approach is general, applicable to many tough hydrogels and methods of strong adhesion. The large design space will enable the development of adhesives to fulfill medical requirements, well articulated in the literature, but long unmet in practice. For example, one can choose the number and the type of networks, as well as the density and the type of cross-linkers, to design the loss of strong adhesion at a desired time. Strong and degradable adhesion may also enable medical applications besides wound closure. Examples include drug delivery and neural interfaces. The abundant tough hydrogels developed in the recent decade, as well as the methods of strong adhesion developed in the past few years, will be an excellent point to start.

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Notes

The authors declare no competing financial interest.

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