Ultrafast self-gelling powder mediates robust wet adhesion to promote healing of gastrointestinal perforations

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Achieving strong adhesion of bioadhesives on wet tissues remains a challenge and an acute clinical demand because of the interfering interfacial water and limited adhesive-tissue interactions. Here we report a self-gelling and adhesive polyethyleneimine and polyacrylic acid (PEI/PAA) powder, which can absorb interfacial water to form a physically cross-linked hydrogel in situ within 2 seconds due to strong physical interactions between the polymers. Furthermore, the physically cross-linked polymers can diffuse into the substrate polymeric network to enhance wet adhesion. Superficial deposition of PEI/PAA powder can effectively seal damaged porcine stomach and intestine despite excessive mechanical challenges and tissue surface irregularities. We further demonstrate PEI/PAA powder as an effective sealant to enhance the treatment outcomes of gastric perforation in a rat model. The strong wet adhesion, excellent cytocompatibility, adaptability to fit complex sites, and easy synthesis of PEI/PAA powder make it a promising bioadhesive for numerous biomedical applications.

INTRODUCTION

Adhesive hydrogels that can strongly adhere to wet tissues have been widely used in wound dressings (1–5), hemostatic agents (6–10), wearable devices (11, 12), drug delivery systems (13, 14), and tissue engineering (15–20), owing to their strong adhesion, excellent biocompatibility, good permeability, high deformability, and tunable mechanical properties. Two main hydrogel design strategies have been adopted to achieve adhesion on wet tissues: adhering prefabricated adhesive hydrogels (21–28) on wet tissues and forming adhesive hydrogels on wet tissues in situ from precursor solutions (9, 10, 29–31). For the first strategy, polymers containing adhesive functional groups in the hydrogel network need to diffuse through the tissue interfacial water to bond with the tissues. However, most adhesive hydrogels are stabilized by chemical cross-linking, which restricts polymer diffusion, thereby leading to weak tissue-hydrogel contact and bonding. For the second strategy, monomers or macromers containing the adhesive functional groups in the precursor solutions also need to diffuse through interfacial water to bond with tissues while undergoing rapid polymerization. However, the short gelation time and the chemically cross-linked hydrogel networks hamper the effective contact and bonding between the hydrogels and tissues. Therefore, the tissue interfacial water and the lack of polymer dynamics in hydrogel network are key hurdles to achieving robust adhesion between hydrogels and wet tissues.

Recent studies have developed adhesive materials that can absorb or remove interfacial water to form tight contact with tissues (8, 32–36). Yuk et al. (35) prepared a dried double-sided tape by dehydrating hydrogels containing carboxylic acid and N-hydroxysuccinimide ester groups. The dried tape absorbs interfacial water and forms effective covalent bonds and strong adhesion on the tissues. Han et al. (36) prepared dynamic hydrophobic hydrogels, which repel interfacial water to form tight contact, effective hydrophobic interactions, and strong adhesion on wet substrates. The bioadhesives secreted by marine organisms such as mussels and sandcastle worms demonstrate that complex coacervates can form strong adhesion on wet substrates because of their fluid-like and water-immiscible properties (32, 34, 37–39). For example, Waite and co-workers (34) reported a polyelectrolyte coacervate that can form strong underwater adhesion on various substrates. Upon depositing the mixture solution containing a catechol-bearing polyanion and a polycation in dimethyl sulfoxide (DMSO) to underwater substrates, the solvent exchange between water and DMSO triggers the electrostatic complexation of dissolved polyelectrolytes, leading to coacervation, catechol-mediated interactions, and wet adhesion. Recently, Cui et al. (8) reported a hyperbranched polymer adhesive containing a hydrophobic backbone and hydrophilic side branches with catechol groups. Upon contacting water, the hydrophobic chains self-aggregate to form coacervates, which displace the interfacial water and promote catechol group exposure, leading to tight contact and strong adhesion between the adhesives and tissues. Therefore, removing interfacial water on wet tissues is an effective approach to achieving wet adhesion. Polyelectrolyte multilayers have been reported to become sticky upon hydration, but the bulky and stable structure may limit their close contact with nonflat substrate surfaces with irregularities and the diffusion of polymers into the substrates, resulting in reduced adhesive-substrate interactions (40). On the other hand, Yang et al. (41) developed a topological adhesion strategy to promote interfacial adhesion by using stitching polymer solutions. Upon spreading the stitching polymer solution between two soft materials, the polymer molecules can diffuse into the polymer...
network of both the materials to form a new network, leading to strong adhesion between the two soft materials.

Here, we report a polyethyleneimine/polyacrylic acid (PEI/PAA) powder that can in situ form physically cross-linked hydrogels on wet tissues within 2 s by absorbing interfacial water. Furthermore, the physically cross-linked polymers can diffuse into the substrate polymeric network to enhance wet adhesion on various tissues, such as chicken skin, porcine heart, and mucosa of porcine stomach and intestine. We demonstrated that the PEI/PAA powder can effectively seal damaged porcine stomach and intestine despite mechanical challenges and tissue surface irregularities in vitro and promote healing of gastric perforation in a rat model. The advantages of the adhesive PEI/PAA powder including low cost, adaptability to fit irregular-shaped target sites, easy delivery by assistive devices, strong adhesion, and excellent cytocompatibility make it a promising adhesive biomaterial for use in a wide array of medical applications.

**RESULTS**

**Preparation and properties of PEI/PAA powder–derived hydrogel**

Self-gelling and adhesive PEI/PAA powder was prepared by freeze-drying and grinding PEI/PAA complexes, which were prepared by mixing equal volume of aqueous PEI ([M_w, ca. 70,000; 10 weight % (wt %)] and PAA ([M_w, ca. 240,000; 10 wt %]) solutions (Fig. 1A and fig. S1). Addition of water or phosphate-buffered saline (PBS) to the obtained PEI/PAA powder that was deposited into different shapes resulted in the rapid formation of hydrogels of the same shape without any additional preparation steps (Fig. 1C and movie S1). As a comparison, we prepared chemically cross-linked PEI-cPAA hydrogels by free radical polymerization of acrylic acid (AA) in the presence of PEI and a chemical cross-linker. However, the dried powder of chemically cross-linked hydrogels cannot form a bulk hydrogel after hydration (Fig. 1B, fig. S2, and movie S2). To further study the self-gelation of PEI/PAA powder, we first observed the changes that occurred while the powder turned into a hydrogel upon hydration by using a microscope. The PEI/PAA powder rapidly absorbed water and swelled to connect with each other to form a bulk hydrogel (Fig. 1D and fig. S3). Moreover, we added Dulbecco’s modified Eagle’s medium (DMEM) to PEI/PAA powder to test the gelation time of PEI/PAA powder. The storage modulus (G’) curve intersected with the loss modulus (G”) curve at 2 s, indicating that the change from powder to hydrogel could be achieved within 2 s, which is much faster than the time required for gelation of fibrin gel (approximately 10 s) (Fig. 1E and fig. S4).

We next examined the cross-linking mechanisms of PEI/PAA hydrogel. Fourier transform infrared (FTIR) spectra of PEI, PAA, and PEI/PAA gels are shown in Fig. 1F. The carboxylic acid (―COOH) peaks at 1697 cm⁻¹ in PAA and the amine group (―NH₂ or ―NH) peaks in PEI at 1585 cm⁻¹ shifted to 1635 and 1546 cm⁻¹ in PEI/PAA gels, respectively. The shifting of the characteristic carboxylic acid and amine group peaks in PEI/PAA gel without generating new characteristic peaks indicated that PEI and PAA are cross-linked through physical interactions, such as hydrogen bonding and electrostatic interaction, instead of covalent bonds. Dynamic oscillatory rheological studies were performed to compare the rheological properties of the PEI/PAA hydrogels with those of the chemically cross-linked PEI-cPAA hydrogels. The storage modulus (G’), loss modulus (G”), and loss factor (tan δ = G”/G’) of the PEI/PAA hydrogels were dependent on frequency and temperature, whereas those of the chemically cross-linked hydrogels were independent of both the parameters (Fig. 1G and fig. S5). These results further indicated that the PEI/PAA hydrogels are only cross-linked through physical interactions.

We investigated the polymer diffusion during the PEI/PAA hydrogel formation. We prepared fluorescent PEI_FITC/PAA powder by labeling 20% of the added PEI with fluorescein isothiocyanate (FITC) and monitored its self-gelation process upon hydration by using confocal microscopy. Initially, fluorescent regions in the PEI_FITC/PAA powder were dispersed. After absorbing water, the fluorescent regions expanded due to swelling of the powder. The area of fluorescent regions in the x-y plane subsequently increased over time, and this indicated the substantial diffusion of polymers over time in the physically cross-linked hydrogel (Fig. 1H). Note that only 20% of the PEI was labeled with FITC, and therefore, we expect that the diffusion of polymers should be more rapid and notable than that observed in the confocal imaging. As a comparison, we then observed the changes occurring in the chemically cross-linked PEI_FITC-cPAA gel powder upon hydration. Due to the high chemical cross-link density of the dried PEI_FITC-cPAA gel, the swelling and the diffusion of polymers were significantly limited. Therefore, the PEI_FITC-cPAA gel powder remained as dispersed fragments without reforming the cohesive bulk hydrogel after swelling for 12 hours (fig. S6). These results showed that polymer diffusion also plays an important role in the self-gelation of PEI/PAA powder. Owing to the strong physical interaction between PEI and PAA and the diffusion of physically cross-linked polymers, the dispersed PEI/PAA powder can absorb water and swell to connect with each other to form physically cross-linked hydrogels within 2 s upon hydration.

We next studied the factors affecting the mechanical properties of PEI/PAA hydrogel. PEI/PAA powders were prepared using varying mass ratios (x:y) of PEI ([M_w, ca. 70,000] and PAA ([M_w, ca. 240,000]). Adding excessive DMEM or deionized water to PEI/PAA powder induced the separation into two phases, a dense phase and a dilute phase. The dense phase of PEI5/PAA5 powders showed higher storage modulus (G’) than loss modulus (G”), and this indicated that these powders formed the hydrogels upon hydration. The dense phase of the other formulations of powders showed higher loss modulus (G”) than storage modulus (G’), indicating that these powders formed the coacervate upon hydration (Fig. 1I). Among these samples, at the weight ratio of 5:5, the charge balance between the PEI and PAA could be achieved, resulting in the optimal zeta potential (−0.1 ± 1.1 mV) and pH (7.0 ± 0.04) (fig. S7). Therefore, PEI and PAA could complex with each other at high cross-linking densities, thereby resulting in the optimal mechanical properties. The powders prepared with low–molecular weight PEI ([M_w, ca. 1800]) and PAA ([M_w, ca. 3000]) formed coacervates instead of hydrogels after absorbing water (fig. S8). Moreover, we first prepared PEI5/PAA3 hydrogels by adding DMEM to PEI5/PAA3 powder and subsequently immersed the obtained hydrogels in DMEM at 37°C for different durations (from 5 min to 30 days) and measured their tensile properties (Fig. 1J). During the first 24 hours, the failure tensile strength of the PEI5/PAA3 hydrogel improved over time due to the formation of more physical cross-linking. The failure tensile strength of PEI5/PAA3 powder remained stable even after being immersed in DMEM at 37°C for 30 days due to limited swelling (fig. S9). Mostly, the PEI5/PAA5 powder prepared using 50% PEI 

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Fig. 1. Preparation and properties of PEI/PAA hydrogel. (A) Schematic illustration of PEI/PAA powder and PEI/PAA hydrogel preparation. (B) Schematic illustration of chemically cross-linked hydrogel preparation and the swelling of the dried gel powder. (C) Heart-, C-, U-, H-, and K-shaped PEI/PAA hydrogels formed upon adding water to the PEI/PAA powder deposited on the glass plates. (D) The process of changing from dispersed PEI/PAA powder to bulk hydrogel. (E) Gelation time of the PEI/PAA powder upon absorbing DMEM at 37°C as determined by rheological analysis. (F) FTIR spectra of PEI, PAA, and dried PEI/PAA gel. (G) The storage modulus ($G'$) and loss modulus ($G''$) as a function of frequency of the physically cross-linked PEI/PAA hydrogels and chemically cross-linked hydrogels. Strain = 1% and $T = 37°C$. (H) Confocal microscopy images of polymer diffusion in PEI/PAA hydrogel and the change in percentage of fluorescence area in the x-y plane over time. (I) Storage modulus ($G'$) and loss modulus ($G''$) of PEI/PAA hydrogels/coacervates prepared with varying mass ratios of large–molecular weight PEI and PAA ($n = 3$). (J) Change of failure tensile strength of the PEI$_8$/PAA$_8$ hydrogels incubated in DMEM at 37°C over time ($n = 3$). (K) Live/Dead staining (left) and cell viability (right) of gastric epithelial cells after being coincubated with hydrogel or positive control media for 24 hours ($n = 5$). All PEI/PAA hydrogels used for mechanical tests were prepared by adding DMEM into PEI/PAA powder at 37°C. Data are shown as the means ± SD. Photo credit: Xin Peng, The Chinese University of Hong Kong.
(M_w, ca. 70,000) and 50% PAA (M_w, ca. 240,000) was used in subsequent experiments.

We next evaluated the in vitro and in vivo biocompatibility and stability of the PEI/PAA hydrogels. After being coincubated with either PEI/PAA hydrogels or control medium for 24 hours, the viability of gastric epithelial cells was greater than 95% with no statistically significant differences between the samples. The live gastric epithelial cells were stained green and exhibited a spindle-like morphology in all samples (Fig. 1K). These results showed good cell viability after 24 hours. We further evaluated in vivo biocompatibility of the PEI/PAA gels by applying the gels on the gastric serosa of rats for 7 and 30 days. On day 7, we first collected blood from the rats, and the results showed that there is no significant difference in white blood cell concentration between the rats treated with PEI/PAA gel and sham control rats with open abdominal surgery, indicating that the PEI/PAA gel did not cause the systemic inflammatory response syndrome (Fig. S10A) (42). Moreover, no abnormal behaviors such as agitation, depression, or anorexia were observed in the rats treated with PEI/PAA gel. Furthermore, histological assessment demonstrated that, on day 7, the PEI/PAA hydrogels induced a mild chronic inflammatory infiltration involving macrophages, multinuclear giant cells, and occasional lymphocytes (yellow frame). Some spindle-shaped fibroblasts were seen to migrate to the surrounding space of the gels (yellow arrows). Meanwhile, the rats treated with fibrin gel have been used as the control for comparison. On day 7, the fibrin hydrogel also induced a mild chronic inflammatory infiltration containing plasma cells, lymphocytes, and macrophages (Fig. S10C). Then, in vivo biocompatibility of the two hydrogels has been quantitatively compared through irritation score by evaluating inflammation (such as polymorphonuclear, lymphocytes, plasma cells, macrophages, and giant cells), neovascularization, and fibrosis according to the evaluation criteria of the U.S. Food and Drug Administration (Fig. S10D) (43). The PEI/PAA gel group and fibrin gel group showed similar absolute irritation score (Fig. S10B). On day 30, fibroblasts (green arrow) and endothelial cells (blue arrow) were active in the context of chronic inflammation, which implies the formation of granulation for the tissue repair and remodeling. Although cell debris was occasionally visible around the PEI/PAA hydrogels (yellow triangle), no evidence of significant necrosis in serosal tissues or invading muscular layers was observed on day 30 (Fig. S11). The inflammatory responses to the PEI/PAA hydrogel had been restricted within the fibrous capsule formed around the hydrogels on day 30, suggesting adaptive tissue-hydrogel reactions (44). These data suggest that the overall biocompatibility of the PEI/PAA gel is acceptable and similar to that of the clinically used fibrin hydrogel. On the other hand, we have observed in vitro and in vivo stability of the PEI/PAA hydrogel. After being immersed in DMEM at 37°C, the wet weight of the PEI/PAA hydrogel remained constant and displayed a good stability for at least 30 days, indicating that the presence of DMEM cannot effectively break the charge balance of PEI/PAA hydrogel (Fig. S12). We next applied the PEI/PAA hydrogels on the serosa of the stomach in rats for 30 days; we did not find any significant degradation of the hydrogels during this period, suggesting that the hydrogels could remain stable in vivo during the tested period (Fig. S13).

**Wet adhesion mechanism of PEI/PAA powder–derived hydrogel**

We next evaluated the wet adhesive properties of PEI/PAA powder. PEI/PAA powder deposited on wet substrates can absorb interfacial water quickly to form physically cross-linked hydrogel in situ. We first assessed the water absorption of prefabricated hydrated PEI/PAA hydrogels prepared from PEI/PAA powder, dried chemically cross-linked PEI-cPAA gel, and PEI/PAA powder by recording the weight change of aqueous rhodamine B solution on a glass plate before and after applying the different test materials. The dried PEI-cPAA gel and the PEI/PAA powder absorbed most of the solution, but the prefabricated PEI/PAA hydrogel only absorbed approximately 50% of the solution (Fig. 2D). This result showed that the PEI/PAA powder and the dried PEI-cPAA gel can quickly absorb substantial amount of interfacial water to form tight contact with substrates, while the contact of the prefabricated hydrated hydrogel with the substrate was limited by the interfacial water (Fig. 2, A to C).

To study the interactions between the adhesives and substrates, we spread PEI/PAA powder on a poly(acrylamide) (PAAm) hydrogel before incubating in water for 30 days and examined the cross sections of the obtained hydrogels by scanning electron microscopy (SEM). There was a dense interface layer (approximately 20 μm) with no notable gap between the PAAm and in situ formed PEI/PAA hydrogels. The element composition of C, N, O, and H of the interface gel was between that of the PAAm and PEI/PAA gels (fig. S14). In contrast, both the dried PEI-cPAA gel and prefabricated PEI/PAA hydrogel adhered to the PAAm hydrogels showed obvious gaps between the adhesives and the substrates because their adhesion was hampered by the limited mobility of the PEI within the chemically cross-linked PAA network and interfacial water, respectively (Fig. 2E). Moreover, the adhered PEIHTC/PAA powder can diffuse into the PAAm hydrogel network as evidenced by the increasing fluorescent area in the y-z plane of the PAAm hydrogel substrate over time (Fig. 2F). These findings together demonstrated that the PEI/PAA powder can effectively absorb interfacial water to form physically cross-linked hydrogels in situ and that the physically cross-linked polymers can diffuse into the substrate network to further promote adhesive-substrate interactions, resulting in the enhanced wet adhesion.

**Strong adhesion of PEI/PAA powder–derived hydrogel on wet tissues**

To demonstrate the potential applications of the PEI/PAA powder, we investigated the adhesion of PEI/PAA powder using the PAAm hydrogel and animal tissues as the substrates in vitro. We first fixed 100 mg of PEI/PAA powder onto a glass plate by a double-sided tape (2.5 cm by 1 cm) and then used the powder to adhere a piece of wet chicken skin (1.3 g). At 13.55 s, the PEI/PAA powder contacted the chicken skin. At 14.88 s, the chicken skin can be adhered by the PEI/PAA powder and lifted against its own weight (Fig. 3A, fig. S15, and movie S3). These results showed that the adhesion of the PEI/PAA powder onto a wet substrate could be initiated after around 1.55 ± 0.27 s. The physically cross-linked polymers could subsequently diffuse into the substrates over time to further enhance adhesion. Next, spreading PEI/PAA powder onto a PAAm hydrogel, the PEI/PAA hydrogel formed in situ can strongly adhere to the PAAm hydrogel substrate without minimal detachment upon repeated bending and stretching of the substrate even after being immersed in deionized water for 30 days (Fig. 3B and movie S4). Moreover, the PEI/PAA powder can also form hydrogels in situ on chicken skin and porcine heart. The PEI/PAA hydrogels strongly adhered to these tissues despite distorting, bending, or water flushing even after being immersed in PBS for 12 hours (Fig. 3, C and D,
and movies S5 and S6). Furthermore, PEI/PAA powder deposited on the mucosa of porcine stomach and intestine can form hydrogels in situ, which strongly adhered on the tissues even after being immersed in the simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) for 12 hours, respectively (Fig. 3, E and F, and movies S7 and S8).

We next evaluated the adhesion performance of different adhesives on chicken skin by using the lap shear test (fig. S16). The PEI/PAA powder showed an adhesion stress of 74.6 kPa, which was much higher than that of the prefabricated PEI/PAA hydrogel (18.4 kPa), dried PEI-cPAA gel powder (21.1 kPa), and fibrin gel (30.1 kPa) (Fig. 3G). Moreover, the PEI/PAA powder showed excellent adhesion on various tissues, including porcine liver, stomach, intestine, and heart (Fig. 3H). The adhesion of PEI/PAA powder increased with increasing temperature because of the enhanced polymer diffusion with increasing temperature (Fig. 3I). The PEI/PAA powder showed an adhesion stress of 74.6 kPa, which was much higher than that of the prefabricated PEI/PAA hydrogel (18.4 kPa), dried PEI-cPAA gel powder (21.1 kPa), and fibrin gel (30.1 kPa) (Fig. 3G). Moreover, the PEI/PAA powder showed excellent adhesion on various tissues, including porcine liver, stomach, intestine, and heart (Fig. 3H). The adhesion of PEI/PAA powder increased with increasing temperature because of the enhanced polymer diffusion with increasing temperature (Fig. 3I).
powder showed the highest adhesion strength among all the formulations (Fig. 3J), and this can be attributed to the best mechanical and therefore cohesion property of the PEI5/PAA5 powder–derived hydrogel (Fig. 1I).

In addition, PEI/PAA powder can seal damaged porcine stomach (1.5-cm-long strip wound) filled with SGF and damaged porcine small intestine (5-mm-diameter circular wound) filled with SIF (Fig. 4, A and B, and movies S8 and S9). The damaged tissues sealed by the PEI/PAA powder showed higher bursting pressure than tissues sealed by fibrin gels, which were much higher than normal gastric and intestinal pressure (Fig. 4, C and D) (45–47). Next, we adhered a stretchable strain sensor on the damaged intestine using an in situ
formed PEI/PAA hydrogel (Fig. 4E). The PEI/PAA hydrogel supported the tight adhesion of the foil strain sensor on the dynamic and curved surface of the beating porcine small intestine and enabled the electrical measurements of tissue shrinking and expansion (Fig. 4F and movie S10). These results showed that the PEI/PAA powder can seal the damaged tissues and serve as a versatile platform to attach wearable and implantable devices onto wet and dynamic tissues.

**Enhanced healing of gastric perforation by PEI/PAA powder treatment**

To further demonstrate that the PEI/PAA powder can be used as sealants to treat gastrointestinal perforation, we used an in vivo rat gastric perforation model (Fig. 5A) (48–50). A 5-mm vertical perforation was made at the gastric antrum using a scalpel, allowing the gastric lumen to open into the abdominal cavity. The gastric perforations were disinfected with iodophor and closed by using a non-absorbable suture, fibrin gel (100 mg), or PEI/PAA powder (40 mg). On day 7 after the treatment, a macroscopic examination on the harvested stomach tissues revealed a significantly smaller wound area in the PEI/PAA treatment group (141 ± 57 mm²) than that in the suture (427 ± 67 mm², \( P < 0.01 \)) and fibrin gel group (1264 ± 101 mm², \( P < 0.001 \)), indicating better wound healing in the PEI/PAA treatment group (Fig. 5B and fig. S17). Meanwhile, the suture and the PEI/PAA powder treatment group showed less abdominal adhesions than the fibrin gel treatment group (fig. S18). Hematoxylin and eosin (H&E) staining showed that the seromuscular layer was observed to be interrupted around the wound in all three groups on day 7. Among these groups, only the gastric perforations sealed with the PEI/PAA powder were completely bridged with the regenerated mucosa. In contrast, perforations treated with the suture and fibrin gel showed larger and clear gaps in the mucosa (Fig. 5C and fig. S19B). The PEI/PAA hydrogel formed in situ still tightly adhered to the stomach wall on day 7 after the treatment (Fig. 5D).

Moreover, the inflammation around the repaired defects of the three groups was compared by inflammation scoring (neutrophil and lymphocyte infiltration) in histopathology of stomach sections (fig. S20). Results showed that the inflammatory infiltration significantly decreased in the PEI/PAA group (1.83 ± 0.41) compared with the fibrin group (2.67 ± 0.52, \( P = 0.046 \)). The suture group showed less inflammatory infiltration than that in the fibrin group, but the difference did not reach statistical significance (2.00 ± 0.63, \( P = 0.134 \)). The scoring of inflammation between the PEI/PAA and suture group was comparable (\( P = 1.00 \)).

We next assessed reepithelialization around the gastric wound margin and at the area of the granulation tissue through immunohistochemical staining against the proliferating cell nuclear antigen (PCNA; a proliferation marker of G1–S phase). The percentage of PCNA-positive cells (yellow arrow) around the wound margin in the PEI/PAA gel group was significantly higher compared with that of the suture group (\( P < 0.001 \)) and fibrin gel group (\( P < 0.001 \)) (Fig. 5E). Meanwhile, treatment with the PEI/PAA gel induced higher expression of PCNA in the granulation tissue compared with that of the suture group (\( P < 0.001 \)) and fibrin gel group (\( P < 0.001 \)) (Fig. 5F). To evaluate the impact of different treatment on neovascularization, we then determined the capillary density at the area of the granulation tissue by immunohistochemical staining against CD31 (a marker for endothelial cells and angiogenesis). CD31 staining showed that the number of CD31-positive capillaries (red arrow) at the granulation tissue in the PEI/PAA gel group was significantly higher than that in the suture group (\( P < 0.001 \)) and fibrin gel group (\( P < 0.001 \)) (Fig. 5G). Together, these results showed that the PEI/PAA powder can seal and promote healing of gastric perforations in vivo.

**DISCUSSION**

In this work, we prepared a self-gelling and adhesive powder based on the complexation of charged polyelectrolytes. After mixing PEI and PAA aqueous solutions at the selected weight ratio (5:5), the strong noncovalent interactions (such as electrostatic interaction and hydrogen bonding) between the two polymers induced phase separation, producing a dense polyelectrolyte-rich and gel-like phase [polyelectrolyte complex (PEC)], which has higher storage modulus (\( G' \)) than loss modulus (\( G'' \)) (fig. S1C) and a more dilute solution phase. Reversible noncovalent interactions among polymer chains endow the PEC with an excellent self-healing capability (51). After being freeze-dried and grounded, the dried PEI/PAA PEC fragments with size ranging from 25 to 300 μm were obtained (fig. S3A). Upon hydration, each PEC fragment would swell rapidly to form a microgel. Meanwhile, upon surface contact with each other, the swollen fragments would undergo rapid self-healing, resulting in the formation of a cohesive bulk hydrogel with loose and weak cross-linking without the need of substantial polymer diffusion. Therefore, the change from powder to hydrogel upon hydration could be finished to establish the initial adhesion rapidly (within 2 s). The polymer chains would further diffuse substantially over time in bulk PEI/PAA hydrogel to form denser cross-linking, thereby further increasing the hydrogel mechanical properties in the first 24 hours (Fig. 1J). Although the PEI/PAA hydrogel obtained the maximum failure strength over 1 day, the mechanical properties of the hydrogel formed in 5 min are sufficient to resist gastric perforation. As shown in Fig. 4D, in vitro bursting pressure of a damaged porcine stomach (wound diameter, 10 mm) sealed with PEI/PAA powder for 5 min is 194 ± 11 mmHg, which is much higher than normal gastric pressure (15 to 25 mmHg) (46, 47). This result shows that even with a short deposition time of 5 min, the formed PEI/PAA hydrogel can provide enough mechanical property to effectively seal gastric perforations. The further increase of failure strength of the hydrogel over 24 hours indicates that the PEI/PAA hydrogel sealing can become more stable in the wound instead of weakening over time. Previous in situ formed hydrogels were prepared from the gelation of precursor solutions, which was triggered by external stimuli, such as light irradiation (6, 10), chemical stimuli (1, 31), and temperature (52). In this work, we demonstrate that addition of water or other aqueous media can induce the rapid gelation of PEI/PAA powder, which can be easier to store, transport, and use in practical settings.

PEI/PAA powder deposited on wet substrates can absorb interfacial water to form hydrogel in situ, resulting in tight contact between hydrogel and substrates. Meanwhile, carboxylic acid and amine groups in PEI/PAA hydrogel can form physical interactions with the functional groups (such as amine and sulfhydryl groups) on the surface of the wet substrates, resulting in rapid adhesion initiation within 2 s (Fig. 3A). The physically cross-linked polymers could subsequently diffuse into the substrates over time to further enhance adhesion. Therefore, the adhesion of PEI/PAA powder is based on both the physical interactions and interpenetration of
polymers. The adhesion of most previous adhesive hydrogel is based on functional groups, such as N-hydroxysuccinimide ester (9, 35) and catechol groups (8, 25, 34), which can form covalent bonds with substrates, but prior works have also reported strong and stable adhesion based on physical interactions (36, 53, 54). For example, Han et al. (36) reported a dynamic hydrophobic hydrogel that shows repeatable and stable long-term underwater adhesion to various substrates, including wet biological tissues, by forming a water-resistant molecular bridge instead of covalent binding between the hydrogel surface and hydrophobic domains on the substrates. Moreover, Chen et al. (54) reported a new adhesive hydrogel containing “triple hydrogen bonding clusters” (THBCs) that achieves strong and long-term adhesion by forming a high density of hydrogen bonds with substrates and the unique equal load sharing configuration of the THBC. In addition, chemically cross-linked PAA gel powder can also adhere two PAAm hydrogels together by absorbing interfacial water and forming weak noncovalent bonds with the surface of the PAAm hydrogels. However, PAA gel powder cannot re-form a complete bulk gel upon hydration, and the resultant adhesion could be hampered by the weak matrix cohesion and limited mobility of the chemically cross-linked bulk PAA network (53).

The PEI/PAA gel adhered on the stomach remained stable and exhibited no significant degradation after a 30-day implantation, indicating that the PEI/PAA gel can act as a physical barrier on the healed perforation site to provide protection for a longer period. Although the gastric perforation has healed, the healing tissue is still mechanically weak than healthy tissues in the early stage of 3 to 6 months after operation (55, 56), and this may lead to a second gastric perforation in the short time. Therefore, we suggest that the stable PEI/PAA gel might act as a robust physical barrier on the healed wound site to avoid the recurrence of perforation. In addition, the prolonged protection by hydrogel can be of potential clinical significance to patients who suffer from gastric perforation due to long-term usage of nonsteroidal anti-inflammatory drugs (NSAIDs) and cannot abruptly stop taking NSAID because of potential complications such as thrombosis (57, 58).

Although the PEI/PAA gel remained stable for a long period, its presence induced little damage on the surrounding tissues and would not affect the normal functions of the organ because of its congruent attachment and soft consistency. Therefore, we believe that this stable PEI/PAA hydrogel not only can act as a sealant to promote the healing of gastric perforation but also can act as a physical barrier on the healed perforation site to provide a sustained...
Fig. 5. Enhanced sealing and healing of gastric perforations by the PEI/PAA powder. (A) Schematic illustration and photos of the surgical procedures performed to seal gastric perforations. Macroscopic photos (B) and H&E staining (C) of gastric wounds acquired on day 7 after treatment with sutures, fibrin gel, or PEI/PAA powder (original magnification: top, ×20; bottom, ×40). (D) Photographs and SEM images of PEI/PAA hydrogel adhered on the stomach wall. (E) Representative images and quantification of staining against PCNA around the wound margin at HPF (original magnification: ×400, hematoxylin counterstain). (F) Representative images and quantification of staining against PCNA in the granulation tissue at HPF (original magnification: ×400, hematoxylin counterstain). (G) Representative images and quantification of staining against the angiogenesis marker CD31 at HPF (original magnification: ×200, hematoxylin counterstain). Yellow arrow indicates PCNA-positive cell, and red arrow indicates blood vessel. Rats, \( n = 3 \). Statistical significance was analyzed by one-way ANOVA followed by a Tukey post hoc analysis between three groups, \( **P < 0.01 \) and \( ***P < 0.001 \). Data are shown as the means ± SD. Photo credit: Xin Peng, The Chinese University of Hong Kong.
protection effect. Nevertheless, we are now planning to investigate the biocompatibility and stability/biodegradation of PEI/PAA gel in vivo for a longer time period such as 1 to 2 years in a follow-up study to achieve better understanding on the tissue-hydrogel interactions.

For gastric perforation experiment, a full-thickness gastric perforation is induced in a rodent model. As shown in Fig. 5A, the mucosal layer is significantly everted out through the perforated wound. The deposition of the hydrogel at the serosal side can help bring the opposing mucosal edges at the perforation into a desired apposition. This hydrogel-enhanced approximation of mucosal layer can promote tissue healing. Our results confirmed that on day 7, a better bridging of the mucosal edges in the PEI/PAA group is developed when compared with that of the suture group and fibrin gel group. For the suture group, although the wound edge could approximate well under stitching, the bridging of the separated mucosal layer may need longer time than 7 days to reconstruct the integrity of the epithelial lining. Our finding in this study is in line with our previous observations, which demonstrates that a complete continuity of the mucosa layer is far from being achieved on day 7 after suturing (48).

The toxicity of freely diffusing PEI is mainly associated with its strong positive charge, which leads to strong interaction of PEI with cell membranes, resulting in cell death and apoptosis (59). To reduce the toxicity of PEI, different chemical modifications of PEI have been explored (60–62). For example, Zhang et al. (62) prepared an alginate/PEI polyelectrolyte hydrogel with balanced charge, which not only showed excellent in vitro cytocompatibility and hemocompatibility but also showed minimal foreign body reaction in a mouse model. In our work, at the selected weight ratio of PEI and PAA (5:5), the charge balance between PEI and PAA could be achieved, resulting in optimal zeta potential (−0.1 ± 1.1 mV) and pH of the mixture (7.0 ± 0.04) (fig. S7). The charge balance between the positive charge of PEI and the negative charge of PAA may have contributed to the observed low cytotoxicity of PEI/PAA hydrogels.

Although PEI/PAA powder showed rapid self-gelation and adhesion, our work still has some limitations. Due to the nature of functional groups contained (carboxylic acid and amine groups), the obtained PEI/PAA hydrogels were pH dependent. We have also immersed PEI/PAA hydrogels in aqueous solution with varying pH. After being immersed in aqueous solutions with the pH ranging from 3 to 10 for 2 weeks, the PEI/PAA hydrogels were stable in these aqueous solutions. However, after being immersed in aqueous solutions with extreme pH, i.e., pH ≤2 or pH ≥11, the PEI/PAA hydrogels gradually swelled and dissolved in these solutions due to the change in charge density of the polyelectrolytes (fig. S21). The pH of gastric lumen can vary significantly at different time points of the day ranging from 1.1 to 7.0 (the pH of gastric lumen is lowest when food is being digested and highest when the stomach is empty) (63, 64). Therefore, the exposure of PEI/PAA hydrogels to highly acidic gastric pH is limited to the brief digestive periods. In addition, we sealed the gastric perforation by applying PEI/PAA hydrogel on the outer wall of the stomach, which is generally less acidic than the gastric lumen (65). Nevertheless, we are now planning to introduce pH-independent noncovalent cross-linking or dynamic covalent cross-linking into the hydrogels to increase their stability under extreme pH conditions. Moreover, in vivo adhesion and sealing performance of the PEI/PAA powder were only evaluated by using rats. Future large animal studies with larger sample sizes and longer follow-up duration are needed to facilitate clinical translations.

In conclusion, we prepared self-gelling and adhesive PEI/PAA powder. Owing to the strong physical interactions between the polymers and free polymer diffusion, the PEI/PAA powder can directly form physically cross-linked hydrogels by absorbing water without additional cross-linking agents. Superficially deposited PEI/PAA powder can absorb interfacial water to form tight contact with various wet substrates. Furthermore, the physically cross-linked polymers can diffuse into the polymeric network of the wet substrates to further promote wet adhesion. Therefore, spreading PEI/PAA powder on various tissues such as chicken skin, porcine heart, and mucosa of porcine stomach and intestine resulted in strong adhesion on these wet tissues over a prolonged time period. Moreover, this adhesive PEI/PAA powder can effectively seal and promote healing of damaged tissues in vivo and facilitate attachment of medical devices. Owing to the strong adhesion and easy preparation of PEI/PAA powder, we believe that these powders are an ideal candidate for several applications, such as wound healing, hemostatic agents, wearable devices, and drug delivery.

**MATERIALS AND METHODS**

**Materials**

PEI (Mw, ca. 70,000 and Mw, ca. 1800) aqueous solution (50 wt %), potassium persulfate, N,N′-methylenebisacrylamide, AAm, and AA were purchased from Aladdin (China). PAA (Mw, ca. 240,000 and Mw, ca. 3000) aqueous solution (25 wt %) and FITC were purchased from J&K Scientific (China). Calcein-AM, propidium iodide, and trypsin were purchased from Sigma-Aldrich (USA). DMEM and fetal bovine serum were purchased from Gibco (USA). Penicillin and streptomycin were purchased from Hyclone (USA). PEI/FITC was prepared by mixing 1 g of PEI with 10 mg of FITC in a mixed solution of DMSO and water at room temperature in the dark for 24 hours. The mixture was purified by dialysis. Fibrin gel was purchased from Beixiu Biotechnology Co. Ltd. (China). SFG was prepared by dissolving NaCl (2 g) in 1000 ml of deionized water and then adjusted the pH to 1.5 ± 0.1 with diluted HCl. SIF was prepared by dissolving potassium phosphate monobasic (10.2 g) in 1000 ml of deionized water and then adjusted the pH to 6.8 ± 0.1 with 1 M NaOH aqueous solution according to previous work (66).

Nonabsorbable suture was purchased from Ethicon, Johnson & Johnson (Somerville, NJ, USA). Anti-PCNA mouse polyclonal antibody and anti-CD31 mouse polyclonal antibody were purchased from Santa Cruz Biotechnology (TX, USA). Anti-mouse immunoglobulin G and peroxidase-labeled streptavidin were purchased from Vector Laboratories (CA, USA). Diaminobenzidine solution was purchased from Dako (Glostrup, Denmark).

**PEI/PAA powder preparation**

We mixed 10 wt % PEI (Mw, ca. 70,000) and 10 wt % PAA (Mw, ca. 240,000) aqueous solution in the following volumetric ratios: 1:9, 3:7, 5:5, 7:3, and 9:1. In addition, we mixed 10 wt % PEI (Mw, ca. 70,000 or 1800) and 10 wt % PAA (Mw, ca. 240,000 or 3000) in a 5:5 volumetric ratio. The mixtures were immediately immersed in liquid nitrogen for about 15 min without pouring out any liquid and freeze-dried to remove water. Last, the dried solids were ground to obtain PEI/PAA powder using a mortar and pestle. The PEI/PAA powders were prepared by mixing 5:5 PEI (10 wt %; Mw, ca. 70,000)
and PAA (10 wt%; \(M_w\), ca. 240,000) aqueous solutions, unless otherwise stated. PEI\(_{FITC}\) was used to prepare PEI\(_{FITC}/\)PAA powder as indicated. Rhodamine B and royal blue dye were physically mixed into the PEI or PAA aqueous solution to prepare pink or blue powder, respectively, for better visualization, and the loss of dyes over time may lead to color change of the hydrogels.

**Lap shear test**

Lap shear tests were performed using a Kinexus rheometer with custom clamps at a crosshead speed of 3 mm min\(^{-1}\). For lap shear tests (fig. S16), different adhesives, such as prefabricated PEI/PAA hydrogel (80 mg), dried PEI-cPAA gel (40 mg), fibrin gel (80 mg), and PEI/PAA powder (40 mg), were sandwiched between two tissues with an adhesion area of 2 cm by 1 cm. Then, the samples were incubated at 37°C for 5 min with pressing (8 kPa pressure applied). The adhesion stress was calculated as follows: adhesion stress = \(F_{\text{max}}/(wl)\), where \(F_{\text{max}}\) is the maximum force, and \(w\) and \(l\) are the width and length of the adhesion area, respectively. All tissues were immersed in DMEM at 37°C for 30 min before use. Three specimens per condition were tested to ensure the reliability of the data.

**Bursting pressure test**

Bursting pressure tests were performed according to previous reports (21). As shown in Fig. 4C, tissues with a penetrating defect (3 mm diameter in intestine and 10 mm in stomach) were fixed on a cylinder and attached to a syringe pump and a pressure monitor through a three-way stopcock. The whole device was then filled with PBS. Five minutes after PEI/PAA powder (40 mg) or fibrin gel (100 mg) was applied, pressure was applied via the pump at a speed of 2 ml min\(^{-1}\). A rapid pressure decrease was considered as the bursting pressure. In addition, the nontreatment group was used as a negative control. The bursting pressure was presented by standardizing the pressures to the negative control.

**Animal models**

Animal experiments were conducted according to the guidelines of the Animal Ordinance (Chapter 340), Department of Health, Hong Kong. The study was approved by the Animal Experimentation Ethics Committee of The Chinese University of Hong Kong (12-052-MIS). Animal experiments are shown in Fig. 5A. After fasting for 12 hours, the rats were anesthetized by intraperitoneal administration of ketamine (80 mg/kg of body weight), and their stomachs were exposed along the midline abdominal incision. A 5-mm vertical perforation was then made at the body of the stomach using a scalpel. The wounds were disinfected with iodophor first. Forceps were used to grasp the opposing wound edge, and then fibrin gel (100 mg) or PEI/PAA powders (40 mg) were applied until gelation in situ was achieved. A positive control group with closing wounds was performed as the negative control. The tissues adhered with PEI/PAA hydrogel were immersed in liquid nitrogen for 15 min and freeze-dried. Cross sections of the tissue-hydrogel were observed by SEM. Other tissues were fixed in phosphate-buffered formalin for 24 hours, dehydrated, and embedded in paraffin.

**Histological assessment**

Paraffin-embedded samples were cut into 5-μm sections, which were dewaxed using xylene and dehydrated using gradient alcohol. Then, the slides were stained with H&E according to established protocols. Histological analysis was conducted by a blinded pathologist to assess the healing of gastric perforations. Histopathology of stomach sections was then examined with the scoring of inflammation (neutrophil and lymphocyte infiltration). It was graded as previously demonstrated with minor modifications: grade 0, no inflammatory cells; grade 1, <10 inflammatory cells per high-power field (HPF) infiltration; grade 2, >10 inflammatory cells per HPF infiltration limited to ≤50% of the submucosa around the wound; grade 3, infiltration involving >50% of the submucosa around the wound (49). Pictures were taken where the inflammation was most visible.

**Immunohistochemistry**

Immunohistochemistry was performed to detect PCNA (a cell proliferation marker) and assess regenerated blood vessels (CD31) in the gastric wound. These methods are described in the Supplementary Materials. PCNA-positive cells and blood vessels were counted as follows: We captured two representative images from each slide under the microscope for quantification (×400 for PCNA-positive cell and ×200 for CD31-positive blood vessels). The proportion of PCNA-positive cells around the wound margin and at the granulation tissues was calculated by dividing by the total number of cell nuclei per HPF (×400). CD31-positive blood vessels were counted manually at a magnification of ×200. Quantification of CD31 and PCNA expression was conducted in a blinded manner.

**Statistical analysis**

All data are shown as means ± SD via at least triplicate samples. Independent Student’s t test and one-way analysis of variance (ANOVA) followed by a Tukey post hoc analysis were used to determine statistical significance between two or multiple groups, respectively. Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) 25.0, and a two-sided \(P < 0.05\) was considered statistically significant.

**Supplementary materials**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/7/23/eabe8739/DC1

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