

Injectable Polymeric Hemostats for Non-compressible Hemorrhage Control

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Abstract Non-compressible hemorrhage arising from torso, junctional, or intracavitary injuries remains a major cause of preventable trauma-related mortality owing to anatomically difficult-to-access bleeding sites, rapid high-pressure blood flow, and the limitations of conventional hemostatic approaches. Injectable polymeric hemostats enable minimally invasive delivery into narrow or irregular wound tracts and conformal adaptation to complex wound geometries, representing a promising strategy for effective hemorrhage control. This review summarizes the recent advances in three classes of injectable polymeric hemostats, including hydrogels, gelable powders, and expandable hemostatic materials, with particular emphasis on material design strategies, hemostatic mechanisms, and performance characteristics. Current challenges and future perspectives are also discussed, providing insights to guide the rational design and clinical translation of advanced polymeric hemostats for safer and more effective management of non-compressible hemorrhage.

Keywords Non-compressible hemorrhage; Injectable hemostatic hydrogels; Gelable powdered hemostats; Expandable hemostatic materials; Biomedical polymers

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1 INTRODUCTION

Non-compressible hemorrhage primarily arises from torso, junctional, or intracavitary injuries, including stab or penetrating wounds, gunshot wounds, large-volume solid-organ lacerations, and major vessel injuries.^[1–4] It remains a major cause of preventable death in both civilian trauma and military settings.^[5–7] These injuries frequently present as deep and narrow wound tracts with limited anatomical accessibility, where external compression or tourniquets are ineffective.^[8–11] Rapid high-pressure bleeding from such concealed sites can overwhelm the body's endogenous hemostatic mechanisms, leading to hypovolemic shock, coagulopathy, organ failure, and death.^[12–14] Conventional approaches, such as blood transfusions, fluid resuscitation, and systemic pro-coagulant agents, provide essential supportive care but are often inadequate for achieving timely hemostasis in prehospital and emergency set-

tings.^[15–17]

Advances in hemostatic technology have led to a wide range of synthetic and natural hemostats, including sponges, foams, cryogels, pastes, hydrogels, and powders.^[1,18–23] These materials achieve hemostasis through three core mechanisms that can act individually or synergistically, including tissue adhesion,^[24–28] pro-coagulant activity,^[29–32] and physical tamponade.^[33,34] Bioadhesive hydrogels form physical barriers by adhering directly to tissue surfaces, enabling rapid sealing even under coagulopathic conditions. However, most clinically used adhesives, including fibrin sealants, cyanoacrylate glues, and bovine serum albumin/glutaraldehyde systems, are limited by their slow curing, weak wet tissue adhesion, low mechanical strength, and potential cytotoxicity.^[35–39] Traditional powdered hemostats, such as zeolite-based QuikClot[®], chitosan-based Celox[®], and starch-based Arista[®], rely on fluid absorption and local clotting factor concentration but often show insufficient mechanical strength and poor performance under high-pressure flow.^[40–42] This coagulation-dependent mechanism is limited by slow clotting kinetics, leading to delayed hemostatic efficacy. Expandable hemostatic materials control bleeding through rapid volumetric expansion and tamponade, allowing minimally invasive delivery into narrow wounds. Commercial products such as XSTAT are limited by their restricted porosity and fluid absorption capacity, which reduces their effectiveness in filling complex cavities and maintaining hemostasis.^[43,44] These challenges highlight a critical unmet

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need for hemostatic systems capable of reliably managing non-compressible hemorrhage in deep and difficult-to-access anatomical regions.

Injectable polymeric hemostats have emerged as a promising strategy for hemorrhage control in anatomically challenging settings. They can be delivered minimally invasively into wound tracts, rapidly conforming to complex geometries, reaching otherwise limited-access bleeding sites, and achieving effective hemostasis without precise localization of vascular injury. While numerous reviews have comprehensively discussed the general biology of hemostasis, material-tissue adhesion mechanisms, raw materials, and design strategies for topical hemostatic agents, relatively few studies have focused on injectable polymeric systems specifically designed for deep and narrow non-compressible hemorrhage.^[1,3,7,18,19,45–53] To address this gap and avoid redundancy, this review concentrates on three major classes of advanced injectable polymeric hemostats: injectable hydrogels, gelable powdered hemostats, and expandable hemostatic sponges (Fig. 1). We examined the underlying hemostatic mechanisms, material design strategies, and preclinical evaluations to provide a critical perspective on their potential to achieve rapid, localized hemorrhage control in anatomically challenging scenarios. Finally, we discuss the outstanding challenges and outline future directions for the rational design of next-generation polymeric hemostats.

2 INJECTABLE HEMOSTATIC HYDROGELS

Injectable hydrogels provide a minimally invasive approach for hemorrhage control in deep or irregular wounds.^[54–60] Upon administration, they undergo *in situ* gelation, allowing them to conform to complex wound geometries and form an adhesive physical barrier that functions independently of the body's clotting cascade. This feature makes them particularly suitable for

rapid hemorrhage control, including in patients with coagulopathy or those receiving anticoagulant therapy. Rapid gelation is therefore essential to prevent precursor washout under blood flow and provide initial mechanical support for wound stabilization. Beyond gelation kinetics, effective hemostatic sealing depends on both the bulk mechanical properties and interfacial adhesion of the hydrogel matrix.^[61–67] The bulk mechanical properties originate from the hydrogel network structure, which determines the physicochemical behavior of the adhesive, including deformation resistance, viscoelasticity, energy dissipation, cyclic loading stability, as well as swelling behavior and degradation in physiological environments. In addition, hydrogel adhesion to tissues involves physical non-covalent interactions, chemical covalent bonding, or a combination of both. Accordingly, injectable hydrogel adhesives typically require the coordinated optimization of rapid gelation, robust interfacial adhesion, and sufficient bulk mechanical performance to ensure reliable adhesive sealing in complex hemorrhagic environments. Representative examples of injectable hemostatic hydrogels, including their composition, tissue adhesion mechanisms, *in vitro* performance metrics, and *in vivo* hemostatic outcomes, are listed in Table 1.

Physical non-covalent interactions at the tissue-hydrogel interface enable the rapid formation of an interfacial adhesive layer, providing dynamic and reversible attachment that facilitates immediate hemostasis on wet tissues. These interactions primarily include hydrogen bonding, ionic/electrostatic interactions, hydrophobic association, and physical entanglement.^[68–71] For instance, Khademhosseini and Annabi *et al.* developed a highly elastic human protein-based sealant through photo-crosslinking of methacrylated recombinant human tropoelastin (MeTro).^[72] This hydrogel achieved a porcine skin adhesive strength of up to 172 kPa in wound closure tests and a burst pressure of approximately 12 kPa, effectively achieving hemostasis in a rat arterial incision model

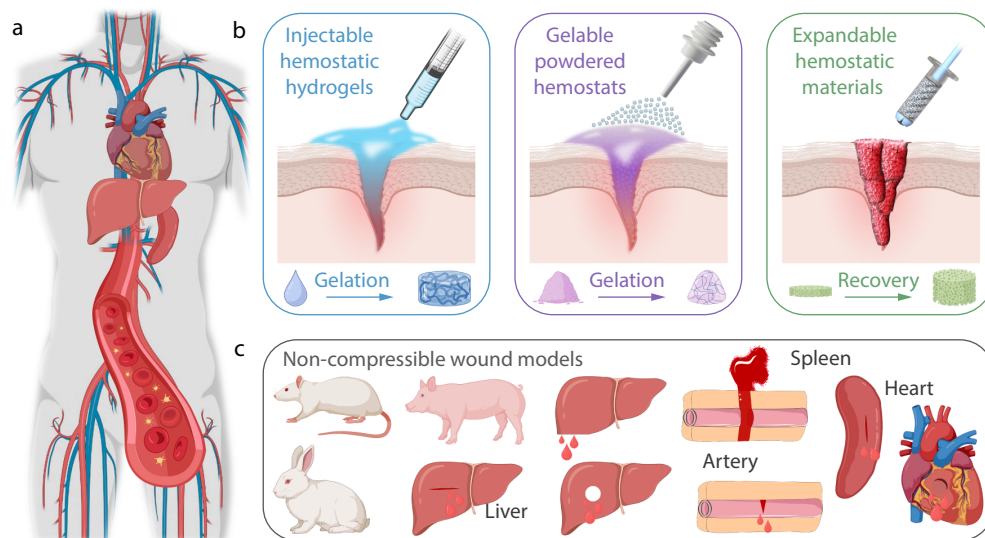


Fig. 1 Overview of advanced injectable hemostats for non-compressible hemorrhage. (a) Major vessels and visceral organs represent key non-compressible hemorrhage sites; (b) Representative injectable hemostats, including hydrogels, gelable powders, and expandable materials, and their corresponding gelation or expansion mechanisms; (c) Typical animal models for hemostatic evaluation include rats, rabbits, and pigs, with injuries to the liver, spleen, heart, and major arteries. Traumatic models include incisions, resections, perforations, transections, lacerations, and punctures.

Table 1 Comparative summary of representative injectable hemostatic hydrogels.

Material	Main constituent	Tissue adhesion mechanism	<i>In vitro</i> performance metrics ^a	<i>In vivo</i> hemostatic outcome ^b
MeTro/SN ^[73]	MeTro Laponite	Hydrogen bonding Electrostatic interaction Interlocking	GT: 80 s BP: 105 mmHg	Pig lung (15-mm incision) 60 s and 39 mg
HAD ^[74]	GelMA Reptilase	Hydrogen bonding Electrostatic interaction	GT: 30 s AS: 93.5 kPa	Rat liver (incision) 45 s and 78.7 mg
EBC ^[75]	Cyclooctene-RBCs Tetrazine-polymer	Hydrogen bonding Electrostatic interaction	GT: 5 s BP: 59 mmHg	Rat liver (7-mm diameter, 3-mm deep incision) 5 s and 24 mg
PCPD/APF ^[89]	Poly(citric acid-co-PEG)- <i>g</i> - dopamine Amino-PF127	Catechol-mediated covalent bonding Schiff base reaction Hydrogen bond Cation- π	GT: 33 s AS: 23.6 kPa BP: 260 mmHg	Rat liver (10-mm length, 3-mm deep incision) 8.4 s and 16.6 mg
PAG ^[91]	NCO-terminated PEG prepolymer Amino acid mimetic crosslinker	Urea/urethane bond Hydrogen bonding	GT: 95 s AS: 45 kPa BP: 510 mmHg	Pig femoral artery (2-mm diameter perforation) 2 min
HA-PEG ^[92]	<i>o</i> -Phthalaldehyde-modified tetra-PEG Hydrazide-modified HA	Schiff base reaction	GT: 1.5 min AS: 27.6 kPa BP: 171.9 mmHg	Rabbit femoral artery (3-mm incision) 30 s
GelMA/ HA-NB ^[93]	GelMA <i>o</i> -Nitrobenzyl-modified HA	Schiff base reaction	GT: 1.4 s BP: 290 mmHg	Pig heart (6-mm diameter puncture) 30 s
Barnacle glue ^[94]	PAA-NHS Chitosan Silicone oil	NHS-amine coupling Electrostatic interaction Hydrogen bonding	GT: < 15 s AS: 40–70 kPa BP: 350 mmHg	Pig liver with heparin (10-mm diameter, 10-mm deep injury) 15 s
OD-C/QGQL-A30 ^[95]	Gallic acid/ lauric acid-QCS Oxidized dextran Acetic acid, CaCO ₃	Schiff base reaction Hydrogen bonding π - π stacking, cation- π	GT: 30 s AS: 10 kPa BP: 235.5 mmHg	Pig subclavian artery (complete transection) 1.3 min and 11 mL
ES ^[100]	EPL Tetra-PEG-SS	NHS-amine coupling Electrostatic interaction Hydrogen bonding	GT: 6 s AS: 29.4 kPa BP: 450 mmHg	Pig liver with heparin (20-mm diameter, 6-mm deep) 2 min and 38.9 g

^a *In vitro* performance metrics include gelation time (GT), tissue adhesion strength (AS), and burst pressure (BP); ^b *In vivo* hemostatic outcomes include the representative animal injury model, hemostatic time, and blood loss (reported as mass or volume).

through charge interactions, physical entanglement, and interlocking with tissue fibers. Building on this system, Annabi *et al.* incorporated Laponite silicate nanoplatelets (SNs) into the MeTro network (Fig. 2a), thereby enhancing mechanical robustness and hemostatic performance, enabling effective intraoperative hemostasis and 14-day pneumothorax-free survival in porcine lung laceration models (Fig. 2b).^[73] In another study, Luo and Xing *et al.* reported a visible-light-activated, blood-resistant hemostatic adhesive hydrogel (HAD) composed of gelatin methacryloyl (GelMA) and reptilase, which promotes platelet activation and aggregation while efficiently converting fibrinogen into fibrin.^[74] The adhesive exhibited a lap-shear strength of 93.5 kPa and a blood clotting time of approximately 45 s, achieving effective hemostasis in liver incisions, partial hepatectomy, and abdominal aortic injuries. More recently, Li and co-workers developed tough cytogels by crosslinking *trans*-cyclooctene (TCO)-modified red blood cells with tetrazine (TZ)-bearing polymer linkers (Figs. 2c and 2d).^[75] The engineered blood clots (EBCs) achieved a 13-fold increase in fracture toughness compared with native clots and a burst pressure of 59 mmHg, effectively controlling hemorrhage in rat liver laceration and puncture models (Figs. 2d–2g). The enhanced bioadhesive performance of these cytogels was attributed to their highly dissipative matrix and interfacial bonding mediated by fibrin and platelets. Other injectable hydrogels that rely on non-covalent tissue interactions include peptide self-assembling gels,^[76] thermoresponsive hydrogels,^[77,78] and polyphenol-based materi-

als.^[79,80] However, because their adhesion relies primarily on reversible non-covalent interactions, these hydrogels often exhibit limited long-term tissue retention and are susceptible to detachment under high-flow bleeding conditions.

Hydrogels capable of covalent tissue cross-linking have received significant attention due to their ability to form stable chemical bonds *in situ*, enabling rapid, robust tissue adhesion and durable wound sealing. Reactive functional groups on tissue surfaces, such as amines and thiols, can react with complementary functional groups on hydrogels, with commonly employed chemistries including *N*-hydroxysuccinimide (NHS) esters,^[58,81–84] aldehydes,^[85–87] catechols,^[88–90] and isocyanates^[91]. For instance, He *et al.* developed an injectable hydrogel adhesive composed of hyaluronic acid (HA) and poly(ethylene glycol) (PEG) crosslinked *via* a catalyst-free *o*-phthalaldehyde/amine (hydrazide) reaction (Fig. 3a).^[92] This hydrogel exhibited a tissue adhesive strength of 27.6 kPa and a burst pressure of 171.9 mmHg, effectively sealing incisions and achieving rapid hemostasis in liver and blood vessel injury models (Fig. 3b). In another study, Shi and Yan *et al.* designed a two-component polyurethane-based biogel consisting of a PEG-based urethane prepolymer and hydrophobic amino acid-mimetic crosslinkers.^[91] By forming covalent bonds with the tissue, the biogel achieved a tissue adhesion strength of approximately 45 kPa and a burst pressure of 68 kPa, enabling reliable hemostasis in rat, rabbit, and porcine arterial injury models and supporting minimally invasive catheter-based delivery. To enhance both mechanical

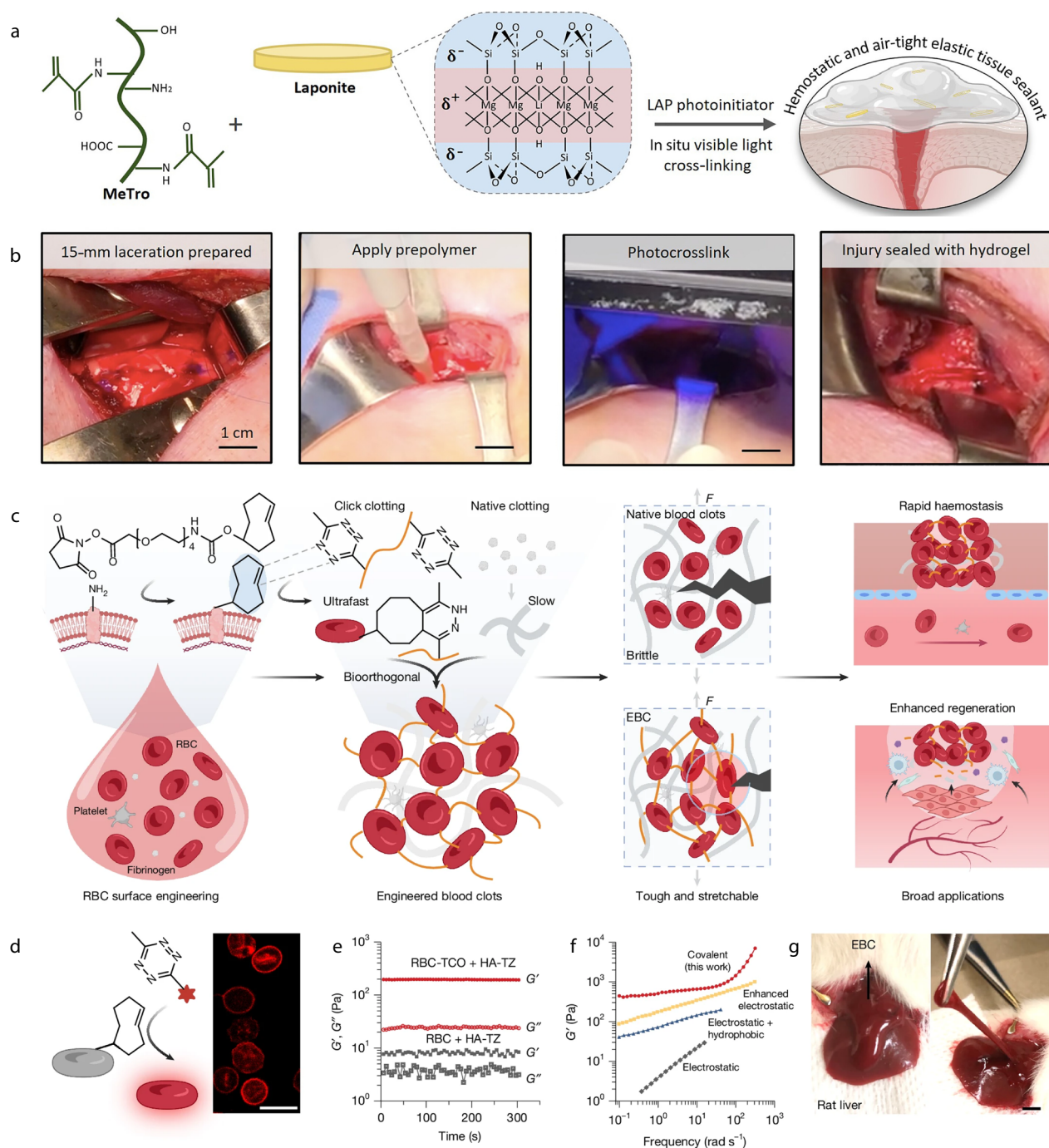


Fig. 2 Injectable hemostatic hydrogels with physically mediated tissue adhesion. (a) Schematic of MeTro and its combination with SNs to form the MeTro/SN hydrogel; (b) Representative images illustrating sealing of a 15-mm porcine lung laceration by MeTro/SN. (a, b: reproduced with permission from Ref. [73]; Copyright (2025), American Association for the Advancement of Science.) (c) RBCs functionalized with TCO are crosslinked via TZ polymers to form cytogels; EBCs show a large process zone, unlike brittle native clots; (d) Confocal imaging confirming uniform TCO labeling; (e) Rheological analysis showing rapid gelation with a higher storage modulus (G') than the loss modulus (G'') for the cytogel, whereas native RBC-polymer mixtures behave as viscous liquids; (f) Rheological comparison; (g) EBCs effectively achieve hemostasis in liver injury models. (c-g: reproduced with permission from Ref. [75]; Copyright (2025), Springer Nature.)

strength and adhesive performance, Ouyang, Zhang, and Zhu *et al.* reported an ultraviolet (UV)-triggered dual-crosslinked system based on GelMA and *o*-nitrobenzyl-modified hyaluronic acid (HA-NB).^[93] Upon UV irradiation, aldehyde groups generated from HA-NB reacted with amino groups to

form dynamic Schiff base linkages, while GelMA underwent simultaneous photo-crosslinking. The resulting double-network hydrogel exhibited a shear strength of up to 80 kPa and a burst pressure of 290 mmHg on porcine sausage skin membranes, successfully sealing 6 mm penetrating wounds on

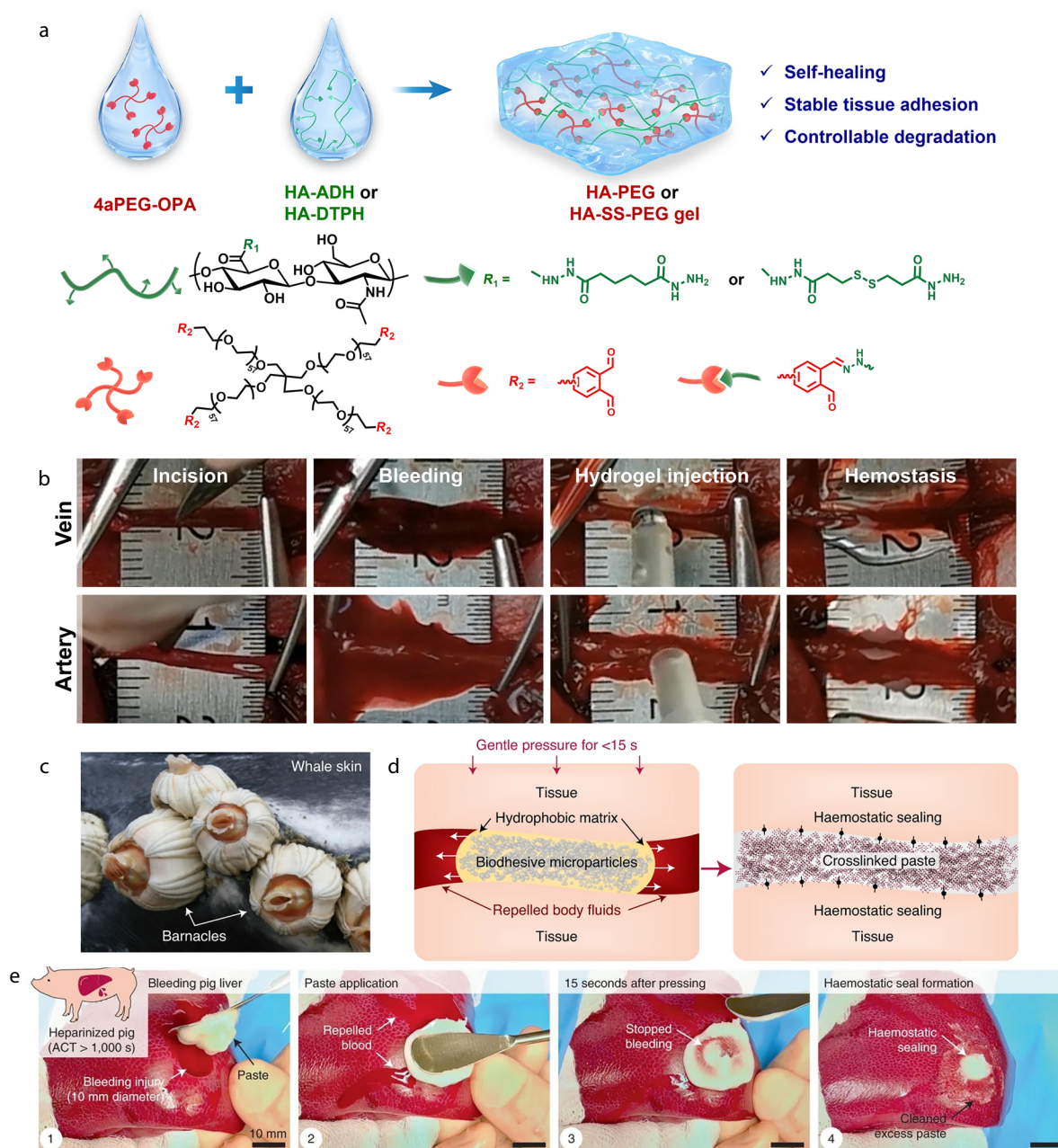


Fig. 3 Injectable hemostatic hydrogels with covalent adhesion to tissue. (a) Fabrication of HA-PEG hydrogel adhesives by mixing adipic acid hydrazide- or 3,3'-dithiobis(propionohydrazide)-modified hyaluronic acid with *o*-phthalaldehyde-terminated four-armed poly(ethylene glycol); (b) Hemostatic sealing of rabbit femoral vein and artery incisions using HA-PEG hydrogel. (a, b: reproduced with permission from Ref. [92]; Copyright (2023), Science.) (c) Barnacles adhered to whale skin; (d) Repel-crosslinking mechanism of barnacle-inspired paste combining blood repulsion and subsequent crosslinking to achieve hemostatic sealing; (e) Rapid hemostasis of a bleeding liver injury in a fully heparinized pig using the barnacle-inspired paste. (c–e: reproduced with permission from Ref. [94]; Copyright (2021), Springer Nature.)

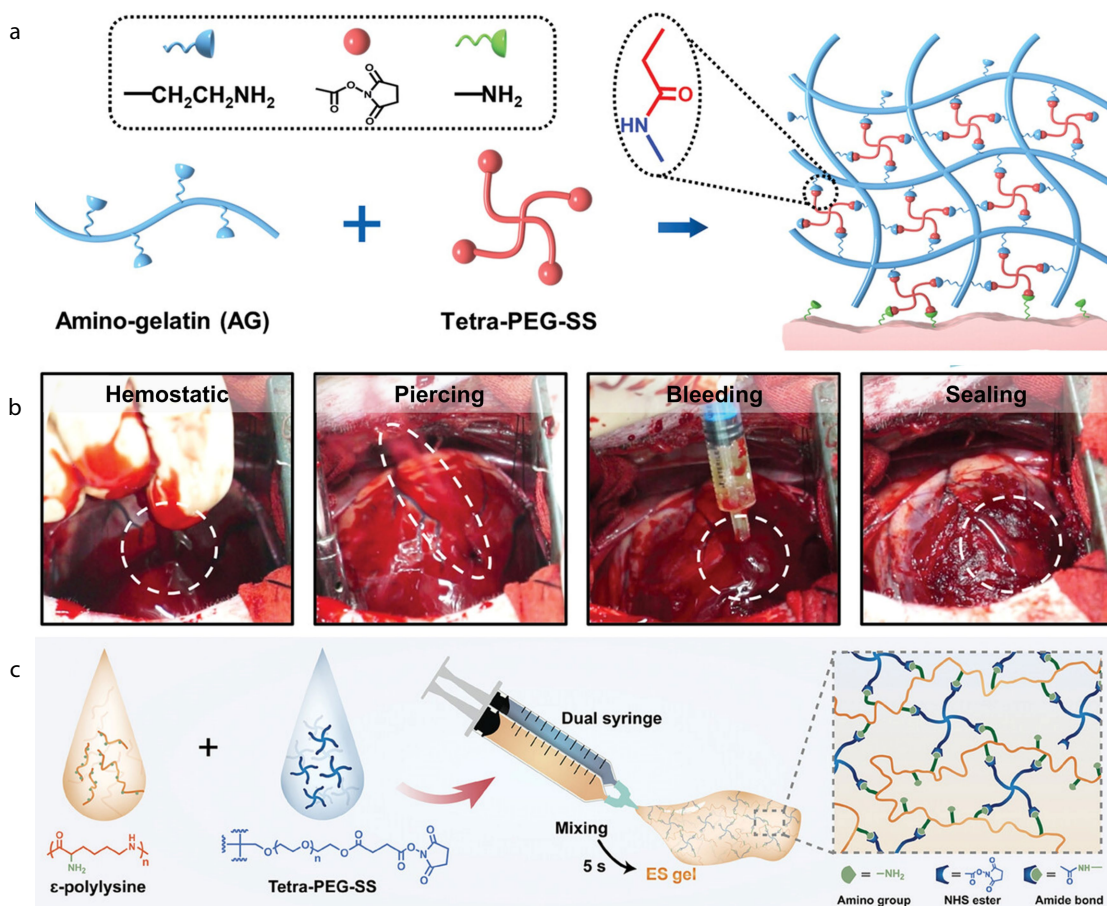
beating porcine hearts. Inspired by barnacle glue, Zhao and Nabzyk *et al.* developed an injectable paste combining a blood-repelling hydrophobic oil matrix with bioadhesive microparticles prepared from poly(acrylic acid) (PAA) grafted with NHS esters and chitosan (Figs. 3c and 3d).^[94] Upon contact with wet tissue, the paste rapidly transitioned into a soft hydrogel, sealing wounds within 15 s, sustaining burst pressures of approximately 350 mmHg, and achieving shear strengths of 40–70 kPa. In rodent and porcine models, it pro-

vided rapid, robust, and coagulation-independent hemostasis, outperforming FDA-approved agents, such as Surgicel, CoSeal, and TachoSil (Fig. 3e). To target deep non-compressible hemorrhage, Guo *et al.* developed a two-component hydrogel (OD-C/QGQL-A30) composed of oxidized dextran and lauric acid- and gallic acid-modified quaternized chitosans, incorporating calcium carbonate microparticles and acetic acid.^[95] Crosslinked *via* a Schiff base reaction, the hydrogel utilized a foaming reaction between calcium carbonate and

acetic acid to achieve self-expanding and self-propelling properties. It exhibited a tissue adhesion strength of approximately 10 kPa and a burst pressure of 235.5 mmHg, effectively achieving hemostasis in swine subclavian artery and vein transection models. Additionally, Seo *et al.* developed a shear-thinning injectable hydrogel composed of poly(vinyl alcohol), dopamine-functionalized sodium alginate, tannic acid, poly(acrylic acid), and sodium tetraborate decahydrate.^[96] Partial oxidation of catechol groups generated reactive quinone species that formed covalent bonds with wet tissue, whereas the incorporated polyphenols accelerate blood clotting, effectively controlling bleeding in large-area liver and spleen injuries in rabbits. Notably, across the representative systems described above, interfacial adhesion between hydrogels and tissues is rarely governed by a single mechanism alone. Instead, it typically arises from the synergistic integration of covalent bonding and non-covalent interactions, which together enhance interfacial stability, mechanical integrity, and resistance to blood washout under dynamic physiological conditions.

Our group has developed a series of injectable hemostatic hydrogels with enhanced efficacy.^[97–104] For example, a self-healing hydrogel based on choline phosphoryl-functionalized chitosan and oxidized dextran was designed, in which choline phosphoryl modification improved chitosan solubility and promoted erythrocyte adhesion and aggregation through electrostatic interactions, thereby enhancing local

coagulation.^[97] This hydrogel gelled within 5 s, achieved a burst pressure of 153.5 mmHg, and rapidly sealed rat liver and spleen injuries, outperforming commercial fibrin sealants. Moreover, we developed a dual-network, photocrosslinkable hydrogel composed of GelMA and NHS-modified poly(γ -glutamic acid) (yPGA-NHS).^[98] UV irradiation triggered rapid hydrogel formation and covalent bonding to the underlying tissue, yielding a lap-shear strength of 47.5 kPa and a burst pressure of 167.3 mmHg. The hydrogel demonstrated superior hemostatic performance compared with fibrin glue and effectively sealed porcine liver and spleen incisions, as well as femoral artery punctures. To enhance the mechanical strength, a super-tough hydrogel (AG-PEG) was constructed using extracellular matrix-mimicking amino-functionalized gelatin and tetra-armed PEG-succinimidyl succinate (tetra-PEG-SS) (Fig. 4a).^[99] The hydrogel achieved a compressive strength of 42.9 MPa, adhesion strength of 70 kPa on porcine skin, and burst pressure of 376 mmHg. It rapidly controlled massive bleeding from a 6 mm penetrating cardiac injury in pigs within 60 s, and postoperative assessments revealed gradual recovery of physiological parameters along with substantial cardiac tissue regeneration at 14 days (Fig. 4b). Additionally, an antibacterial hydrogel (ES) based on ϵ -polylysine (EPL) and tetra-PEG-SS was developed to address infection-prone traumatic wounds (Fig. 4c).^[100] The optimized formulation gelled within 5 s, exhibited a strong adhesive strength of 30 kPa, and an ultrahigh burst pressure of 450



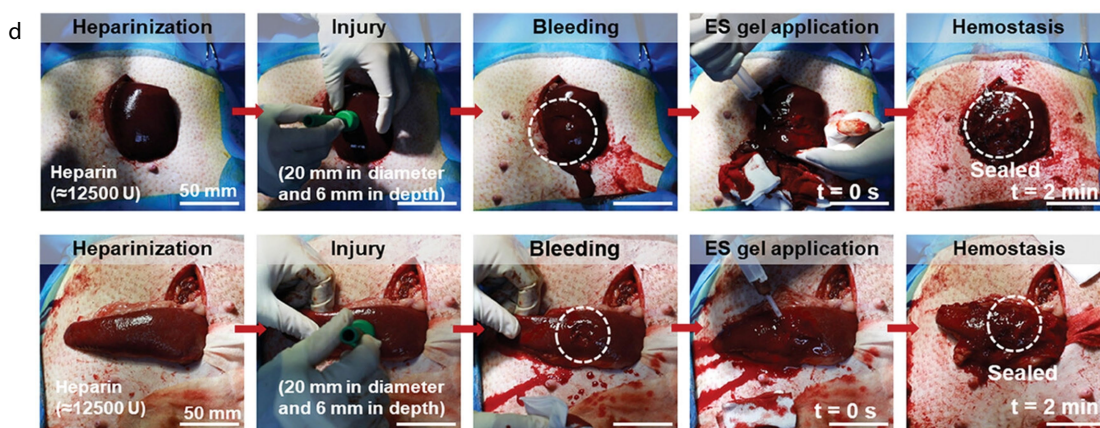


Fig. 4 (a) Schematic of the crosslinking mechanism of the super-tough AG-PEG hydrogel composed of amino-functionalized gelatin and tetra-PEG-SS; (b) Rapid hemostasis and sealing of a 6 mm cardiac puncture in pigs using AG-PEG hydrogel. (a, b: reproduced with permission from Ref. [99]; Copyright (2023), John Wiley and Sons.) (c) Chemical structures of ϵ -polylysine and tetra-PEG-SS, and schematic of ES gel preparation and crosslinking mechanism; (d) Representative images of porcine liver and spleen hemostasis achieved by ES gel after systemic heparin administration. (c, d: reproduced with permission from Ref. [100]; Copyright (2024), John Wiley and Sons.)

mmHg, providing rapid, robust, and fluid-tight sealing of bleeding wounds. Its superior hemostatic efficacy compared with fibrin glue has been confirmed in multiple injury models in rats and rabbits. Importantly, this adhesive hydrogel effectively halted lethal non-compressible hemorrhages in visceral organs (the liver, spleen, and heart) and femoral artery injuries in fully anticoagulated pigs (Fig. 4d). It also outperformed commercial products in sutureless wound closure and repair, showing enhanced efficacy in treating rat liver defects, skin incisions, and infected full-thickness skin wounds.

3 GELABLE POWDERED HEMOSTATS

Gelable powdered hemostats are designed to combine the rapid fluid absorption and coagulation-promoting properties of traditional powders with the mechanical stability and wet tissue adhesion of hydrogels. Upon contact with blood or wound exudate, these powders quickly absorb interfacial fluid to enhance adhesion and undergo *in situ* gelation, forming a cohesive hydrogel that conforms to the wound geometry and seals irregular or non-compressible cavities. This transformation improves clot retention, strengthens mechanical integrity under high-pressure flow, and supports hemostasis, even under coagulopathic conditions. By bridging the advantages of powders and hydrogels, gelable powdered systems provide a versatile and minimally invasive approach for rapid hemorrhage control in anatomically challenging wounds. Table 2 summarizes some representative examples of *in situ* gelable powdered hemostats.

Non-covalent gelable powdered hemostats undergo a powder-to-hydrogel transformation upon contact with physiological fluids through physical interactions, including hydrogen bonding, electrostatic complexation, and hydrophobic association.^[105–113] These systems are typically based on polyelectrolyte polymers, such as poly(acrylic acid), poly(ethyleneimine), hyaluronic acid, and chitosan, where oppositely charged functional groups drive spontaneous polyelectrolyte complexation *in situ*.^[114,115] Alternatively, polyphenol-based systems, particularly tannic acid, can interact with a broad range of polymers through multivalent non-covalent

interactions to form coacervate complexes, enabling rapid hydrogel formation and enhanced wet-tissue adhesion.^[116,117] These non-covalent interactions confer ultra-fast gelation, self-healing capability, and adaptability to complex bleeding environments. For example, Bian and Duan *et al.* developed poly(ethyleneimine)/poly(acrylic acid)/quaternized chitosan powders (PEI/PAA/QCS) that formed self-healing adhesive hydrogels *in situ* within 4 s via electrostatic interactions.^[118] The powders achieved a blood uptake of approximately 400% and hemostasis within 10 s in rat models, which was further validated in non-compressible porcine spleen and liver hemorrhage models. In another approach, Zhang *et al.* reported multifunctional coacervate powders (TCP) composed of tannic acid, chitosan, and PEG, which rely on hydrogen bonding and hydrophobic interactions (Fig. 5a).^[119] TCP exhibited 200% water uptake, an adhesion strength of 57.9 kPa, and a burst pressure of 134 mmHg, effectively controlling bleeding in carotid artery and porcine liver and spleen defect models (Fig. 5b). Interestingly, Wu *et al.* developed a natural biological powder (d-SMG) derived from snails mucus, consisting of a network of positively charged proteins and polyanionic glycosaminoglycans that rapidly forms a glue within 15 s and effectively achieves hemostasis in a rat liver bleeding model.^[120] Recently, Guo *et al.* developed a dopamine-modified montmorillonite/poly(ethyleneimine)/poly(acrylic acid)/protonated tranexamic acid/sodium carbonate (PP/PT-TXA) powder that rapidly undergoes physical crosslinking and spontaneously foams CO₂, causing system expansion and self-propelling behavior (Fig. 5c).^[121] It achieved 271% blood uptake, 400% expansion in 5 s, an adhesion strength of 34.8 kPa, and a burst pressure of 421.3 mmHg. *In vivo*, the powder outperformed commercial products in rat, rabbit, and lethal porcine hemorrhage models, effectively controlling non-compressible bleeding (Fig. 5d).

Hydrogels formed from gelable powdered hemostats through covalent crosslinking can offer enhanced mechanical strength and tissue adhesion, providing improved structural integrity in wet environments (Table 2).^[122–130] For in-

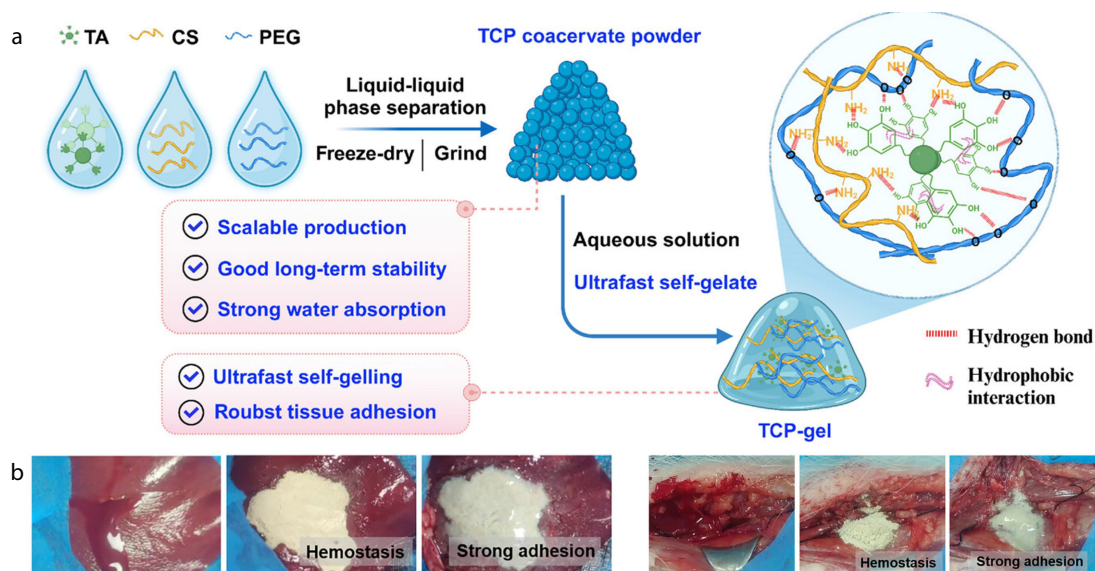
stance, Dong *et al.* reported a microgel assembly powder (MAP) prepared by freeze-drying and grinding UV-crosslinked oxidized dextran/methacrylated gelatin with long-chain alkyl quaternized chitosan (Fig. 6a).^[127] When mixed with blood, MAP formed a gel exhibiting a burst pressure of 201.2 mmHg and a tissue adhesion strength of 5.2 kPa, achieving superior hemostatic performance in rat heart puncture and rabbit liver injury models compared with commercial Celox® (Fig. 6b).

In an alternative strategy, Xie *et al.* developed a hemostatic powder based on thiol-functionalized carboxymethyl chitosan and aldehyde/maleimide-modified sodium alginate, which rapidly crosslinks via thiol-Michael addition and Schiff base reactions to achieve self-gelation within 10 s.^[128] The powder demonstrated high absorption (PBS: 340%, blood: 467%) and a burst pressure of 129 mmHg, and significantly reduced blood loss while shortening the bleeding time in rat,

Table 2 Comparative summary of representative gelable powdered hemostats.

Material	Main constituent	Gelation mechanism	<i>In vitro</i> performance metric ^a	<i>In vivo</i> hemostatic outcome ^b
CoITA ^[108]	Tannic acid Collagen-II	Hydrogen bonding	AS: 85.9 kPa	Rat liver (5-mm incision) 20 s and 30 mg
PEI/PAA/QCS ^[118]	PEI, PAA, QCS	Electrostatic interaction	GT: 4 s BP: about 240 mmHg	Pig spleen (20-mm length, 10-mm deep incision) 60 s and 1.5 g
TCP ^[119]	Tannic acid Chitosan, PEG	Hydrogen bonding Hydrophobic interaction	AS: 57.9 kPa BP: 134 mmHg	Rat femoral artery (incision) 10 s and 16 mg
d-SMG ^[120]	Snails mucus	Hydrogen bonding Electrostatic interaction π - π and hydrophobic interaction	GT: 15 s AS: 35.7 kPa	Rat liver (2.5-cm length, 0.5-cm width resection) 114.2 mg
PP/PT-TXA ^[121]	PEI, PAA, Na ₂ CO ₃ , Tranexamic acid Dopamine-modified montmorillonite	Hydrogen bonding Electrostatic interaction	GT: 2 s AS: 34.8 kPa BP: 421.3 mmHg	Pig subclavian arterial/venous (transection) 1.2 min and 11.7 mL
MAP ^[127]	Oxidized dextran GelMA Alkyl QCS	Schiff base reaction	GT: 8 s AS: about 10 kPa BP: 201.2 mmHg	Rabbit liver (partial resection) <1 g
PAA-db/PEI ^[129]	Double bond-modified PAA and PEI	Photo-crosslinking Electrostatic interaction	GT: 2 s AS: 48 kPa BP: 282 mmHg	Rat liver (8-mm diameter, 3-mm deep incision) 30 s and 133 mg
BICMs ^[130]	o-Phthalaldehyde-modified HA	Schiff base reaction	GT: 2 s AS: 8.5 kPa BP: 266.5 mmHg	Coagulopathic pig liver (10-mm diameter, 10-mm deep defect) 30 s and 1 g
GAP ^[131]	Tetra-PEG-NH ₂ , Tetra-PEG-SS Chitosan microsphere	NHS-amine coupling	GT: 5 s AS: 29 kPa BP: 175 mmHg	Pig liver (20-mm length, 10-mm deep incision) 3 min

^a *In vitro* performance metrics include gelation time (GT), tissue adhesion strength (AS), and burst pressure (BP); ^b *In vivo* hemostatic outcomes include the representative animal injury model, hemostatic time, and blood loss (reported as mass or volume).



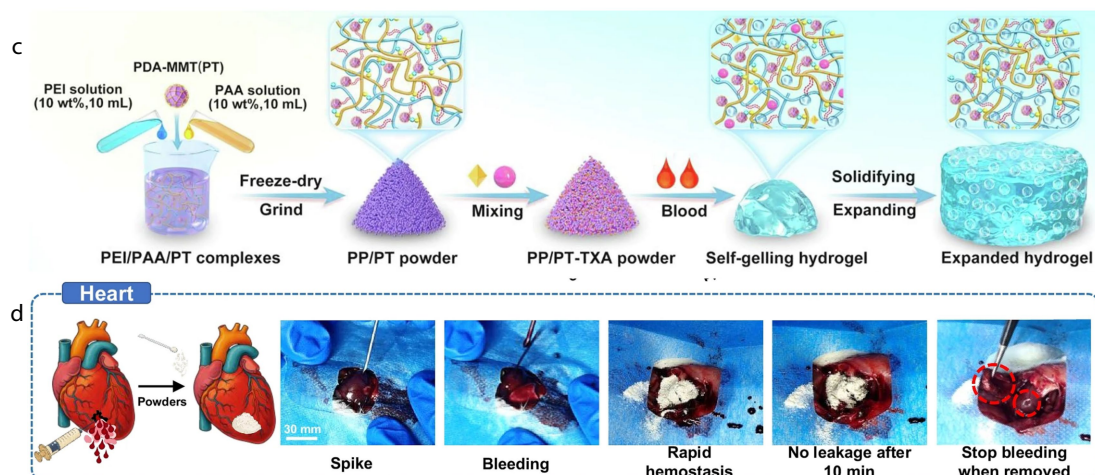


Fig. 5 Non-covalent gelable powdered hemostats form hydrogels through physical interactions upon contact with physiological fluids. (a) Schematic of TCP coacervate powder preparation from tannic acid, chitosan, and PEG, illustrating its self-gelation behavior; (b) Hemostatic performance of TCP powder in porcine liver and carotid hemorrhage models. (a, b: reproduced with permission from Ref. [119]; Copyright (2025), John Wiley and Sons.) (c) Schematic of self-gelling and self-expanding PP/PT-TXA powder preparation; (d) Representative hemostatic efficacy of PP/PT-TXA powder in a rat cardiac puncture model. (c, d: reproduced with permission from Ref. [121]; Copyright (2026), Springer Nature.)

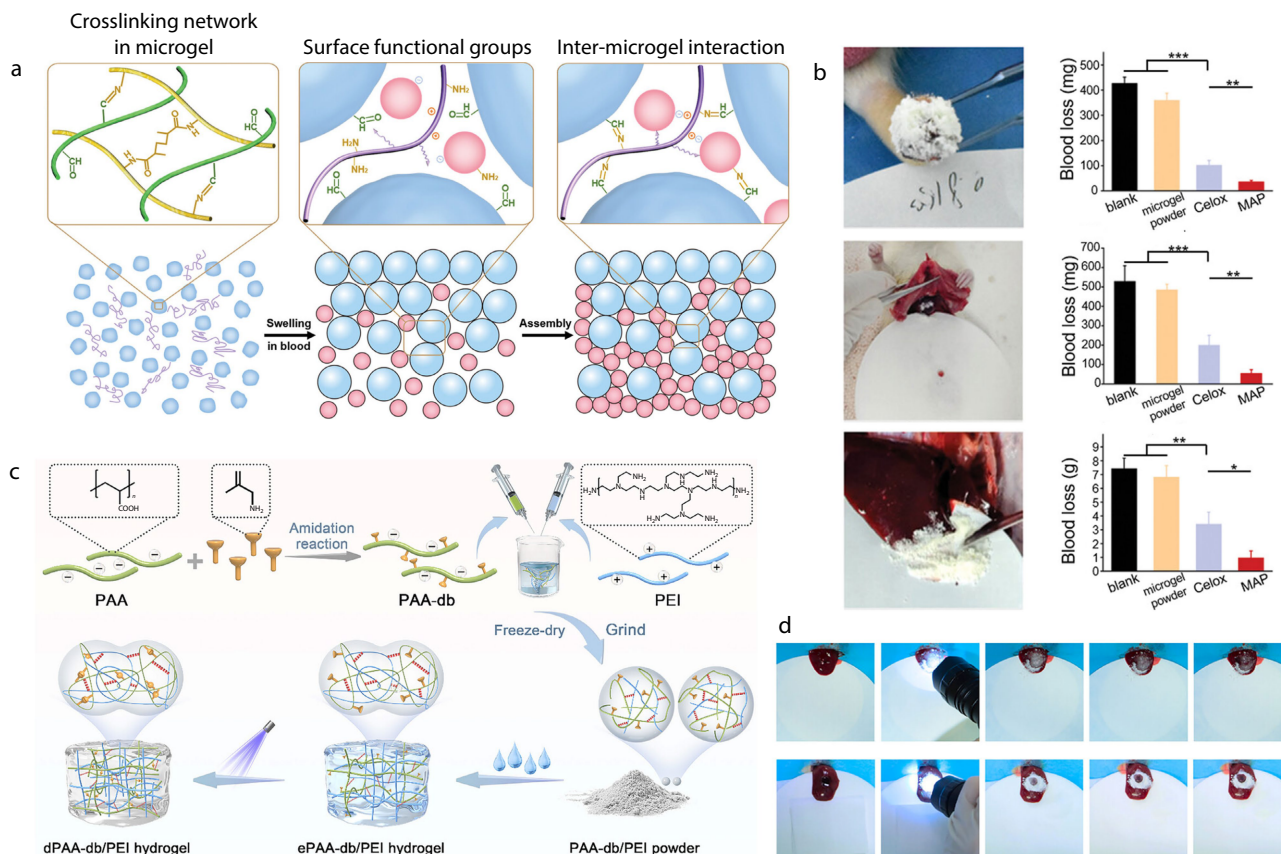


Fig. 6 Gelable powdered hemostats via covalent crosslinking. (a) Schematic illustration of *in situ* co-assembly of erythrocytes and microgels; (b) *In vivo* hemostatic performance of MAP in rat tail, rat heart, and rabbit liver bleeding models (top to bottom). (a, b: reproduced with permission from Ref. [127]; Copyright (2023), John Wiley and Sons.) (c) Schematic diagram of PAA-db/PEI powder preparation; (d) Hemostatic performance of PAA-db/PEI powder in rat liver incision and perforation models (top and bottom, respectively). (c, d: reproduced with permission from Ref. [129]; Copyright (2025), Springer Nature.)

rabbit, and canine models of massive hemorrhage compared to Yunnan Baiyao. In another method, Tong and Yu *et al.* designed a sequentially dual-crosslinked powder (PAA-db/PEI)

consisting of negatively charged double-bond-functionalized PAA and positively charged PEI, combining hydration-triggered electrostatic gelation with photo-activated covalent

lent reinforcement (Fig. 6c).^[129] This system achieved ultra-fast fluid absorption within 2 s, a lap shear adhesion strength of 48 kPa, and a burst pressure of 282 mmHg, outperforming fibrin glue and Celox® in rat liver incision and perforation models (Fig. 6d). Furthermore, Zhu and Lin *et al.* developed crosslinked hyaluronic acid microparticles functionalized with *o*-phthalaldehyde groups (BICMs), which absorb blood at the bleeding site and rapidly form a mechanically reinforced clot with enhanced tissue adhesion.^[130] The microparticles demonstrated a shear strength of 8.5 kPa and burst pressure

of 266.5 mmHg, effectively achieving rapid hemostasis in rat and coagulopathic porcine liver injury models.

To achieve both high fluid absorption and strong wet-tissue adhesion, our group developed a gelable adhesive powder (GAP) composed of chitosan microspheres, tetra-armed poly(ethylene glycol) amine (tetra-PEG-NH₂), and tetra-PEG-SS (Fig. 7a).^[131] Upon application, the macroporous chitosan microspheres rapidly absorbed interfacial liquids, while the hydrated GAP transformed into a hydrogel through covalent crosslinking. The optimized GAP exhibited excellent fluid ab-

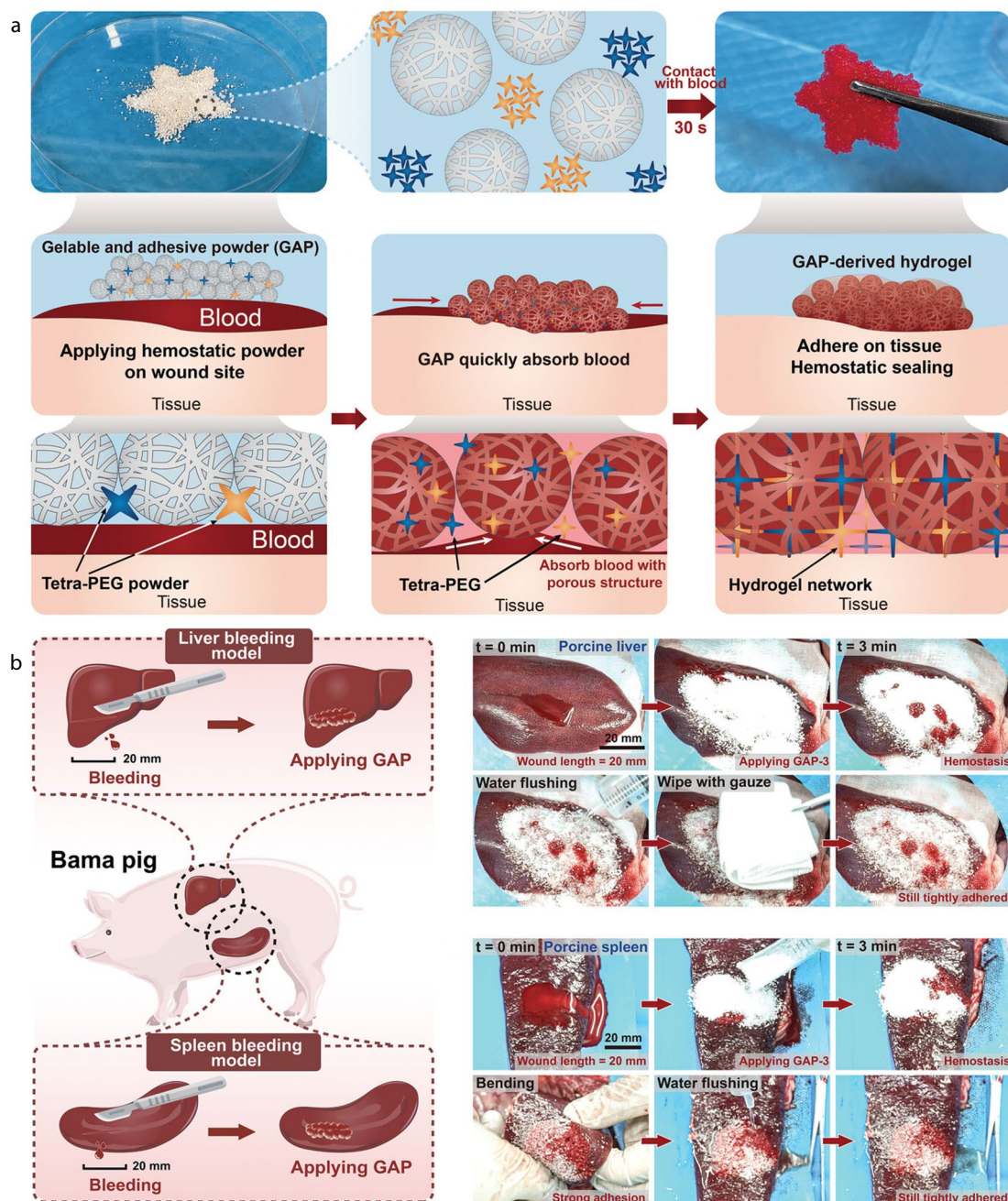


Fig. 7 (a) Design and mechanism of the gelable adhesive powder (GAP). Upon contact with blood, the macroporous CM rapidly absorbs fluid, triggering hydrogel formation through crosslinking between tetra-PEG-SS and CM/tetra-PEG-NH₂, while terminal NHS esters react with tissue amine and thiol groups to establish strong interfacial adhesion. (b) *In vivo* hemostatic efficacy of GAP in porcine liver (top) and spleen (bottom) hemorrhage models. (Reproduced with permission from Ref. [131]; Copyright (2023), John Wiley and Sons.)

sorption capacity, achieving approximately 960% uptake in water, PBS, and blood, which was substantially higher than that of commercial products such as zeolite molecular sieves, Celox®, and Yunnan Baiyao. It also achieved an adhesion strength of 29 kPa and a burst pressure of 175 mmHg. In rat liver, spleen, and femoral artery injury models, GAP demonstrated superior hemostatic efficacy compared with fibrin glue and Yunnan Baiyao, while effectively controlling severe bleeding in pig visceral organ hemorrhage models (Fig. 7b). Leveraging this system, we developed an antibacterial gel-forming adhesive powder (SLC) composed of tetra-PEG-SS, ϵ -polylysine, and chitosan microspheres.^[132] SLC achieved a lap shear strength of 50.3 kPa, a burst pressure of 201.3 mmHg, and approximately 99% inhibition of *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*). In preclinical models, SLC outperformed commercial hemostats in rat liver and femoral artery injuries, provided effective hemostasis in porcine liver, spleen, and femoral artery defects, and accelerated full-thickness skin wound healing by reducing inflammation, promoting collagen deposition, and enhancing neovascularization.

4 EXPANDABLE HEMOSTATIC MATERIALS

Unlike adhesive sealing or coagulation-promoting systems, expandable hemostatic materials primarily achieve hemorrhage control through rapid volumetric expansion and physical tamponade.^[1,45] Their porous three-dimensional architectures and shape-memory behavior enable compression for minimally invasive delivery into deep or narrow wounds, followed by recovery to the original volume upon contact with blood. This rapid expansion efficiently fills irregular wound cavities, generates localized pressure, and enables hemostasis without requiring precise localization of bleeding vessels. These properties make expandable materials particularly effective for managing non-compressible and junctional hemorrhages.

The hemostatic efficacy of expandable materials arises from multiple synergistic mechanisms. Rapid and high-capacity blood absorption enables swift filling of wound cavities, while efficient shape recovery and sufficient mechanical strength maintain structural integrity under blood flow, generating effective tamponade pressure. Additional pro-coagulant activity further accelerates clot stabilization. Currently, XSTAT, an FDA-approved chitosan-coated cellulose sponge device, is used for severe hemorrhage control in junctional and extremity wounds with narrow entrances. However, its non-degradable nature necessitates surgical removal, which may enlarge the wound cavities and cause secondary tissue injury.^[133] In addition, the limited expandability and fluid absorption capacity of the cellulose-based structure restrict its ability to conform to complex wound geometries and sustain durable tamponade. Another representative system, ResQ-Foam™, is an investigational *in situ* polyurethane foam generated from polyol and isocyanate precursors after injection into the wound cavity.^[34,134,135] Although it can rapidly expand to fill internal spaces, its deployment is technically demanding, and improper administration may increase the risk of complications, including potential mortality.^[7] Moreover, the non-degradable polyurethane foam requires surgical removal, while limited fluid absorption and relatively uncontrolled expansion may compromise hemostatic precision and increase the risk of compression-related tissue damage.

To enhance fluid absorption and accelerate volumetric expansion, extensive efforts have been focused on engineering highly interconnected porous architectures. Various fabrication strategies have been developed to construct porous foams,^[136–139] cryogels,^[140–147] aerogels,^[148–152] and sponges^[153–161] for expandable hemostatic applications, including conventional lyophilization, pore-forming agents, gas foaming, ice templating, and 3D printing. Representative examples of highly efficient expandable hemostatic materials are presented in Table 3. Conventional lyophilization (freeze-

Table 3 Comparative summary of representative expandable hemostatic materials

Material	Main constituent	Fabrication strategy	Liquid uptake ^a	Shape recovery time ^b	<i>In vivo</i> hemostatic outcome ^c
MACS ^[43]	Chitosan	3D printed and microfiber leaching	1.1 g/cm ³ (water) 1.1 g/cm ³ (blood)	2.1 s (water) 2.5 s (blood)	Pig liver (15-mm diameter perforation) 2 min and 17.6 g
Peanut ^[168]	PCL nanofiber Gelatin Thrombin	Electrospinning gas foaming	4326% (water)	10 s (water)	Pig liver (5-cm diameter X-times injury) 300 mL
Pollen cryogel ^[179]	Sunflower bee pollen	Ice-templating Compression-driven self-crosslinking	4 g/cm ³ (water) 1.8 g/cm ³ (blood)	about 1.25 s (water) <2.5 s (blood)	Rabbit kidney (8-mm diameter defect) 2.7 min and 380 mg
SALC ^[180]	Amino-gelatin Lignin Tetra-PEG-SS	Ice-templating Lignin-enhanced	4047% (water) 3010% (blood)	<1 s (water)	Rat femoral artery (transection) 36 s and 1.7 g
NMA ^[181]	PLA nanofibers PCL microfibers	Electrospinning Freeze-casting Nano-microfiber network	about 5300% (water) about 2500% (blood)	2.5 s (water) 4.8 s (blood)	Pig femoral artery and vein (transection) 42.9 mL
A-spCS ^[183]	Chitosan	Temperature-assisted secondary network compaction Phase separation	about 2200% (water) about 1700% (blood)	1.1 s (water) 4.4 s (blood)	Pig spleen (15-mm-diameter perforation) 73 s and 13.4 g
IHMS ^[184]	Chitosan Gelatin Tetra-PEG-CHO	Vacuum-assisted foaming Double-network	7279% (water) 6280% (blood)	0.9 s (water) 3.0 s (blood)	Pig groin (2-cm diameter gunshot injury) <20 s and <4 g

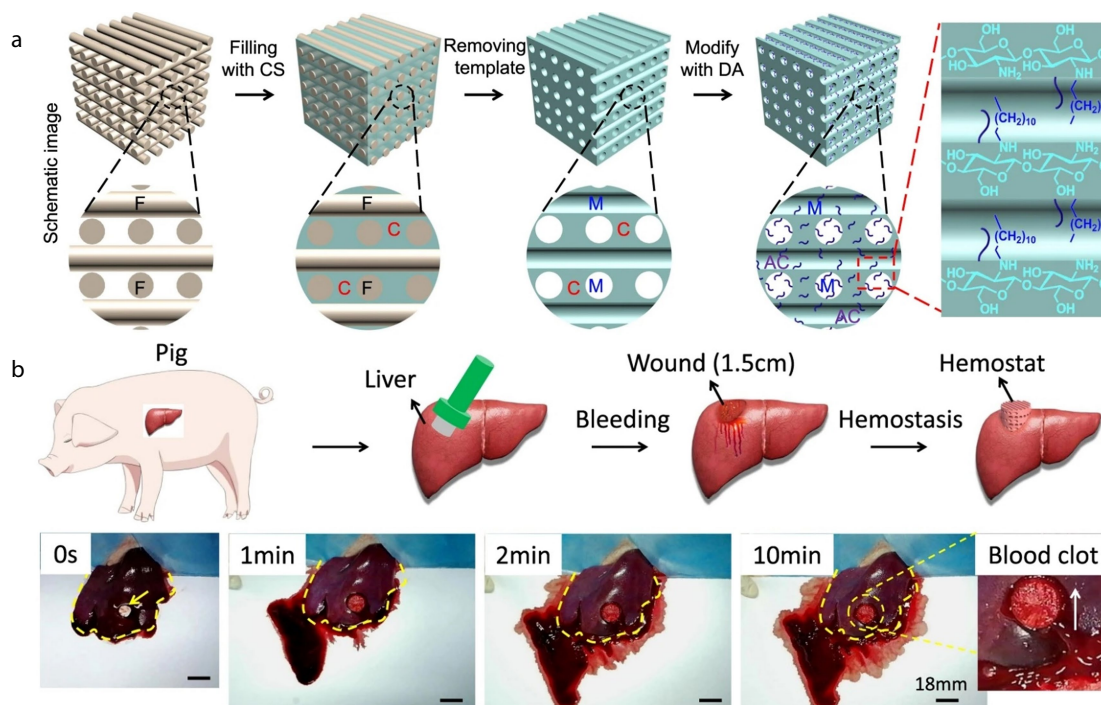
^a Liquid uptake is reported either as a mass-based swelling ratio (%) or volumetric absorption capacity (g/cm³) in water or blood; ^b Shape recovery time refers to the time required for a compressed material to recover its original structure upon fluid uptake in water or blood; ^c *In vivo* hemostatic outcomes include the representative animal injury model, hemostatic time, and blood loss (reported as mass or volume).

drying) generates porous materials by freezing a polymer solution, followed by ice sublimation under vacuum. Although simple and widely used, this method often yields limited control over pore size distribution and porosity. Pore-forming strategies introduce sacrificial templates, such as NaCl and Na_2SO_4 , which are subsequently removed to generate pores.^[162–164] However, the pore size is typically limited and often requires a combination with other techniques.

Gas foaming offers an alternative strategy by generating gas bubbles within polymer matrices through chemical or physical processes.^[165,166] As gas expands, interconnected porous structures are formed without harsh solvents or extreme freezing conditions, enabling rapid fabrication with tunable porosity and enhanced fluid uptake. For example, Monroe *et al.* fabricated shape-memory polyurethane foams using a chemical gas-foaming process, in which CO_2 bubbles generated a porous structure, enabling effective hemorrhage control.^[167] In another strategy, Xie *et al.* developed polycaprolactone nanofiber “peanuts” via electrospinning, followed by NaBH_4 -induced gas foaming, which were then gelatin-coated and functionalized with thrombin for hemostatic applications.^[168] Alternatively, Shi *et al.* prepared starch/PEG-based sponges using surfactant-assisted stirring-induced foaming and demonstrated its hemostatic efficacy in liver volume defects and femoral artery injury models in rats.^[169] 3D printing combined with post-processing has emerged as a versatile strategy for constructing hierarchical porous hemostatic materials.^[43,170] Zhu and Wang *et al.* developed a microchanneled alkylated chitosan sponge (MACS) by integrating 3D-printed microfiber leaching, freeze-drying, and superficial alkyl modification (Fig. 8a).^[43] This approach produced a hierarchical porous architecture composed of interconnected microchannels and micropores, enabling ultra-fast shape recovery within seconds of blood absorption. In

addition, the engineered structure enhanced pro-coagulant activity and conferred resistance to blood washout under liver perforation conditions, demonstrating its potential for rapid and reliable hemorrhage control (Fig. 8b).

The ice-templating method involves freezing a polymer solution, allowing ice crystals to form within the matrix and serve as temporary templates.^[171–173] Subsequent sublimation of ice produced a highly interconnected and porous structure. Cryogels represent a typical application of this approach and have been extensively developed by Guo *et al.*^[44,174–177] For instance, they fabricated a variety of cryogels, including injectable antibacterial conductive cryogels based on carbon nanotubes and glycidyl methacrylate-functionalized quaternized chitosan,^[44] biodegradable interpenetrating polymer network dry cryogel hemostats via cryo-polymerization of gelatin and dopamine,^[178] and multifunctional cryogels designed for lethal non-compressible hemorrhage control and wound healing. Cho and Suresh *et al.* utilized natural pollen as a raw material to fabricate cryogels through compression-driven self-crosslinking.^[179] These cryogels demonstrated water-triggered shape recovery within 2 s and an effective hemostatic performance in a mouse liver penetration model. To enhance fluid transport, our group developed an anisotropic shape-memory cryogel (SALC) with oriented macroporous channels through the cryo-gelation of a tetra-PEG-SS, amino-gelatin, and lignin mixture (Fig. 8c).^[180] The resulting cryogel possessed hierarchical pore structures that conferred excellent shape recovery and mechanical resilience, enabling it to withstand repeated compression cycles. Compared to commercial gelatin sponges and XSTAT, SALC demonstrated substantially higher swelling and fluid absorption capacities, resulting in significantly improved hemostatic performance in rat femoral artery transection models. In preclinical porcine models of lethal hemorrhage,



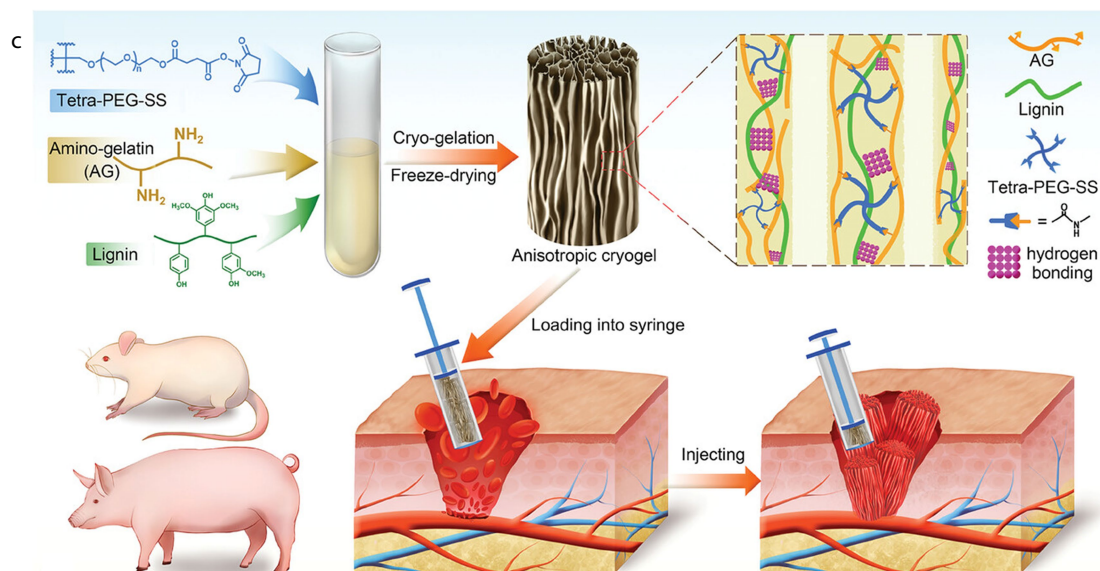


Fig. 8 Expandable hemostatic materials. (a) Fabrication of microchanneled alkylated chitosan sponges (MACS). Sacrificial poly(lactic acid) microfiber templates were 3D-printed, filled with chitosan solution, lyophilized, and the poly(lactic acid) removed, followed by grafting with hydrophobic alkyl chains. (b) Schematic illustration of the hemostatic process and representative photographs demonstrating the efficacy of MACS in a lethal pig liver perforation model. (a, b: reproduced with permission from Ref. [43]; Copyright (2021), Springer Nature.) (c) Chemical structures of tetra-PEG-SS, amino-gelatin, and lignin, and schematic illustration of SALC preparation, crosslinking, and application in non-compressible hemorrhage models in rats and pigs (Reproduced with permission from Ref. [180]; Copyright (2025), John Wiley and Sons.).

SALC provided rapid and durable tamponade in liver, femoral artery, and cardiac injuries. Beyond its hemostatic function, SALC also acted as a scaffold for tissue regeneration, facilitating cell migration and angiogenesis, while eliciting minimal inflammatory responses.

However, increasing the pore size and porosity often compromises the mechanical robustness and structural stability, limiting the ability of expandable materials to maintain effective tamponade pressure under high-flow hemorrhagic conditions. To overcome this trade-off, various reinforcement strategies have been developed to simultaneously enhance mechanical strength and rapid shape recovery while maintaining large, highly interconnected pores. By incorporating nano- and micro-fibers for reinforcement, Xie and Carlson *et al.* developed a bicomponent aerogel (NMA) composed of poly(lactic acid) (PLA) nanofibers (NFs) and poly(ϵ -caprolactone) (PCL) microfibers (MFs) (Fig. 9a).^[181] In this system, the microfiber network provided elasticity and rapid shape recovery, whereas the nanofiber network enhanced rigidity and structural integrity. The combined networks facilitated efficient stress dissipation and improved mechanical adaptability under compression. In lethal swine junctional hemorrhage models (Fig. 9b), the aerogel achieved immediate hemostasis and full survival without rebleeding. Another strategy relies on dual crosslinking combined with hierarchical porous structure. Cai and Ye *et al.* engineered ultra-highly deacetylated chitosan (DC-UDCS) aerogels by combining covalent crosslinking with ethylene glycol diglycidyl ether, reinforced hydrogen-bonded networks, and bidirectional ice-templating.^[182] This multiscale design enabled rapid fluid transport while maintaining structural integrity under wet conditions, yielding a high porosity of 88%, robust compressive strength (134 kPa), rapid stress-bearing capacity, and cationic surface

functionality that contributed to antimicrobial activity. In an alternative approach, Wei, Zhao, and Bian *et al.* developed an alkylated superporous chitosan sponge (A-spCS) using a temperature-assisted secondary network compaction strategy after phase-separation-induced primary structuring, forming a highly interconnected macroporous architecture with large pore size and high porosity (Fig. 9c).^[183] The superporous structure enabled rapid fluid absorption and shape recovery in water and blood, leading to fast actuation and high fluid absorption capacity. *In vivo* studies showed superior hemostatic performance compared with commercial gauze, gelatin sponge, and chitosan powder in rat liver perforation models, with efficacy further confirmed in porcine spleen and liver injury models (Fig. 9d).

Recently, our group reported an interconnected hierarchical macroporous sponge (IHMS) fabricated *via* a synergistic vacuum-assisted foaming strategy combined with a physically and chemically double-network structure (Fig. 10a).^[184] Air bubbles generated in a chitosan/gelatin (CS/Gel) solution were expanded under reduced pressure, and sequential immersion in a tetra-armed poly(ethylene glycol) aldehyde (tetra-PEG-CHO) ethanol solution and PBS yielded a double-network sponge comprising a chemically crosslinked network (*via* Schiff base reaction) and an entangled, ionically crosslinked chitosan network. The resulting IHMS exhibited a hierarchically interconnected macroporous architecture with robust mechanical strength, retaining over 94% of the peak stress and 92% of the strain after 100 compression cycles at 80% strain. It also displayed exceptional liquid uptake (7279% in water, 6870% in PBS, and 6280% in anticoagulated whole blood), far exceeding that of commercial sponges, including poly(vinyl alcohol), poly(vinyl formal), chitosan, gelatin sponge, and XSTAT. In preclinical studies, IHMS achieved

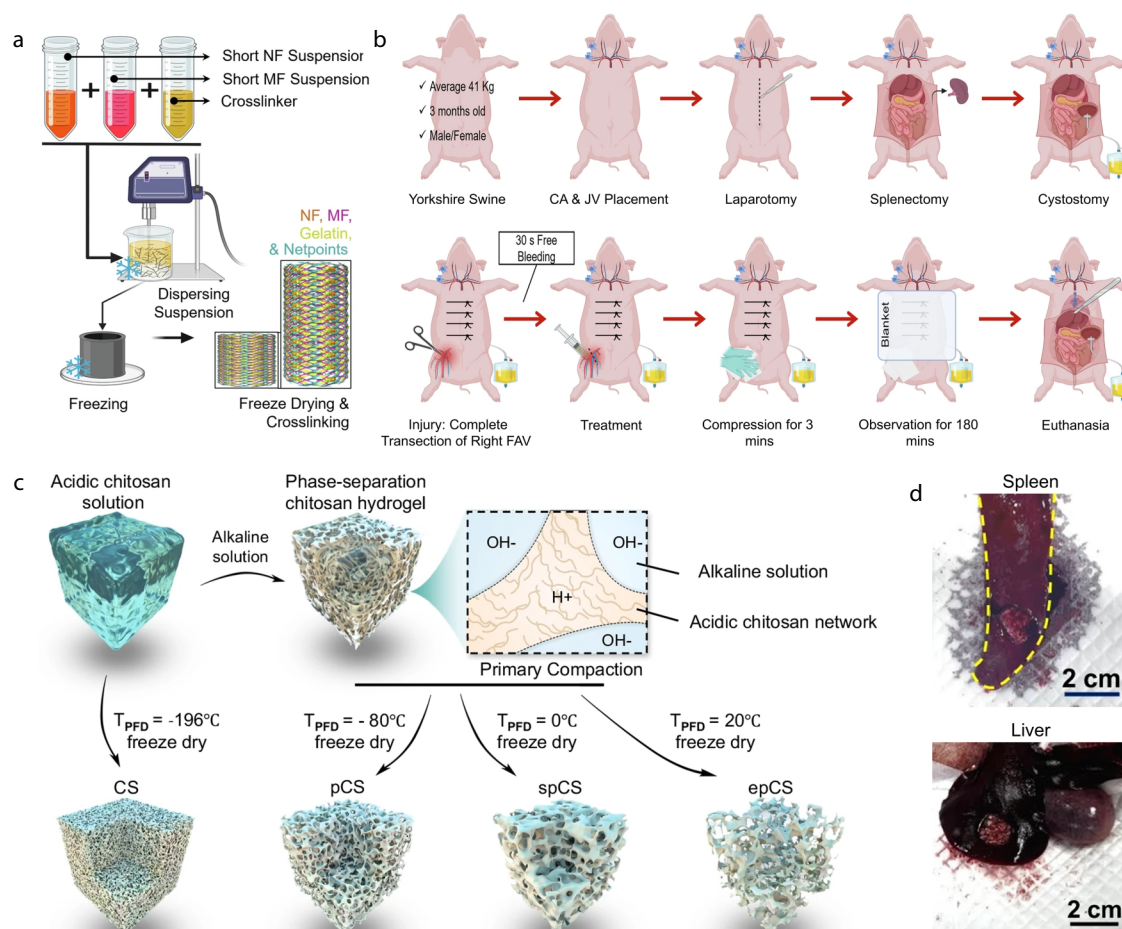


Fig. 9 (a) Schematic of NMA fabrication by freeze-casting a suspension of NFs and MFs with gelatin as a crosslinker, followed by glutaraldehyde vapor crosslinking and mold removal; (b) Schematic of a lethal porcine femoral artery and vein complete dissection model and treatment using injectable NMA. (a, b: reproduced with permission from Ref. [181]; Copyright (2025), Springer Nature.) (c) Fabrication of sponges by the temperature-assisted secondary network compaction strategy. The chitosan solution underwent phase separation, pre-freezing, and freeze-drying to produce CS sponges. (d) Hemostatic performance of A-spCS in pig liver and spleen perforation models. (c, d: reproduced with permission from Ref. [183]; Copyright (2024), Springer Nature.)

rapid and effective hemostasis, outperforming commercial products in rat liver perforation and femoral artery transection models. In lethal porcine hemorrhage models, it provided durable tamponade under normal and anticoagulated conditions and was easily removed after hemostasis (Fig. 10b). Importantly, its efficacy was further validated in junctional gunshot wound models, where miniaturized IHMS delivered through an approximately 2 cm exit wound achieved hemostasis within 20 s without external compression, limiting blood loss to less than 4 g (Fig. 10c). These results demonstrate that the synergistic integration of interconnected hierarchical macroporosity and double-network reinforcement simultaneously promotes rapid fluid absorption, shape recovery, mechanical resilience, and effective tamponade, offering a promising strategy for enhancing expandable hemostatic materials.

5 CONCLUSIONS AND PROSPECTS

Injectable polymeric hemostats represent a promising strategy for the management of non-compressible hemorrhage, which

remains a major cause of preventable trauma-related mortality. Their minimally invasive delivery and inherent conformability to complex wound geometries enable rapid control of bleeding, even under high-flow or coagulopathic conditions. This review systematically summarizes recent advances in three major classes of injectable polymeric hemostats for deep and narrow hemorrhages, including *in situ*-forming hydrogels, gelable powdered systems, and expandable materials, each exhibiting distinct functional mechanisms and deployment characteristics. Across these systems, current design strategies converge on a few fundamental engineering principles, including interfacial adhesion enhancement through covalent and multivalent interactions, mechanical reinforcement *via* double-network and fibrous architectures, and highly interconnected porous structures for enhanced fluid uptake and promotion of coagulation. By effectively leveraging and optimizing these design strategies, researchers have successfully developed numerous injectable polymer-based hemostats that demonstrate promising performance in preclinical models and often exhibit superior performance compared with commercial products in lethal hemorrhage animal models.

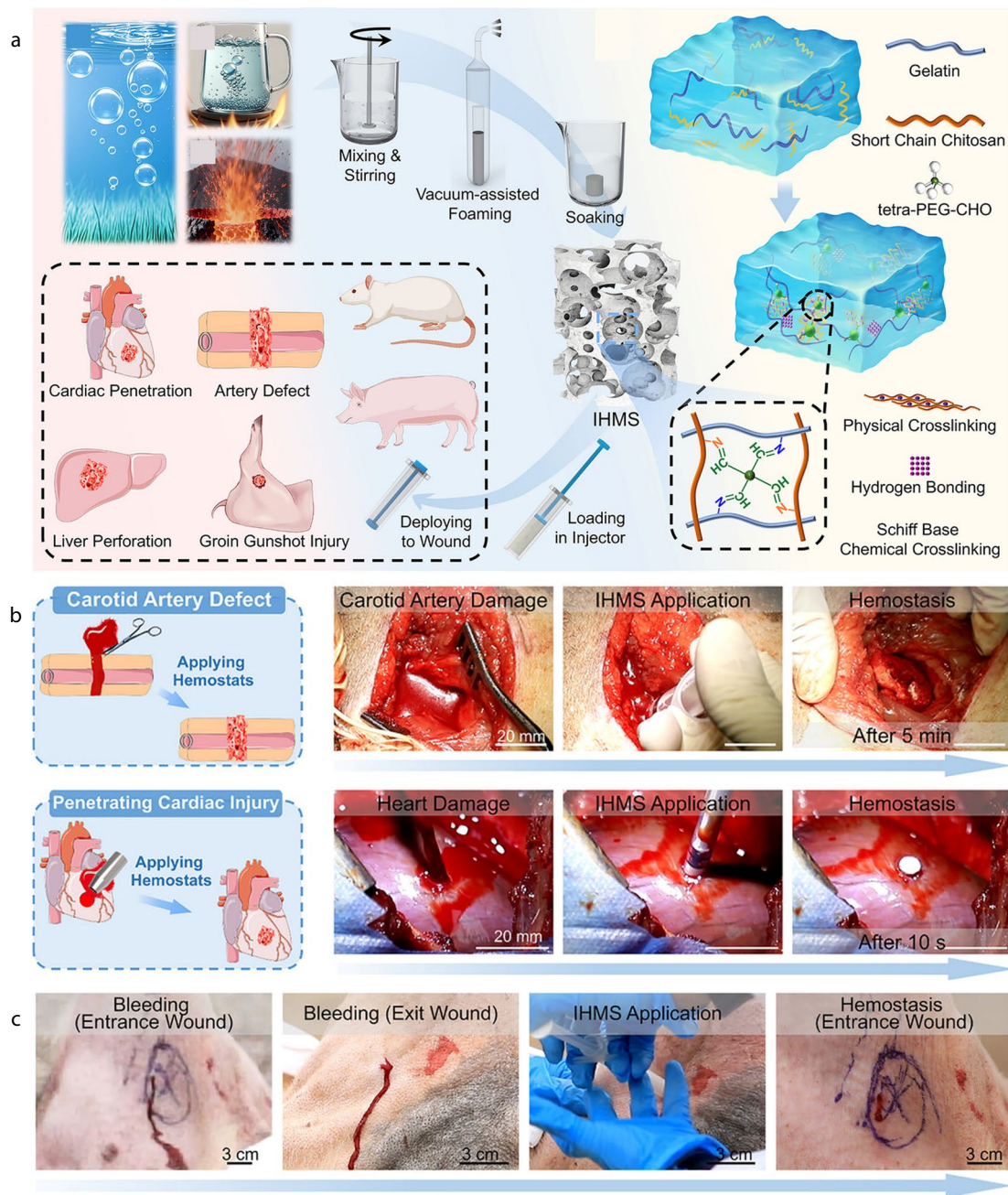


Fig. 10 (a) Schematic of bubble evolution in representative systems; IHMS fabrication, hierarchical porous structure, and formation of chemical and physical crosslinked networks; application of IHMS in non-compressible hemorrhage models in rats and pigs; (b) Schematic and representative photographs of bleeding and hemostasis in porcine heparinized carotid artery incision and cardiac penetrating injury models treated with IHMS; (c) Representative photographs of a pig gunshot wound and subsequent hemostasis achieved by IHMS. (Reproduced with permission from Ref. [184]; Copyright (2026), John Wiley and Sons.)

Despite these advances, most newly developed injectable polymeric systems remain at the preclinical proof-of-concept stage and several fundamental limitations continue to hinder their clinical translation. For instance, photo-crosslinkable hydrogels typically require ultraviolet irradiation and initiators, which restrict their applicability in prehospital settings and raise safety concerns. Similarly, nanomaterial-based reinforcements, such as graphene oxide and carbon nanotubes, can improve mechanical performance but remain associated with

concerns regarding biodegradation kinetics, biodistribution, and long-term inflammatory responses. Furthermore, interfacial adhesion and gelation strategies based on non-covalent interactions enable rapid, on-demand formation of adhesive or gel networks. However, their weak and reversible nature renders them highly susceptible to physiological fluctuations. Dynamic wound environments with variations in pH, ionic strength, and oxidative conditions can disrupt physical crosslinking networks, thereby compromising both the inter-

facial adhesion stability and bulk gel network integrity, ultimately reducing the *in vivo* durability. Moreover, catechol-based chemistries that are widely used for wet adhesion often require oxidative activation under external redox conditions (e.g., Fe^{3+} , H_2O_2 , and periodate), increasing system complexity and raising concerns regarding biocompatibility. Excessive oxidation may further impair the adhesive performance and long-term stability. Although polyphenol-based systems provide strong initial wet adhesion, their clinical translation should consider potential dose-dependent cytotoxicity. More broadly, strong wet adhesion in wet environments may raise general clinical concerns such as off-target tissue interactions and postoperative adhesion formation. Meanwhile, in gelable powdered systems, the powder-to-gel transition is often accompanied by structural densification, representing a key design limitation that reduces fluid uptake capacity and compromises sustained hemostatic efficacy under high-flow bleeding conditions. In addition, the mechanical properties of the resulting hydrogels are frequently not systematically characterized, limiting the reliable assessment of their functional performance. Additionally, expandable materials often rely on multistep fabrication processes to construct interconnected macroporous structures, which increases the manufacturing complexity and limits scalability and reproducibility.

The optimal selection of injectable polymeric hemostats depends on the injury characteristics, anatomical constraints, deployment scenarios, material residence behavior, and potential post-treatment complications. Injectable hydrogels are well-suited for non-compressible hemorrhage at anatomically complex sites, including vascular injuries, solid organ injuries, and irregular tissue defects requiring conformal sealing and strong tissue adhesion. However, their clinical use in prehospital or battlefield environments remains limited by the need for multi-component mixing and precise delivery, as well as precursor washout under high-flow bleeding prior to complete gelation, reducing efficacy in diffuse hemorrhage, large cavities, or deep penetrating injuries. Gelable powdered systems are attractive for emergency and prehospital applications in irregular, poorly accessible wounds with diffuse hemorrhage, without requiring precise visualization of the bleeding source. However, their particulate nature introduces safety concerns, including particle migration, distal embolization, and thrombosis, particularly in high-pressure vascular injuries or compromised vessel integrity. Expandable materials are uniquely suited for deep or narrow-entry penetrating wound tracts, such as gunshot and stab injuries or junctional hemorrhages commonly encountered in military trauma. However, prolonged implantation may lead to compression-related complications, including tissue ischemia, nerve injury, and impaired organ function, highlighting the importance of defining an appropriate and safe dwell time to minimize secondary injury.

Looking forward, the development of next-generation injectable hemostatic materials will require a transition from isolated material optimization toward integrated, scenario-oriented design principles. This shift necessitates close interdisciplinary collaboration among materials scientists, clinicians, trauma surgeons, and emergency care providers to

align material properties with real-world clinical requirements. Future systems should not only prioritize rapid and reliable hemostasis but also emphasize operational simplicity, user-independent deployment, and robust performance under austere conditions, while ensuring safe biodegradation or removal after bleeding control. However, the increasing complexity of the material design space, involving multiscale structure-property relationships and competing performance requirements, challenges traditional empirical optimization approaches. Artificial intelligence (AI)-driven approaches, particularly machine learning and deep learning techniques, have demonstrated substantial success in biomedical engineering.^[185–188] These advances provide a strong foundation for their application in hemostatic material design by enabling rational engineering of adhesive chemistries, physicochemical properties, porous architectures, and structure-property relationships. Recent studies have validated machine-learning-based strategies in bioadhesives and hydrogels, highlighting their growing role in the design and optimization of high-performance hemostatic materials.^[189–191] Concurrently, the development of multifunctional hemostatic materials (e.g., antibacterial, anti-inflammatory, antioxidant, and pro-angiogenic functions) represents a shift from simple bleeding control toward systems that promote wound healing and functional tissue regeneration.^[46,47,192–194]

From a translational perspective, the development of injectable polymeric hemostats is governed by a multi-level constraint system spanning material safety, preclinical evaluation, and clinical implementation. At the material level, biosafety remains the primary prerequisite for clinical translation, given the direct interaction of these systems with blood and surrounding tissues. Accordingly, biocompatibility must be ensured by minimizing cytotoxicity, hemolysis, immunogenicity, and adverse responses associated with degradation products, while carefully controlling degradation kinetics to avoid long-term inflammatory or toxic effects. In addition to intrinsic biosafety considerations, injectable hydrogels must achieve effective sealing while controlling swelling to preserve mechanical stability and minimize local tissue compression in confined anatomical spaces. Gelable powdered systems require optimized particle size distributions to reduce the risk of systemic embolization and distal thrombosis. Expandable materials should exhibit predictable expansion behavior and allow safe and straightforward removal, while also requiring long-term *in vivo* validation to assess potential complications, such as tissue compression, nerve injury, or foreign body responses.

At the preclinical level, substantial heterogeneity in material characterization and experimental design significantly limits cross-study comparability. This variability is reflected in the inconsistent evaluation of key physicochemical parameters, including gelation time, mechanical strength, tissue adhesion, burst pressure, expansion behavior, fluid absorption, and pro-coagulant activity. Although the American Society for Testing and Materials (ASTM) and International Organization for Standardization (ISO) guidelines provide established reference standards for material evaluation, their adoption in current research remains limited. Most reports still rely on non-uniform or self-defined testing protocols, reducing the

reliability of cross-study benchmarking and hindering systematic comparisons between different hemostatic systems. Similar variability is also evident in *in vivo* studies, in which animal models vary substantially in species selection (mice, rats, rabbits, dogs, and pigs), wound geometry (linear incisions, partial organ resections, penetrating wounds, large-volume liver or spleen defects, cardiac puncture, and arterial transection or laceration), anticoagulation status, and surgical protocols. These inconsistencies introduce substantial uncertainty in outcome interpretation and significantly hinder objective comparison of hemostatic performance across different materials. In addition, most studies have focused primarily on acute bleeding control, while long-term outcomes, such as survival rates, complications, tissue regeneration, functional recovery, and systemic responses have rarely been systematically evaluated. Therefore, more standardized and clinically relevant evaluation protocols are required to enable robust benchmarking and to support the rational development of injectable polymeric hemostats.

Finally, clinical translation of injectable polymeric hemostats is constrained by a combination of technical, manufacturing, and regulatory factors.^[195–198] Reliable clinical performance depends on standardized administration protocols and delivery systems that enable accurate placement in deep or narrow wounds under minimally invasive conditions. Stability during storage under diverse environmental conditions is also essential to preserve functional integrity, particularly for emergency and battlefield deployment. In addition, scalable and cost-effective manufacturing under Good Manufacturing Practice (GMP) is required to ensure reproducibility, batch-to-batch consistency, and broad accessibility. From a regulatory perspective, approval requires rigorous evaluation of material quality, hemostatic efficacy, and safety, including biocompatibility and degradation behavior. Clinical translation further depends on practical usability, such as ease of application, rapid deployment, and compatibility with existing clinical workflows in emergency and military settings.

In conclusion, injectable polymeric hemostats have demonstrated strong potential in the management of non-compressible hemorrhage through advances in material design and hemostatic mechanisms. Continued progress in material innovation, standardized evaluation protocols, and translational validation will be essential for accelerating clinical translation.

BIOGRAPHIES

De-Cheng Wu received his Ph.D. degree from the National University of Singapore (NUS) in 2006. From 2005 to 2010, he worked at the Institute of Materials Research and Engineering (IMRE), A*STAR, Singapore, as a research engineer. He joined the Institute of Chemistry, Chinese Academy of Sciences (ICCAS) as a professor in 2011. He has been a Professor at the University of Chinese Academy of Sciences (UCAS) since 2015 and a Chair Professor in the Department of Biomedical Engineering at the Southern University of Science and Technology (SUSTech) since 2019. Prof. Wu received the National Science Fund for Distinguished Young Scholars in 2017, the Innovative Talent Promotion Plan of the Ministry of Science and Technology in 2018, and the National Special Support Program for High-level Personnel

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Chong Zhang received his Ph.D. degree from the University of Science and Technology of China (USTC) in 2016. He joined the Department of Biomedical Engineering at the Southern University of Science and Technology (SUSTech) in 2021 and was appointed as a Research Associate Professor in 2025. He conducted postdoctoral research at Peking University with Prof. Hua Lu and at The University of Tokyo with Prof. Takashi Kato. He is now working on high-performance biomedical dressings.

Conflict of Interests

The authors declare no interest conflict.

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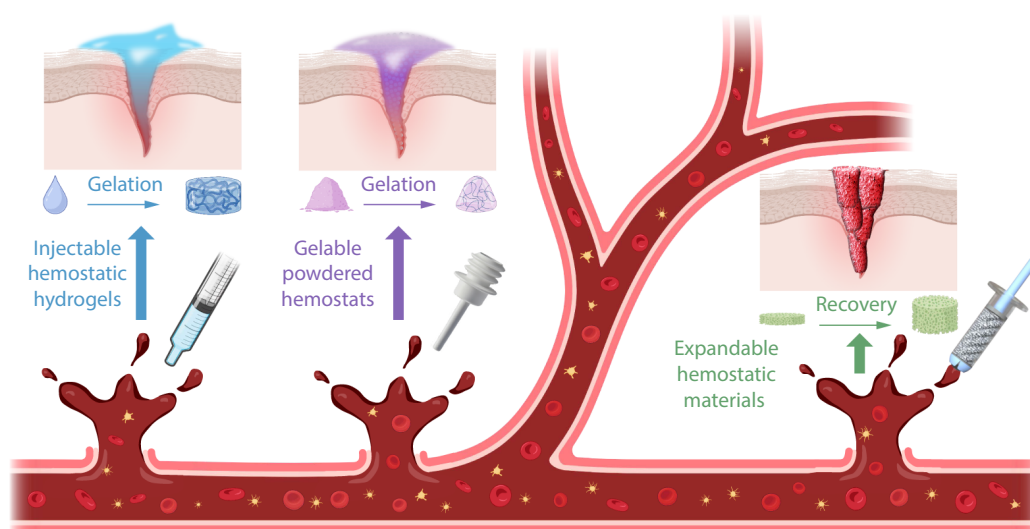
Graphical Abstract

Injectable Polymeric Hemostats for Non-compressible Hemorrhage Control

Zheng Pan, Gang He, De-Cheng Wu, and Chong Zhang

Southern University of Science and Technology

This review summarizes recent advances in injectable polymeric hemostats for non-compressible hemorrhage, including hydrogels, gelable powders, and expandable materials, highlighting material design, hemostatic mechanisms, performance characteristics, and remaining challenges.



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