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"Double-sided protector" Janus hydrogels for skin and mucosal wound repair: applications, mechanisms, and prospects

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Abstract

Skin and mucous membranes serve as crucial barrier tissues within the human body. Defective wound healing not only inflicts pain but also heightens the risk of infection and impairs immune function. Janus hydrogels possess two-sided distinct asymmetric structures that endow them with diverse properties such as high water absorbency, flexibility, anti-adhesion ability etc. These hydrogels also exhibit great potential in biofluid transport, drug delivery and promoting tissue repair. Currently, research efforts predominantly concentrate on the preparation techniques, properties, and biomedical applications. This review summarized its structural characteristics and different forms of designations, and focused on the possible mechanisms, the existing problems and improvement strategies for the skin and mucous tissues wound, aiming to provide new design ideas for repairing complex skin and mucous membrane tissue defects.

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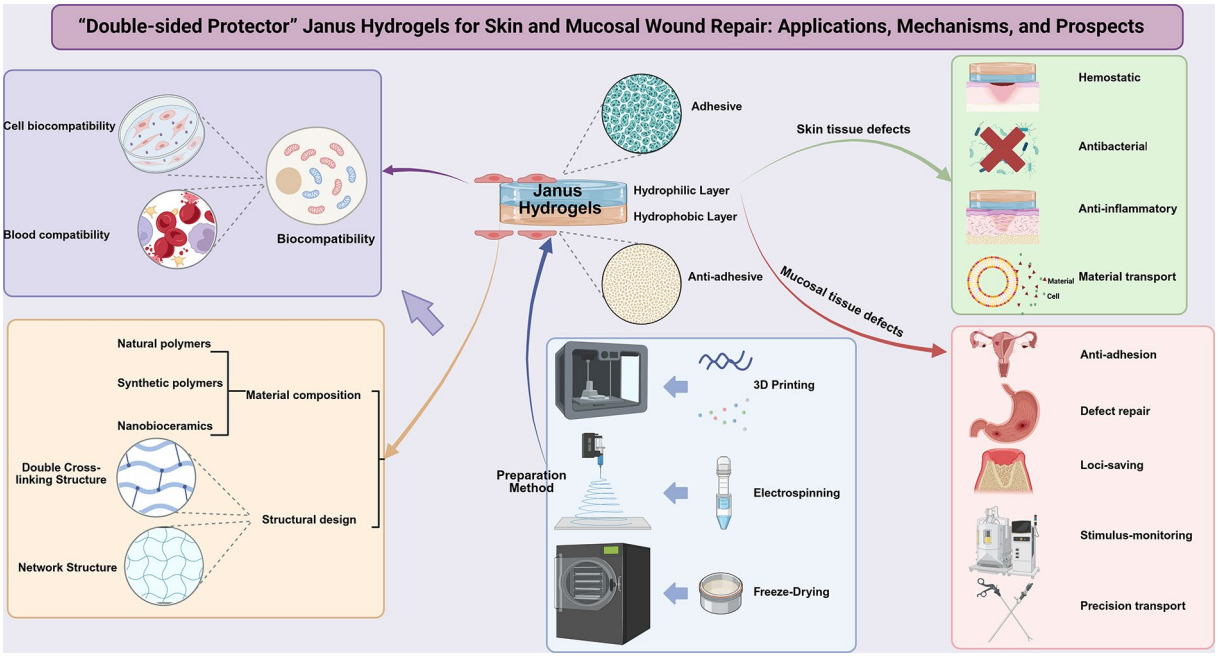
Graphical abstract



Keywords Janus hydrogels, Skin and mucosal repair, Biomedical applications, Tissue engineering, Regenerative medicine

Background

The skin and mucosa function as two critically important barrier tissues within the human body, each possessing distinct physiological architectures. The skin, which consists of the epidermis, dermis, and subcutaneous tissue, undergoes a sequential series of processes including hemostasis, inflammation, proliferation, and remodeling during the wound-healing phase [1]. Mucosa, covering internal cavity surfaces, features a thin structure without a stratum corneum, emphasizing rapid damage response, moisture maintenance, and microorganism defense [2]. Thus, designing mucosal tissue materials requires wet adhesion at humid tissue interfaces.

To mimic the hierarchical structure of natural skin and integrate multiple functions, recent advancements have focused on bilayer or multi-layered hydrogel [3, 4]. Inspired by the ancient roman double-sided protector, Janus hydrogels, are characterized by unique asymmetric structures, combine extracellular matrix-mimicking properties with superior water absorption, flexibility, and anti-adhesive capabilities. Compared with the uniform adhesion of traditional hydrogels [5, 6], Janus hydrogels exhibit two-sided and distinct asymmetric structures, endowing them with a diverse array of properties including hemostasis, anti-inflammatory and drug delivery etc. (Fig. 1).This hydrogel can simultaneously exhibit the characteristics of being hydrophilic on one side and hydrophobic on the other, or being adhesive on one side and non-adhesive on the other [7, 8]. Similar to human skin and mucosa, the two sides of this hydrogel have different chemical compositions and physical properties. One side can form a protective barrier between the wound and its surroundings, which solves the problem of adhesion of traditional hydrogels to contaminants on the non-skin/mucosal contact surfaces and self-adhesion due to two-sided adhesiveness. The other side firmly adheres to the tissue interface and promotes healing of the defective tissue [9, 10] (Fig. 2). Moreover, its asymmetric structure enables precise regulation of biological interactions, facilitating functions like targeted drug delivery, microenvironment modulation, and synergistic promotion of tissue regeneration. Such unique structural advantages and functional versatility make the Janus hydrogel a groundbreaking advancement in skin and mucosal tissue defect repair, offering transformative solutions for biomedical applications and significantly pushing the boundaries of tissue engineering material research [11–13]. This review breaks through the universal framework of traditional Janus hydrogel reviews in the field of "hydrogel materials for nanobiotechnology" by systematically focusing on the specific needs of skin and mucosal repair for the first time. This paper deeply analyzes the multi-scale

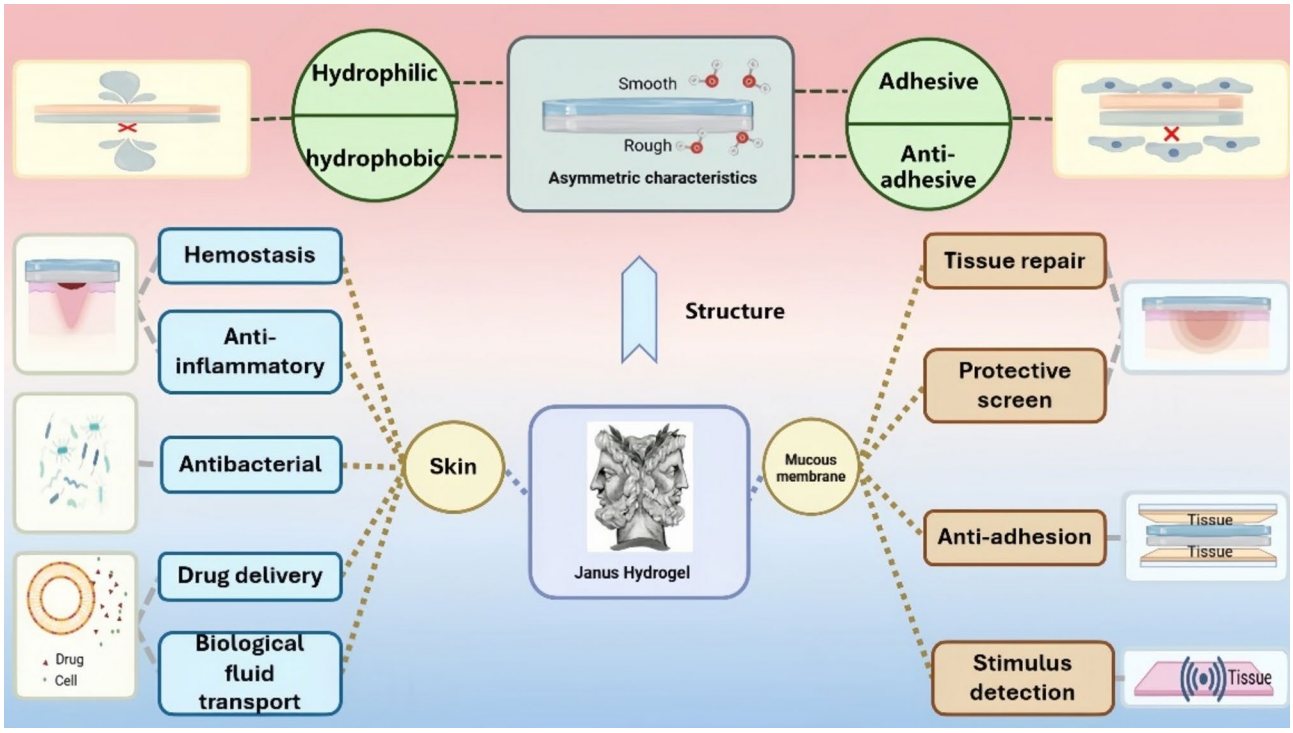


Fig. 1 Structural and functional architecture of Janus hydrogels

structure-function relationships, revealing the molecular mechanisms by which Janus hydrogels solve core challenges in mucosal repair through interfacial functional separation. Furthermore, this review innovatively integrates clinically translational systematic research, demonstrating therapeutic potentials in complex diseases such as myocardial infarction and diabetic foot ulcers through real clinical trial data, while proposing intelligent solutions to provide new paradigms for personalized medicine. It also clearly identifies critical challenges such as long-term stability and large-scale production, providing solutions and advocates interdisciplinary research to advance Janus hydrogels toward "smart responsive" biomaterials. Currently, research on Janus hydrogels mainly centers on their preparation methods, properties, and biomedical applications.

Preparation and design strategies for Janus hydrogels

The methods of preparation of Janus hydrogels include three-dimensional (3D) printing [14, 15], freeze-drying [15], electrostatic spinning [16, 17], and layer-by-layer assembly [18].

3D printing

In the 3D printing method, the precise construction of hydrogels with asymmetric structure and functional complexity is achieved mainly by combining photopolymerization and dark polymerization techniques, dual-network structure design, and special ink formulations [14, 15]. Photopolymerization uses UV-sensitive monomers (e.g., Poly (ethylene glycol) diacrylate (PEGDA)) to form crosslinked networks, while dark polymerization with polydopamine (PDA) introduces catechol moieties for adhesion and antioxidation. This combination creates gradient mechanical properties (Young's modulus: 0.8–1.5 MPa) and pH-responsive drug release, enabling sustained delivery in inflamed tissues (pH 6.5-7.0). Beyond traditional 3D printing, recent advancements in four-dimensional (4D) printing techniques have introduced dynamic capabilities for fabricating stimuli-responsive Janus hydrogels. This innovative approach combines smart materials-such as shape memory polymers and responsive hydrogels-with additive manufacturing to enable programmed structural transformations over time [19]. This innovation enhances wound conformity and on-demand drug release. The Janus hydrogel can exhibit anisotropic swelling at 37 ℃to adapt to wound geometry while maintaining its mechanical integrity.

Freeze-drying

In the freeze-drying method, a pre-gel is formed from the blending of two or more polymers followed by freeze-drying to remove the water and enhance its structural stability. This process may involve an ionic cross-linking step to build an ionic network between the polymers to enhance the mechanical strength and stability of the

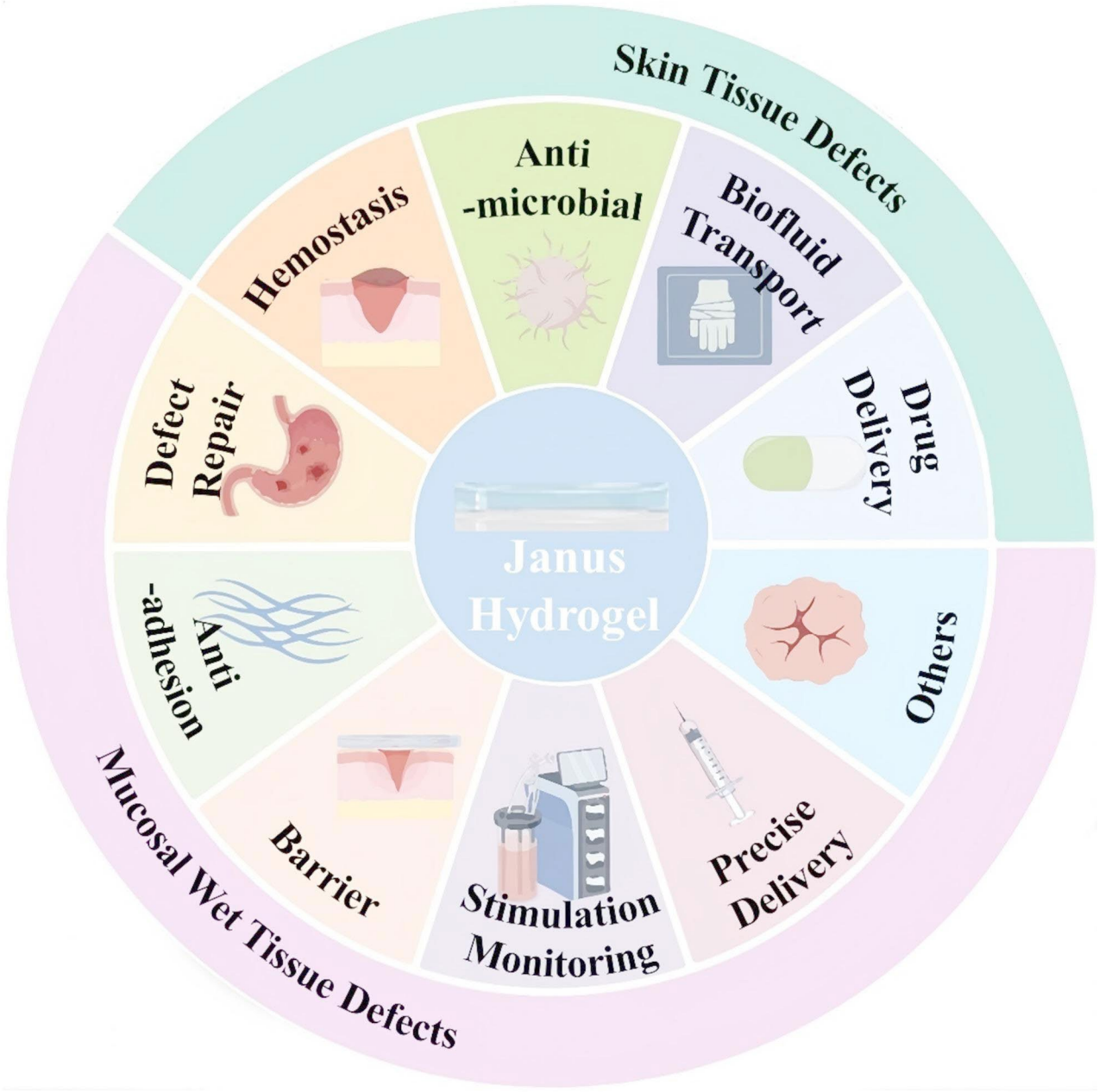


Fig. 2 Applications of Janus hydrogels

hydrogel. Ionic Crosslinking creates stable networks with tunable degradation rates (half-life: 7–14 days). Freeze-dried Janus hydrogels can demonstrate pH-responsive swelling, optimizing drug release profiles. By alternating impregnation in different solutions, different chemical components are introduced to impart different chemical and physical properties (e.g., antimicrobial gradients) to both sides of the hydrogel. Finally, unreacted chemicals or additives are removed by dialysis to obtain Janus hydrogels with specific functionalities [12].

Electrostatic spinning

In the electrostatic spinning method, Janus fibers with specific structures and functionalities are formed using electrostatic spinning technology whereby spinning liquids containing two or more polymer solutions with different properties are passed through a microfluidic device to form Janus hydrogels with anisotropic wettability or other properties [16, 17]. This design reduces bacterial colonization (adhesion: <200 cells/cm^2) by minimizing moisture retention. Recent advancements in

electrospinning technology have focused on constructing hierarchical structures such as core-shell and multilayer composites. Coaxial electrospinning enables spatial functional separation: Pluronic F127-Mupirocin/ Pectin-Keratin (F127-Mup/Pec-Kr) core-shell nanofibers [20] achieve sustained antibiotic release via a Pluronic core while enhancing cell adhesion through a keratin-pectin shell. Similarly, Polycaprolactone (PCL)/Kr/Platelet-rich fibrin (PRF) multi-layer systems [21] integrate PRF into nanofibers, accelerating wound closure and collagen deposition through localized platelet-derived growth factor (PDGF) release. Gradient electrospinning creates Janus membranes with gradient wettability, achieving unidirectional fluid transport that is critical for exudate management and anti-adhesion properties [22]. Kazemi et al. [23]expanded this approach by incorporating L-arginine into polyacrylamide/(aloe vera-keratin) core-shell fibers, promoting angiogenesis through pH-responsive nitric oxide release. Multi-layer composite Polyvinyl Alcohol (PVA)/chitosan (CS) bilayer nanofibers [24]enhance mechanical strength (12.5 MPa) and moisture permeability (2800 g/m^2/24 h), effectively addressing chronic wound challenges. These innovations highlight electrospinning's versatility in the controlled-release of drugs, biofunctional modulation, and gradient functional design. These strategies allow precise control of the composition and structure of the hydrogel and improve properties such as biocompatibility, bioactivity and stimulus responsiveness of the material. Consequently, the preparation and design of Janus hydrogels show considerable superiority in terms of multifunctional integration, interfacial activity, and innovative design.

In summary, when comparing these three methods (Table 1): 3D printing can precisely fabricate complex asymmetric structures with high reproducibility. However, the equipment cost is extremely high [25]. The total price of a professional 3D printer and its supporting photopolymerization system can reach around $300,000. The material cost for each experiment, such as PEGDA/PDA inks, is relatively high, ranging from $10 to $50 per milliliter. In laboratory-scale settings, the single-batch preparation volume of Janus hydrogels ranges from tens to hundreds of cubic centimeters. While demonstrating scalability at the lab level, industrialization requires an investment of at least $5 million for specialized equipment and production line modifications, potentially increasing costs by several to dozens of times compared to laboratory-scale production. Freeze-drying for preparing Janus hydrogels has a relatively low cost [26]. A set of freeze-drying equipment costs approximately $10,000-$50,000. The material cost for each experiment ranges from tens to hundreds of dollars. The energy consumption cost per experiment is about $50-$200, and the labor cost per experiment is approximately $100-$300 (calculated based on 3–5 h per experiment at a rate of $30-$60 per hour). Compared to the simple material cost, the total cost increases by approximately 100-200%. In terms of scalability, through automated upgrades, the single-batch production scale can be expanded to around 100–500 L. However, since this process involves multiple steps and requires manual intervention, the batch-to-batch variability may increase as the production scale expands, which affects the reproducibility to some extent. The equipment cost of electrospinning is generally between $20,000-$100,000 [27]. The material cost per experiment is approximately $100-$500, which is about 50-150% higher than that of freeze-drying. In terms of scalability, the length of fibers that can be prepared in a laboratory setting is usually between several tens to hundreds of meters per run. However, during large-scale production, due to the complexity of the equipment and the variability of biological materials, there are challenges in increasing production volume, and the equipment maintenance cost is high. For every additional 100 m of production scale, the equipment maintenance cost increases by approximately $500-$1000. The increase in production volume during large-scale production may only be 5–10 times. During the transition from laboratory to industrial production, electrospinning has relatively limited production volume growth, and cost control is difficult.

The main design strategies for Janus hydrogels are interfacial self-assembly [28], layer-by-layer stacking [29], and asymmetric chemical modification [30] (Fig. 3). Interfacial self-assembly is the spontaneous formation of ordered structures at the interface using intermolecular interactions. This interfacial self-assembly behavior is mainly influenced by its anisotropic structure and chemical composition, which not only enhance the functional diversity of the material, but also provide more precise microenvironmental regulation for the cell. This enhancement helps achieve multiple functions such as catalysis and drug release in a single material, thus improving the efficiency and selectivity of the material in specific applications. This has potential applications in areas such as drug delivery, catalyst carriers, and tissue engineering (Fig. 3A) [28]. Layer-by-layer stacking is a technique for building multilayer structures by depositing alternating layers of different materials on the surface of a substrate. Using this technique, Janus particles can be deposited layer by layer on the surface of fibers or other substrates to obtain composites with specific functions (Fig. 3B) [29]. The advantage of this method is the ability to precisely control the material composition and thickness of each layer, thus allowing for a more diverse and customized design of Janus hydrogels by enabling, the composition and structure of the material to be adapted to specific needs. Asymmetrization modification (Fig. 3C) involves specific chemical modifications on one

Table 1 Summary of hydrogel Preparation methods and their features

Preparation Method	Hydrogel Name	Materials or Formulas	Functional Advantages	Existing Deficiencies	References
3D Printing	PEGDA/PDA Composite Hydrogel	Photopolymerization, dark polymerization, dual-network design, special inks	Precise asymmetric structure, complex functions (sonodynamic bactericidal, wound healing)	High equipment and technical requirements, high cost	[14]
	PCL/CS Composite Membrane	Polycaprolactone (PCL)/chitosan (CS) hybrid ink	Antibacterial and hemostatic Janus membrane with physical barrier and biocompatibility properties	Time-consuming multi-step process (printing + freeze-drying)	[15]
	PEGDA-PDA Gradient Hydrogel	Polyethylene glycol diacrylate (PEGDA) and polydopamine (PDA)	Unidirectional drug delivery, avoiding reverse diffusion and drug leakage	Specific light source for photopolymerization, limited materials	[31]
	CS-PAA Double-Crosslinked Hydrogel	Chitosan (CS) and polyacrylamide (PAA), double-crosslinked	Excellent biocompatibility, reducing fibrous encapsulation and inflammatory responses	Increased process complexity due to double-crosslinking steps	[40]
	PLA-Hydrogel Microfiber Composite	Polylactic acid (PLA) and hydrogel microfibers, hierarchical spinning	Anisotropic wettability, exudate management, moist wound	Complex hierarchical spinning equipment and high operational difficulty	[49]
Freeze-drying	Chitosan-Alginate-Gelatin Composite Hydrogel	Chitosan/alginate/gelatin, ionic crosslinking (Ca^{2+}), alternate immersion (polydopamine/silver nanoparticles)	Asymmetric hydrophilic/hydrophobic, mechanical strength, antimicrobial	Laborious alternate immersion steps requiring multiple dialysis purifications	[12]
	PCL/CS Composite Scaffold	Polycaprolactone (PCL)/chitosan (CS) hybrid materials	Structural stability, antimicrobial, hemostatic	Increasing material brittleness	[15]
	PLA-PVA Composite Fiber Membrane	Polylactic acid (PLA) and polyvinyl alcohol (PVA)	Porous, breathable, moist wound	Fiber structural collapse	[49]
	PAA-PU Composite Hydrogel	PAA-PU hydrogel using polyacrylic acid (PAA) and polyurethane (PU)	Rapid hemostasis with excellent biocompatibility	Non-uniform Janus hydrogel dispersion affects performance	[63]
	GT-PEG Tissue Patch	Gelatin (GT) and polyethylene glycol (PEG)	Dual adhesive/anti-adhesive functions, wound closure and reduce postoperative adhesions	Gelatin degradation shortens material lifespan	[65]
Electrospinning	F127-Mup/Pec-Kr Core-Shell Fibers	Pluronic F127/Pec-Kr loaded with mupirocin (Mup)	Sustained antibiotic release (core layer) and cell adhesion promotion (shell layer)	Coaxial spinning needle blockages reduce production efficiency	[16]
	PCL/CS Amphiphilic Fiber Membrane	Polycaprolactone (PCL) and chitosan (CS)	Unidirectional wound exudate drainage and bacterial adhesion inhibition	Limited solvent choices for simultaneous PCL/CS dissolution	[17]
	PCL/Kr/PRF Multilayer Fibers	PCL/Kr/PRF loaded with platelet-derived growth factor (PDGF)	Accelerates wound closure, collagen deposition, and angiogenesis	PRF extraction requires fresh blood, limiting availability	[21]
	PAA-Aloe-Kr Gradient Membrane	PAA and aloe-keratin (Aloe-Kr)	Unidirectional biofluid transport, moist wound environment	Multi-channel synchronization, increasing operational complexity	[22]
	PCL/CS-L-Arginine Fibers	Polycaprolactone (PCL) and chitosan (CS)	pH-responsive nitric oxide (NO), angiogenesis	Difficulty precisely controlling L-arginine loading amount	[23]
	PVA/CS-AgNP Bilayer Fibers	Polyvinyl alcohol (PVA)/chitosan (CS), silver nanoparticles (AgNPs)	High mechanical strength, moisture permeability, antimicrobial properties	AgNPs aggregation reduces antibacterial efficacy	[24]

Table 1 (continued)

Preparation Method	Hydrogel Name	Materials or Formulas	Functional Advantages	Existing Deficiencies	References
Layer-by-layer assembly	CMCS-Ag/PCL Janus Nanofiber Scaffold	Carboxymethyl chitosan/nanosilver (CMCS-Ag) and polycaprolactone (PCL)	Unidirectional biofluid transport, antibacterial properties for wound healing	Efficiency decreases with increasing layers, high operational complexity	[18]
	SiO_2/Au Janus Particles	SiO_2/Au, deposition, self-assembly and chemical modification	Controllable asymmetric wettability, adsorption for catalysis and drug delivery	Efficiency decreases with increasing layers, high operational complexity	[28]
	CNT-PDMS Photothermal Fabric	Carbon nanotube (CNT), polydimethylsiloxane (PDMS)	High photothermal conversion, textile thermal management	Poor CNT dispersion	[29]
	APTES/SH-Modified Janus Particles	Janus particles (APTES/SH), chemical modification	Asymmetric interfacial behavior control	Strict pH and temperature control	[30]
	QAS-SiO_2 Polyurethane Patch	Polyurethane (PU), quaternary ammonium salts (QAS) and hydrophobes (SiO_2)	Inhibit bacterial colonization, promote wound healing	Difficulty controlling QAS release rates	[72]

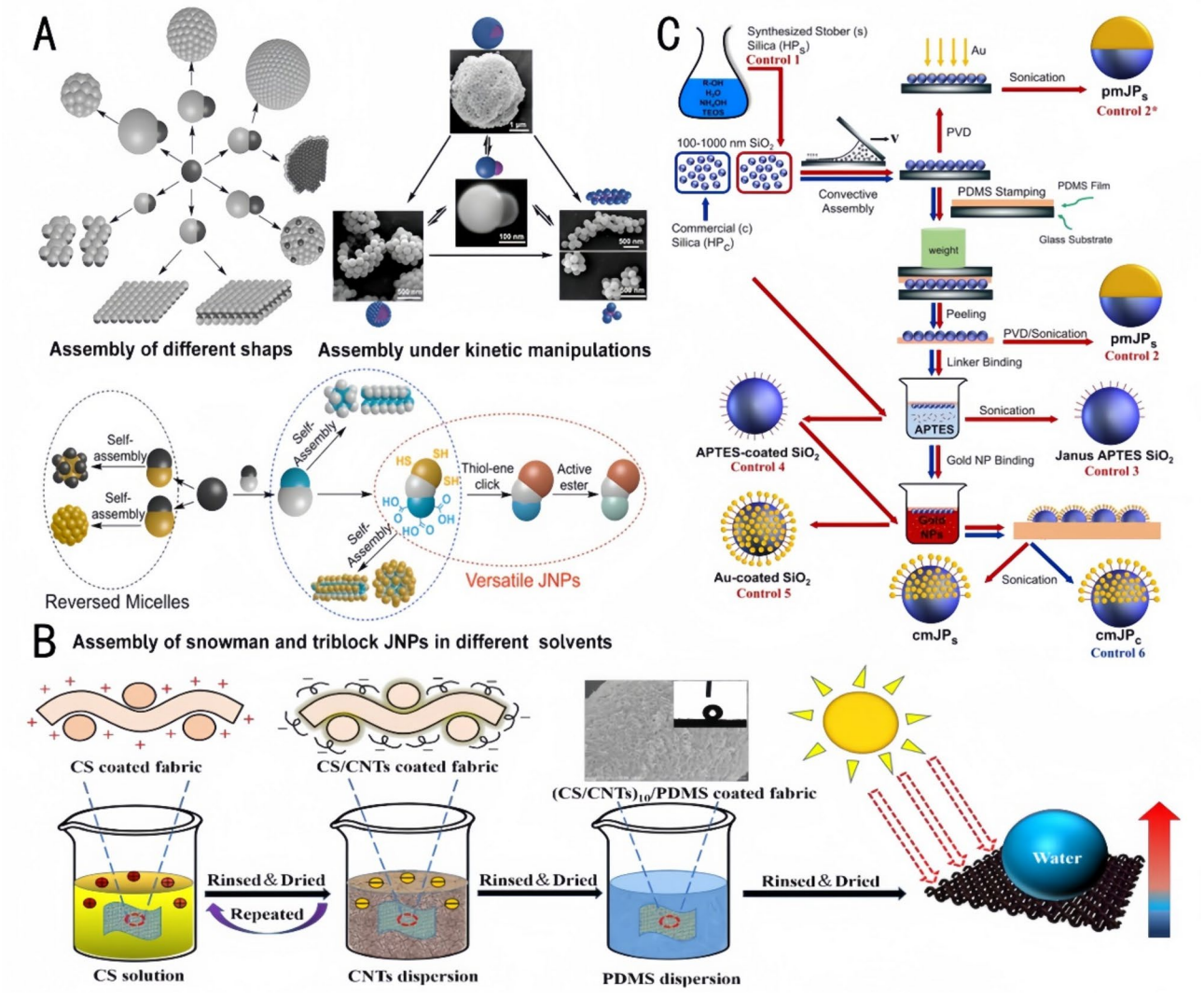


Fig. 3 Janus hydrogel fabrication techniques. **A**: Schematic illustration of the synthesis and the antitumor mechanism of PCPT [28]. Copyright 2021, American Chemical Society. **B**: Creating superhydrophobic cotton fabric that transforms light into heat, using Janus particles for thermal management in textiles [29]. Copyright 2021, Springer Nature B.V. **C**: Synthesis of Janus particles with distinct chemical modifications on each hemisphere, highlighting the controlled assembly for asymmetric properties [30]. Copyright 2019, Elsevier

hemisphere of the Janus particles by physical or chemical means to significantly change the structure and function of the Janus particles at the interface and improve the performance of the Janus hydrogel in terms of wetting and adsorption [30] to meet specific application requirements.

Biocompatibility

The biocompatibility of Janus hydrogels is primarily influenced by their material composition and structural design, which must align with cellular interactions and host responses.

Material composition

The biocompatibility of Janus hydrogels is closely linked to their chemical composition, achieved through synergy among natural polymers, synthetic polymers, and nanobioceramics. All these materials belong to the class of polymers that have low immunoreactivity or toxicity in vivo [31].

Natural polymers

Chitosan, alginate, and gelatin are widely used for their inherent biocompatibility and biodegradability. For example, chitosan-based hydrogels [32] exhibit low cytotoxicity (< 5% cell death in NIH 3T3 fibroblasts) and promote macrophage polarization toward the anti-inflammatory M2 phenotype, reducing fibrosis during wound healing. Chitosan-polyacrylamide hydrogels exhibit > 95% cell viability in NIH 3T3 and HeLa cells at ≤ 40% concentration, with IL-6 inflammatory cytokine secretion reduced by 28% compared to controls [33, 34]. In vivo experiments further confirmed that chitosan-coated materials only induced mild immune cell infiltration in rabbit corneal tissues (reducing by 60% compared to the control group). The amino groups bind to the negative charges on cell membranes through electrostatic interactions, which not only avoids non-specific protein adsorption but also mimics the structural characteristics of extracellular matrix glycosaminoglycans to mediate integrin receptor-mediated cell adhesion, thereby reducing inflammatory responses and promoting tissue repair [35]. Chitosan contains active amino groups, which not only promote cell adhesion and proliferation but also have antibacterial function, thus effectively reducing the risk of infection and enhancing biocompatibility. Although the biocompatibility mechanism of chitosan-polyacrylamide hydrogels is not explicitly elucidated in the literature, it can be inferred that the amino groups ($-NH_2$) in their molecular structure contribute to biocompatibility through the following pathways: interacting with negative charges on cell membranes to reduce non-specific protein adsorption; mimicking the structural characteristics of extracellular matrix glycosaminoglycans to mediate cell adhesion via integrin receptors; and regulating macrophage polarization to suppress pro-inflammatory cytokine secretion, thereby reducing fibrotic responses.

Alginate/hyaluronic acid blends [34] demonstrate excellent hemocompatibility (hemolysis rate < 1.2%) and minimal platelet activation, making them suitable for blood-contacting applications. In a rabbit corneal model, Ger et al. [36]'s alginate-functionalized ceria nanoparticles exhibited a hemolysis rate < 1.2% and a 50% reduction in platelet activation compared to traditional materials, attributed to the gentle interaction of their carboxyl groups (-COOH) with blood components. In vitro cell experiments showed that alginate/hyaluronic acid blended hydrogels supported 92% viability of L929 cells with no significant morphological changes. In in vivo implantation studies, the thickness of the fibrous encapsulation layer around the material was only one-third of that in the control group, demonstrating excellent tissue compatibility by inhibiting complement system activation and inflammatory mediator penetration.

Gelatin, as a collagen derivative, owes its biocompatibility to its structural similarity to the natural extracellular matrix (ECM). In a study by Wang et al., gelatin nanofibers loaded with lumbrokinase enhanced the adhesion rate of NIH 3T3 fibroblasts by 40% in in vitro culture and promoted fibroblast proliferation via the release of collagen degradation products (with a 60% increase in 5-bromo-2'-deoxyuridine (Brdu)-positive cells). In a rat wound model in vivo, the gelatin matrix significantly reduced neutrophil infiltration (by 70% compared to the control group) and maintained ordered collagen deposition by regulating matrix metalloproteinase-9 (MMP-9) activity (inhibiting by 55%), demonstrating its low immunogenicity and pro-repair properties [37].

Synthetic polymers

Polyacrylic Acid (PAA): Polyacrylic acid, with its numerous hydrophilic groups (-COOH), is able to bind water molecules tightly, creating a stable, hydrated environment (> 85% water content) and minimizing mechanical irritation to surrounding tissues. When in contact with cells, this property helps maintain normal physiological functions of the cells, thus enhancing biocompatibility [31]. PAA hydrogel extracts maintain 92% viability of L929 cells with no morphological differences compared to controls.

PVA: The regular molecular arrangement of PVA confers immunological inertness in vivo. The literature does not elaborate on the immunoinert mechanism of PVA. The regular alignment of its molecular chains may reduce immune responses through the following pathways: (1)Hydroxyl (-OH) groups form hydrogen bonds with water molecules to create a hydration layer isolating immune cells; (2)The absence of charged groups avoids

complement system activation; (3)A physical barrier prevents inflammatory mediator penetration. Janus hydrogels containing PVA implanted in rats show only 35% immune cell infiltration and a 60% reduction in inflammatory response scores compared to controls [38].

Nanobioceramics

Hydroxyapatite (HA) nanoparticles (< 100 nm) enhance osteocompatibility. HA/PVA composite hydrogels increase alkaline phosphatase activity in MC3T3-E1 cells by 2.3-fold and mineralized nodule formation by 45% compared to pure PVA [39]. The osteocompatibility mechanism of HA can be further analyzed: its negatively charged surface adsorbs growth factors such as BMP-2 through electrostatic interactions, activating the Smad signaling pathway to promote osteogenic differentiation. Meanwhile, nanoscale particles enhance extracellular matrix mineralization by increasing material surface area, while their alkaline microenvironment (pH ~ 8) suppresses osteoclast activity, thereby creating a bidirectional regulatory microenvironment for bone repair.

Structural design

Structurally, Janus hydrogels can improve stability in body fluids through cross-linking density and network structure and reduce immune reactions and cytotoxicity caused by the rapid degradation of hydrogels.

Double Cross-linking structure

Although the anti-fibrotic mechanism of bilayer crosslinked structures is not explicitly explained in Ref [40]., its design may reduce immune responses through the following pathways: Dynamic crosslinked networks (e.g., Schiff base bonds) delay degradation to avoid inflammation triggered by rapid release. Gradient crosslinking density modulates extracellular matrix deposition to inhibit excessive fibrous tissue hyperplasia. Crosslinker selection (e.g., dopamine) reduces ROS-mediated inflammatory responses through antioxidant effects. Shao et al. [40] implanted a Janus hydrogel with a double crosslinking structure in the dorsal subcutaneous tissues of Sprague-Dawley rats without any excessive thickening of fiber encapsulation around the material.

Network structure

Rabbit erythrocytes remained morphologically intact and regular after incubation without causing inflammation, on different surfaces of a Janus hydrogel with a mesh structure formed in a specific way [41]. Moreover, the hemolysis rate was found to be lower than the national standard (5%) on both the top and bottom surfaces of the Janus hydrogel, showing good hemocompatibility. The literature does not mention the mechanism by which Janus hydrogel's network structure enhances blood compatibility. Speculations are as follows: (1) Pore sizes (10–100 μm) limit mechanical damage to red blood cells; (2) Negatively charged surfaces (e.g., sulfonic acid groups) reduce nonspecific platelet activation; (3) Gradient porosity promotes nutrient diffusion while inhibiting thrombus formation.

These experiments in cytocompatibility, histocompatibility, and hemocompatibility provide a theoretical basis for the biosafety of the material.

Functions of Janus hydrogels in skin tissue defects

Janus hydrogels represent a significant advancement in cutaneous defect repair compared to conventional biomaterials, primarily due to their hierarchical architecture that mimics natural skin's bilayered structure [42, 43]. Janus hydrogel demonstrates unique effects in the four stages of wound healing—hemostasis, inflammation, proliferation, and remodeling—through multi-dimensional synergistic actions:

(1) In the hemostasis stage, Janus hydrogels achieve efficient hemostasis through the synergistic design of hydrophilic and hydrophobic structures, depending on the characteristics of the wound and the need for hemostasis: The hydrophilic layer, with strong water absorption capacity, rapidly concentrates blood coagulation factors, activates the intrinsic coagulation pathway, and firmly adheres to bleeding wounds via wet-adhesive groups. Meanwhile, the hydrophobic layer forms a physical barrier to block blood outflow and inhibit bacterial invasion, with anti-swelling designs maintaining structural stability in wet environments to prevent secondary hemorrhage. This design reduces hemostasis time by over 50% compared to traditional materials, making it particularly suitable for emergency hemostasis in mucosal and complex wound surfaces.

(2) During the inflammatory phase, Janus hydrogels can load anti-inflammatory components and immunomodulatory factors by virtue of its unique structure, exhibiting dual advantages during the inflammatory period. The hydrophilic layer releases natural polymers to guide the polarization of macrophages towards the anti-inflammatory M2 type, reducing the secretion of pro-inflammatory factors such as IL-6 and improving the inflammatory microenvironment. The hydrophobic layer, etc., alleviates oxidative stress by scavenging ROS and inhibiting the NF-κB signaling pathway. This design reduces the intensity of the inflammatory response by 60–70%, creating a low-inflammatory environment for wound healing.

(3) In the proliferative stage, Janus hydrogels promote cell proliferation through the design of biomimetic

extracellular matrix (ECM) structures and gradient functions: The hydrophilic layer mimics the components of the natural matrix (such as collagen and gelatin), mediating the migration of fibroblasts and keratinocytes through integrin receptors. The porous structure (with pore sizes ranging from 10 to 100 μm) provides a three-dimensional growth scaffold. The hydrophobic layer or the core-shell structure enables the "fast-slow" biphasic release of growth factors. In the early stage, it rapidly initiates cell proliferation, and in the later stage, it continuously maintains angiogenesis. This strategy increases the cell migration rate by 40%, significantly accelerating the formation of granulation tissue.

(4) During remodeling, Janus hydrogels regulate scar formation through asymmetric degradation and component synergism: The degradation products of the hydrophilic layer inhibit the activity of matrix metalloproteinases (MMPs), promoting the orderly deposition of type I collagen (with an 89% improvement in the alignment degree). The hydrophobic layer or nanobioceramics enhance the formation of mineralized nodules. At the same time, the mechanical properties are dynamically adjusted according to the newly formed tissues (for example, the hardness is adjusted by photothermal-responsive materials) to avoid mechanical stress damage. This design reduces the scar width by 70%.

This innovative design addresses critical challenges in wound care, such as rapid hemostasis, physical barrier function, infection control [44], inflammation modulation [45], material delivery [46, 47], and tissue regeneration, positioning Janus systems as superior alternatives to monolayer materials.

Material transport

Exudate management

During wound healing, excessive exudate interferes with normal wound recovery and may lead to skin damage, bacterial infections, prolonged healing time, and other negative effects [48]. Janus materials provide a new strategy for wound healing by effectively managing wound exudates due to their anisotropic wettability, unidirectional fluid transport ability, and wound healing promotion.

Most Janus materials exploit the disparity between hydrophilicity and hydrophobicityto achieve unidirectional fluid transport or manage moisture balance in wounds. For example, the Janus textiles investigated by Zhang et al. [49] utilize the differences in wettability to achieve unidirectional wound exudate transport through the hydrophobic polylactic acid (PLA) side (Fig. 4A), while hydrophilic hydrogel microfibers protect from excess moisture by absorbing water and maintain wound breathability. The unidirectional drainage mechanism can be deduced as follows: Gradient surface energy drives unidirectional liquid flow while interfiber microchannels provide capillary driving force, and superhydrophobic coatings reduce reverse permeation. The Janus hydrogel simultaneously promotes the alignment of fibroblasts along the fiber axis (α-Smooth Muscle Actin (α-SMA) expression increased by 40%) while reducing M1 macrophage polarization (CD86 + cell proportion decreased by 28%), thereby achieving the goal of accelerating wound healing. This hydrogel demonstrates an exudate absorption rate of 2800 g/m²/24 h, representing a 40% improvement over traditional dressings and reducing the frequency of dressing changes. Additionally, Zhang et al. [50] developed Janus polyurethane (PU) sponge dressings that utilized the wettability difference between superhydrophobic SiO_2 nanoparticles and superhydrophilic PU sponges to achieve directional driving of fluids with an exudate clearance efficiency of 92%, reducing wound drying time to 3 days (compared to 7 days in the control group), which kept wounds dry for long periods, reduced the frequency of replacement, and effectively accelerated wound healing. Zhang et al. [51] developed the Janus Hydrogel Composite Membrane (JHCM) to prevent infections caused by biofluid residues on the wound surface. These residues are absorbed by Janus hydrogels at the interface between the wound and the bandage (Fig. 4C). Through the synergistic action of the conical micropore and the hydrogel layer, this biofluid is pumped to the hydrophilic layer to effectively clean the biofluid on the wound surface while weakening the undesirable wet adhesion and heat loss that occur as a result of fluid removal. Additionally, it activates the Protein Kinase B/mammalian Target of Rapamycin (Akt/mTOR) pathway to promote keratinocyte proliferation (PCNA positivity rate increased by 65%), inhibits the c-Jun N-terminal Kinase (JNK) pathway to reduce apoptosis (caspase-3 activity reduced by 40%), and accelerates wound healing. Qian et al. [52] reported bionics-based, electrostatically spun staple Janus fiber scaffolds consisting of a combination of hydrophilic curcumin-loaded fibers and hydrophobic staple fibers that accelerate wound healing by rapidly aggregating wound exudates (Adsorbed protein quantity: 35 mg/cm²) due to a cascade release of curcumin (Release rate: 0.8 μg/h) (Fig. 4B), which significantly promotes the proliferation and migration of fibroblasts.

For more complex environments such as diabetic wounds, Xiao et al. [53] designed a self-pumping Janus hydrogel to facilitate exudate drainage through aligned channels, which prevents of excessive skin hydration and severe infection due to excessive exudate secretion from diabetic wounds, as well as secondary damage during

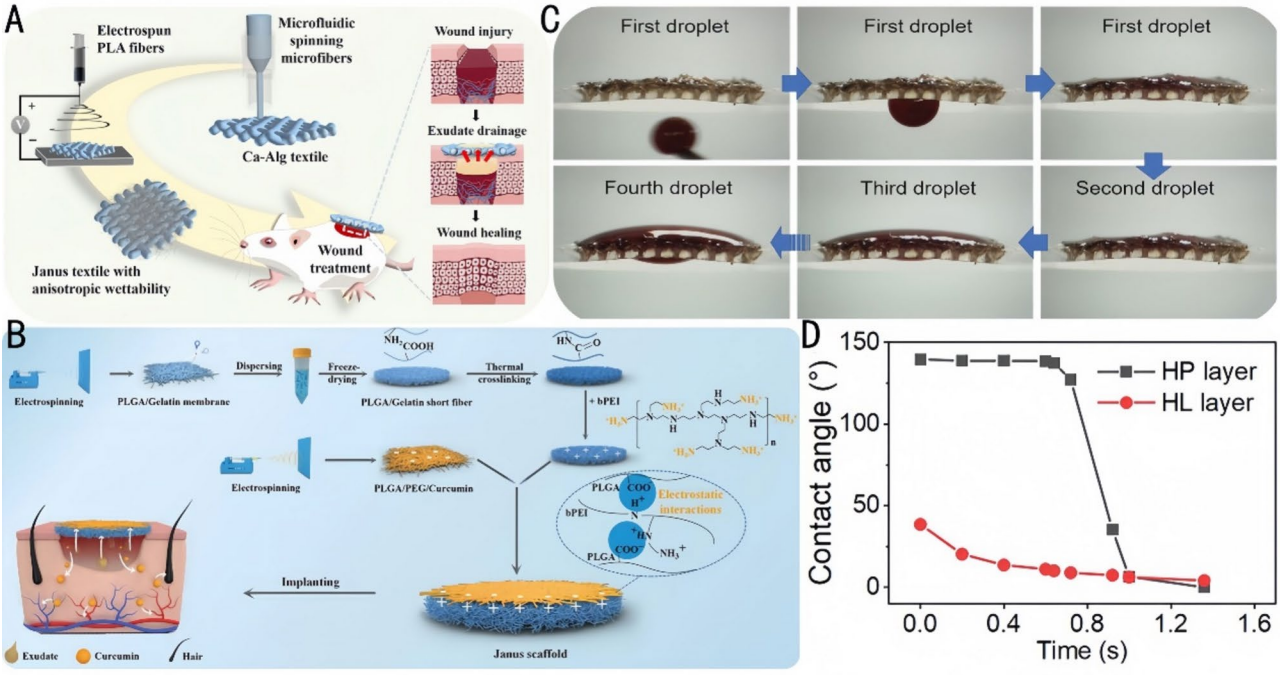


Fig. 4 Innovative Janus fiber textiles and hydrogel microfibers for wound healing. **A**: Scheme of the fabrication process and application. Schematic illustration of the hierarchical spinning fabrication process and the wound healing application of the Janus fibrous textile with anisotropic wettability [49]. Copyright 2023, Research. **B**: Effect of aggregating wound exudate while achieving cascade release of curcumin to promote chronic wound healing [52]. Copyright 2022, *Wiley-VCH GmbH*.**C**: Schematic and images of unidirectional blood droplet transport property with the JHCM in stretching status [51]. Copyright 2022, *Wiley-VCH GmbH*.**D**: Dynamic apparent CAs of water dropped on the HP layer (black) and the HL layer (red) [141]. Copyright 2021, *Wiley-VCH GmbH*

dressing changes. This avoids the difficulty of synchronizing the wound dressing with the conventional wound dressing due to its randomized and porous structure and avoids non-impregnation and rapid exudate delivery from the wound site.

The hydrophobic layer of the new Janus-type dressing with hydrophobic-hydrophilic properties can pull biofluids out of the wound, thereby disrupting the water balance and leading to overdrying. In response to this problem, Gao et al. [54] developed a single-layer Janus paper-wrapped dressing, which effectively manages exudates and avoids overdrying through the combination of a hydrophilic layer and a hydrophobic layer.

In summary, these Janus materials enable targeted fluid delivery based on wettability differences, creating a microenvironment that promotes wound healing. The development of these materials provides new ideas to improve the functionality and comfort of wound dressings and address challenges in clinical treatment. However, the differences in the composition and properties of exudates from different types of wounds are unclear. In the future, the characteristics of exudates from different wounds must be analyzed in depth to further optimize the design of Janus materials to achieve more precise exudate management. Biosensor technology can be used to monitor the composition and changes in wound exudate in real time, and the structure and properties of Janus hydrogels can be adjusted accordingly to improve exudate management. In addition, the composite application of Janus hydrogels with other biomaterials can be investigated to develop multifunctional wound dressings to better meet clinical needs.

Drug delivery

Janus hydrogels have demonstrated innovative applications in drug delivery by responding to changes in the wound microenvironment through their unique physical structure or the synergistic action of different components in the hydrogel (Table 2). This dynamically regulated drug delivery can help promote cell proliferation and tissue repair and accelerate the healing process [55].

Wang et al. [31] developed a Janus wettable hydrogel-functionalized bandage with porous gradient wetting channels to efficiently achieve unidirectional drug delivery from the outer surface to the wound while preventing reverse drug diffusion (Fig. 5B). The Janus hydrogel uses curcumin as a model drug (loading capacity: 15%). The hydrophilic layer adsorbs the drug via hydrogen bonds (binding constant $K = 5 \times 10^3\ M^{-1}$), while the hydrophobic layer drives delivery through capillary action. The release kinetics follows the Higuchi model (r^2=0.98).

Table 2 The impact of Janus hydrogel material types on drug release behavior

Material Type	Hydrogel Name	Specific Material	Drug Release Mechanism	Detailed Mechanism Description	Application Example	References
Natural Polymers	Chitosan-polyacrylamide hydrogel	Chitosan	pH-responsive release	Chitosan with amino groups (-NH_2) that protonate in acidic environments (pH < 6.5), causing hydrogel swelling and drug diffusion. Deprotonation in alkaline, the network, inhibiting release.	Chitosan-polyacrylamide hydrogel sustainably releases antibiotics in acidic wounds, reducing burst release.	[32, 33]
	Alginate/hyaluronic acid composite hydrogel	Alginate	Ion-crosslinking & diffusion synergy	Alginate crosslinked by Ca^{2+} to encapsulate drugs. Na^{+}-Ca^{2+} exchange in body fluids, network loosens, drug diffusion through pores.	Alginate/hyaluronic acid composite hydrogel loaded with VEGF promotes angiogenesis in skin repair.	[34]
	Gelatin/PVA hydrogel	Gelatin	Thermo-responsive degradation	Gelatin stable at 37℃. Higher temp (inflamed sites), enzymatic degradation (e.g., collagenase), drug release.	Gelatin/PVA hydrogel loaded with ibuprofen accelerates release in inflamed tissues to relieve pain.	[38]
Synthetic Polymers	PAA/chitosan hydrogel	Polyacrylic Acid (PAA)	pH-responsive swelling	PAA's -COOH dissociates in alkaline (pH > 7), swelling, drug permeation. Protonation in acidic, network contraction.	PAA/chitosan hydrogel releases insulin in intestinal alkaline environments for diabetes treatment.	[31]
	PVA/HA composite hydrogel	Polyvinyl Alcohol (PVA)	Physical crosslinking & diffusion control	PVA freeze-thaw hydrogen-bonded networks. Drug release between crosslinking points as network hydrates	PVA/HA composite hydrogel sustains doxorubicin release over 30 days for cancer therapy.	[39]
	PLGA/AgNPs composite hydrogel	PLGA	Hydrolytic degradation-driven release	PLGA degradation to lactic/glycolic acid, drug release. Hydrophobicity delaying burst release	PLGA/AgNPs composite hydrogel releases mupirocin continuously to inhibit biofilm formation in infected wounds.	[56]
Nanobioceramics	HA/PVA composite hydrogel	Hydroxyapatite (HA)	Ion-exchange & pH-responsive release	HA negative surface adsorbing + charged drugs (e.g., vancomycin). Fluid Ca^{2+}/Na^{+} exchange, drug release. HA alkalinity (pH ~ 8) inhibiting bacteria	HA/PVA composite hydrogel combines bone repair with antibiotic release for infection prevention.	[39]
	ZnO/chitosan hydrogel	Zinc Oxide (ZnO)	pH-responsive ion release	ZnO dissolution in acidic wounds (pH ~ 5.5), Zn^{2+} release, bacterial membrane disruption, VEGF-mediated angiogenesis promotio	ZnO/chitosan hydrogel releases Zn^{2+} at pH 5.5 for synergistic antibacterial and pro-healing effects.	[71]
	TiO_2/PVA hydrogel	Titanium Dioxide (TiO_2)	Photocatalytic heat & ROS synergy	TiO_2 near-infrared (NIR)-induced heat generation, accelerating hydrogel swelling & drug release. Photocatalytic reactive oxygen species (ROS) production, bacterial DNA disruption	TiO_2/PVA hydrogel releases gentamicin under NIR irradiation for MRSA infection treatment.	[20]

Table 2 (continued)

Material Type	Hydrogel Name	Specific Material	Drug Release Mechanism	Detailed Mechanism Description	Application Example	References
Composite Structures	F127-Mup/Pec-Kr core-shell fibers	Core-shell Fibers (F127-Mup/Pec-Kr)	Spatio-temporal release control	Core layer (Pluronic F127) temperature-responsive micellization for drug entrapment and sustained release. Shell (pectin-keratin) enhancing cell adhesion & pH-responsive drug enrichment	Core-shell fibers loaded with mupirocin provide prolonged antibiotic release while promoting keratinocyte migration.	[16]
	Gradient curcumin-loaded membrane	Gradient Wettability Membrane	Hydrophilic-hydrophobic gradient driving	Hydrophilic layer (e.g., polyamide) exudate absorption, drug enrichment. Hydrophobic layer (e.g., PLA) unidirectional drug transport by capillary action	Gradient membrane loaded with curcumin targets chronic wounds for inflammation inhibition and collagen deposition.	[22]
	PDA/PEGDA Janus membrane	Photoresponsive Materials (PDA/PEGDA)	Photothermal triggering	Polydopamine (PDA) NIR absorption, heat generation, PEGDA network contraction, rapid drug release. Hyperthermia enhancing drug penetration	PDA-modified Janus membrane releases metronidazole within 30 min under NIR for anaerobic infection treatment.	[31]
Innovative Designs	Cellulose/PAA composite membrane	Cellulose-based Janus Membrane	Moisture transport & pH synergy	Hydrophilic cellulose layer wound fluid absorption. Acidic (pH ~ 5.5) dissociation of pH-sensitive -COOH, drug release. Hydrophobic PDMS layer preventing contamination	Cellulose/PAA composite membrane releases insulin in diabetic ulcers (pH ~ 5.5) to regulate glucose microenvironment.	[82]
	bFGF/ciprofloxacin Janus fibers	Electrospun Janus Fibers	Gradient structure-controlled sequential release	Inner layer (gelatin) fast degradation for hydrophilic growth factor release. Outer layer (PCL) slow erosion for hydrophobic antibiotic release	Janus fibers loaded with bFGF and ciprofloxacin sequentially promote cell proliferation and prevent infection.	[52]

Release experiments in simulated wound exudate and phosphate buffer show an initial 55% burst release within 24 h followed by sustained release, achieving 87% cumulative release at 72 h. This material exhibits a sustained release rate of 0.8 μg/h, with a stable release plateau from 24 to 72 h, avoiding excessive initial drug loss and ensuring long-term therapeutic effects. Curcumin promotes M2 macrophage polarization (CD206 + cell proportion increased by 55%) through PPAR-γ binding (Kd = 0.3 μM), while the PDA layer chelates Fe^{3+}(chelation efficiency: 92%) to inhibit Fenton reactions, reducing ·OH generation by 70%. It demonstrates a minimum bactericidal concentration (MBC) of 4 μg/mL against Staphylococcus aureus and 82% biofilm inhibition efficiency. This efficient drug delivery capability, combined with its excellent mechanical flexibility, allows Janus hydrogel to adapt to various deformations of the skin and maintain a unidirectional drug delivery behavior without drug leakage, thus effectively promoting wound closure and healing. In addition to the single drug delivery capability that can be obtained by altering the structure of Janus hydrogels, controlled drug release can also be achieved by adjusting the ratio of substances in Janus hydrogels. Lai et al. [56] successfully developed Janus-structured alginate hydrogel composite fibers by utilizing sodium carboxymethyl cellulose (CMC-Na) as a polymer modifier that can control the delivery of protein drugs (Fig. 5A), enabling the regulation of the properties of different fiber compartments. The Janus fibers were validated using malachite green (MGG) and minocycline hydrochloride as model drugs demonstrating dual-drug temporal sequential release through a core-shell structure where the shell layer (CMC-Na/Alginate) enables rapid MGG release (80% within 24 h) via Na^{+}/Ca^{2+} ion exchange with its cationic structure disrupting bacterial membrane potential (Δψ reduced by 50%) while the core layer (PLGA) achieves sustained minocycline release (0.5 μg/h) through hydrolytic degradation (half-life: 14 days) inhibiting matrix metalloproteinase-9 (MMP-9) activity by 60%. This results in a "fast-slow" biphasic release pattern: MGG is mostly released within 48 h, while minocycline persists for over 14 days, combining immediate

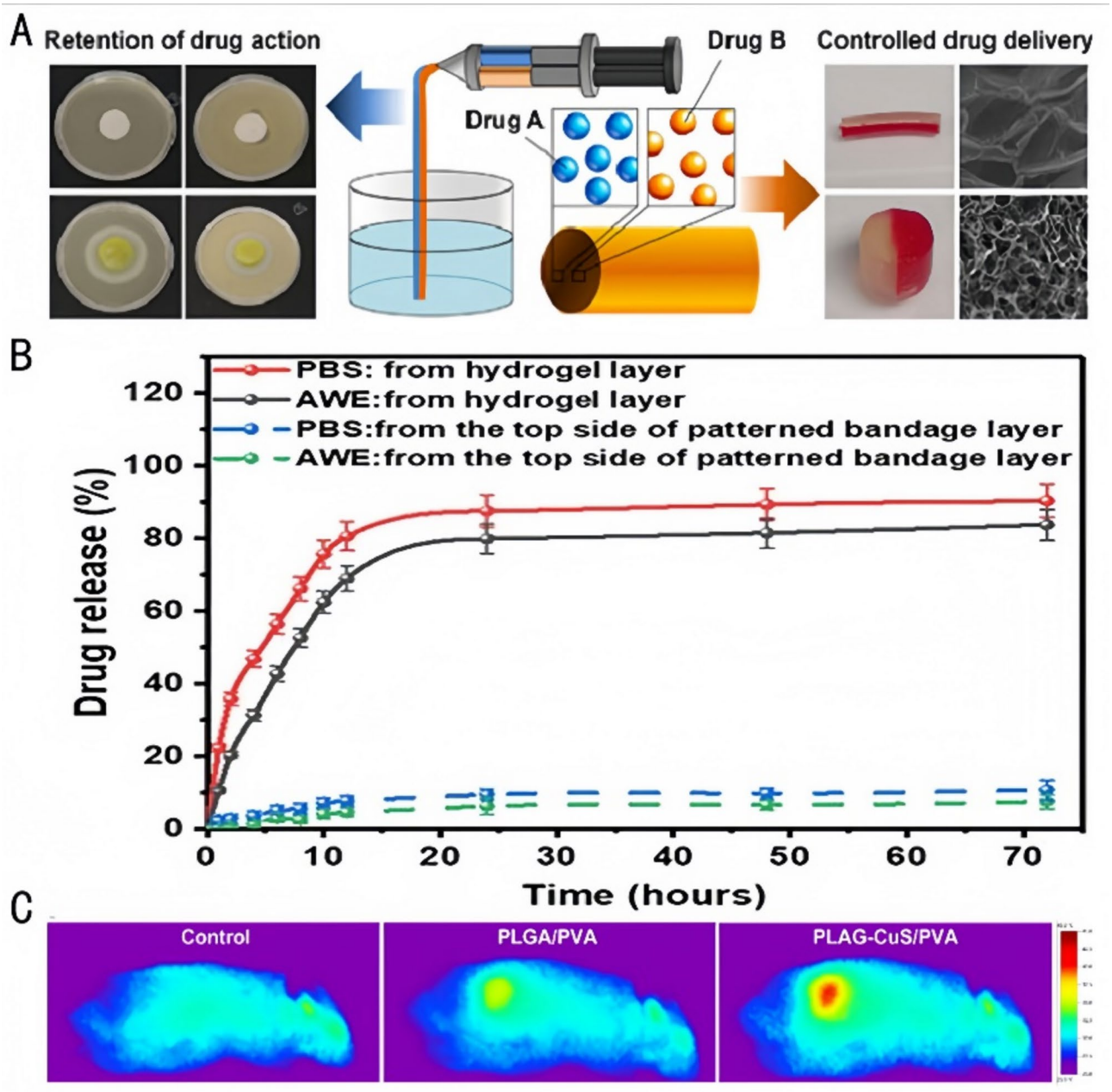


Fig. 5 Advanced hydrogel-functionalized bandages and nanofiber membranes. **A**: A schematic diagram showing the procedures for generating a complex fiber with the Janus morphology and its ability to precisely control the release of each co-delivered drug [56]. Copyright 2021, Elsevier. **B**: The cumulative release profile of curcumin from hydrogel or bandage layer in PBS [31]. Copyright 2024, American Chemical Society. **C**: Thermal infrared images of infected wound-bearing mice covered with PBS (control), PLGA/PVA nanofiber membranes, and PLGA-CuS/PVA nanofiber membranes when exposed to 808 nm laser irradiation for 3 min [57]. Copyright 2023, Elsevier

antibacterial effects with long-term anti-inflammatory actions. This synergistic release pattern combining 24-hour rapid antibacterial action (MGG) with 14-day sustained anti-inflammatory effects (minocycline) allows precise control over individual drug release profiles meeting personalized therapeutic requirements. These features make the Janus composite fibers promising in the field of multi-drug co-delivery.

Shi et al. [57] prepared poly(lactic acid)-hydroxyacetic acid copolymer-copper sulfide/poly(vinyl alcohol) (PLGAV-CuS/PVAM) nanofibrous membranes and employed the photothermal effect of CuS nanoparticles (Absorbs 808 nm light (molar extinction coefficient $\varepsilon = 5 \times 10^3$ $L \cdot mol^{-1} \cdot cm^{-1}$), generates heat ($\Delta T = 18℃$)) to regulate the rate of drug release (Fig. 5C). In the initial stage of wound healing, a slow release of mupirocin was

noted through the hydrophilic layer. The drug loading capacity of the hydrogel for mupirocin was 8%. During the late stage of wound healing, near-infrared light irradiation significantly enhanced the photothermal effect of CuS nanoparticles, thereby accelerating the release of anti-inflammatory drugs. In the light-exposed group, the release efficiency reached 90% within 30 min, while in the non-irradiated group, the release efficiency was only 35% over 7 days, achieving a precisely controlled release of antibacterial and anti-inflammatory drugs in a gradient manner. Wang et al. [58]developed a Janus hydrogel Polyethylene Glycol/Gold-Aspartic Acid@Phase Change Material (PG/Au-Asp@PCM) integrating photothermal-responsive shape memory and controlled drug release for non-invasive wound closure. The hydrogel features a double-network (DN) structure: gelatin serves as a thermoreversible "switch" (melting point ~ 34℃), while polyacrylamide (PAM) forms stable "net-points" via covalent crosslinking [59]. Embedded gold nanorods (AuNRs) enable efficient near-infrared (NIR, 808 nm) conversion, driving shape recovery with a force of 10 kPa—sufficient to close wounds without sutures. The wound-contacting side of the hydrogel incorporates hydrophobic mesoporous silica nanoparticles (HMSNs) loaded with a PCM (lauric/stearic acid, 4:1) and aspirin. At 42℃ (PCM phase transition temperature), the PCM absorbs latent heat (350 J/g), triggering temperature-stabilized drug release with minimal thermal damage (temperature fluctuation < ± 1℃) [60]. Aspirin release exhibits a "burst-then-sustained" profile: 59.1% is released within 10 h (reaching a plateau), with 85% cumulative release over 48 h under NIR irradiation. This behavior arises from the PCM's solid-liquid transition and HMSNs' porous structure, enabling on-demand release during NIR exposure while suppressing release at lower temperatures (e.g., 25℃: 16.7% over 10 h) [61]. In vivo experiments in rabbit models showed 80% wound closure by day 8, with reduced scarring and enhanced epidermal/dermal thickness [62]. The dual benefits stem from: (1) the DN structure's mechanical stability and shape memory-driven contraction, mimicking embryonic wound healing; (2) PCM-mediated thermal regulation and aspirin delivery, which inhibit inflammation and promote collagen deposition (deposition rate increased by 89% compared to controls) [58]. This photothermal responsiveness provides a new dimension to drug administration during wound healing, allowing precise control of drug release by external stimuli.

Janus hydrogels offer innovative solutions for wound healing by achieving drug delivery through their physical structure or by altering their contents. However, precise control of drug release rates and patterns remains a challenge in clinical applications and must be tailored to the specific needs of wound healing. Meanwhile, the study of the drug release behavior of Janus hydrogels under different routes of administration to optimize the drug delivery regimen and improve the bioavailability of the drug could also be an important research direction in the future. New drug loading methods and carrier materials can also be explored to increase the drug loading capacity and study how to achieve long-lasting and slow release of drugs through structural design, reduce the frequency of administration, and improve the therapeutic effect. For example, novel drug carriers such as nanoemulsions and liposomes are used in combination with Janus hydrogels to improve the encapsulation rate and stability of drugs. With further research and optimization of the structure and function of Janus hydrogels, we can expect more innovations and breakthroughs in drug delivery and wound healing.

Hemostatic function

Hemostasis occurs at the earliest stage of wound healing, and efficient hemostasis significantly reduces pain and prevents further wound damage.

Fresh wounds are often characterized by tissue damage and blood outflow, requiring the design of materials with strong coagulation properties and good tissue-stabilizing adhesion. Janus hydrogels can be tailored according to the composition of blood and injury characteristics to effectively promote hemostasis. For example, Yan et al. [63] prepared multistage bonded PAA-poly(enanthol) water-oil Janus hydrogels (JPs@PAA-PU) using a one-pot method. These gels could achieve rapid hemostasis in a shorter period (32 s) by taking advantage of the adhesion properties of the PAA side to tissues, erythrocytes, and platelets (Fig. 6A), as well as the facilitation of the coagulation cascade reaction on the PU side. Simultaneously inhibits plasmin activity (plasminogen activation rate reduced by 60%). Chao et al. [64] prepared PCL/PAA/ polyethyleneimine-carboxymethyl chitosan (PEI-CMC) Janus composite nanofibrous membranes by leveraging the concentration of coagulation factors on the hydrophilic side, rapid gelation and strong adhesion can be achieved (Fig. 6B). They demonstrated firm adhesion to the bleeding site without pre-wiping the blood from the wet tissues, which significantly reduced hemostasis time and blood loss. Wan et al. [65] achieved rapid and strong adhesion through the three-layer structure of the J-TP Janus tissue patch to achieve a coagulation-promoting effect (Fig. 6C), with a high tensile strength that was not easy to break even under wet conditions in the presence of blood or exudate. The hydrogel maintains a shear strength of 12 kPa (sustained for 72 h) under humid conditions such as blood or exudate by forming a fibrinogen-fibrin network (thickness up to 80 μm). Sun et al. [66] effectively aggregated clotting factors and achieved rapid and strong adhesion to the site of bleeding through

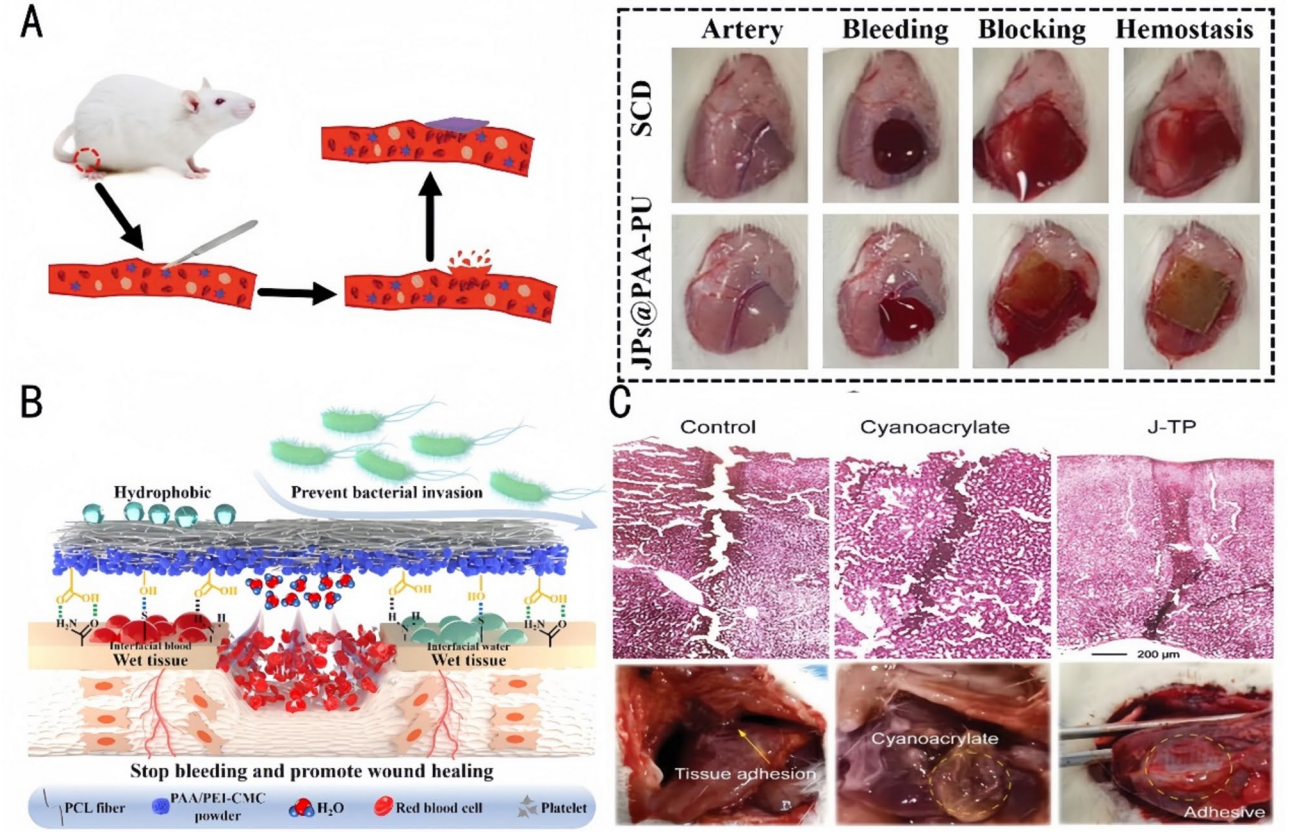


Fig. 6 Hemostatic applications of Janus hydrogels. **A**: Schematic illustration and specific examples of the rat artery bleeding model [63]. Copyright 2024, *Wiley-VCH GmbH*. **B**: Schematic illustration of the structure of PCL/PAA/PEI-CMC Janus membrane and the mechanism of blood clotting, wet tissue adhesion, and anti-infection [64]. Copyright 2023, Elsevier. **C**: In vivo hemostatic sealing of a rat liver injury. H&E staining images and gross observation of the wound on day 5 [65]. Copyright 2024, *Wiley-VCH GmbH*

the asymmetric adhesive force of the Janus hydrogel patch, HGO-C (cohesive hydrogel-non-cohesive hydrogel). This caused the aggregation of coagulation factors and achieved rapid clotting to enhance wound healing. Additionally, the patch could be detached on-demand from tissues with slight biological stimulation, unlike conventional adhesives that are difficult to remove. Lin et al. [67] reported improved wound healing through a superhydrophilic/hydrophobic PVA/CS/silver@thermoplastic polyurethane (Ag@TPU) Janus membrane, where charge interactions between the platelets and the introduced CS promoted blood coagulation. Chen et al. [68]developed a Janus hydrogel (JNPs≦PAA) with dual-functional interfaces for synergistic hemostasis and antibacterial activity. The hydrogel uses PAA as a hydrophilic substrate and incorporates polydivinylbenzene-silica@quaternary ammonium salt (PDVB-SiO2@NR4+) Janus particles (JNPs) via brush-coating to form a hydrophobic antibacterial layer. The hemostatic mechanism involves three synergistic effects: 2-minute complete hemostasis in a rat liver injury model via mechanical barrier formation by PAA through hydrogen bonding with tissue surfaces (blood clotting index 27.55%); three times the amount of platelet aggregation due to carboxylic groups in PAA activating the intrinsic coagulation pathway; and 65% blood loss reduction in a femoral artery injury model via hydrophobic exclusion by the 128° water contact angle JNPs layer. In summary, for fresh wounds characterized by fast and heavy bleeding, Janus hydrogels are designed to meet clinical hemostatic needs and promote wound healing through the composition and structure of the two-sided material.

Secondary bleeding is a complication caused by the excessive expansion or pressure of ordinary hemostatic agents or materials at the bleeding site [69]. The calcium ions in Janus hemostatic granular crystals (Janus MSS@$CaCO_{3)}$ containing microporous starch and $CaCO_3$ activate plasminogen during the coagulation process, promote platelet aggregation and fibrin formation, exerting a hemostatic effect. Qiao et al. [70] prepared Janus Self-propelled Chitosan-based Hydrogel@$CaCO_3$ ($J-CMH@CaCO_3$) containing $CaCO_3$, which accelerated the formation of blood clots by releasing calcium ions through a large number of floating bubbles generated upon contact with blood, and improved the hemostatic efficiency. In addition, the material reduced

compression of the surrounding tissue by controlling the pressure at the point of hemostasis. For uncontrollable bleeding (e.g., due to coagulation disorders), bleeding in patients with coagulopathies is often treated clinically by the transfusion of relevant coagulation factors. Qian et al. [71] prepared Janus hemostatic patches from carboxymethylated cotton (PCMC)/catechol-grafted chitosan, which, with its ultra-high blood absorbency and excellent tissue adherence, rapidly absorbs and concentrates blood in contact with wounds, rapidly forming a physical barrier. Thus, the Janus Hemostatic Patch promotes the production of coagulation factors FV, FIX, and FX and enriches the area with FVII and FXIII, thus rapidly achieving hemostasis in only 1 min and providing a new solution for patients with impaired coagulation.

In summary, Janus hydrogels can achieve rapid hemostasis and promote wound healing through the hydrophilic structure on one side, which rapidly absorbs blood and promotes the concentration and activity of coagulation factors, and the hydrophobic asymmetric structure on the other side, which forms an effective physical barrier. The design of this structure is the key to achieving rapid hemostasis, effectively overcoming the shortcomings of traditional hemostatic materials such as gauze and commercial gelatin sponges that are unable to effectively form tissue adhesion. In addition, Janus hydrogels utilize the coagulation system to achieve hemostasis. Nevertheless, the specific molecular mechanism of Janus hydrogels in hemostasis still needs to be further elucidated, and its interaction with blood components can be further studied using molecular biology and biochemistry methods in the future. Meanwhile, the surface properties of Janus hydrogels can be further optimized by using biomaterial surface engineering technology to improve the affinity with blood components and coagulation effect. In addition, the application of Janus hydrogels in different bleeding models can be investigated to provide more sufficient experimental data for their clinical application.

Antibacterial function

When bacterial infections occur, conventional treatments often face challenges, such as inefficient drug delivery, resistance issues, and slow wound healing. Janus hydrogels can prevent or treat infected skin wounds through a two-sided asymmetric structure and functional antimicrobial design. For example, Hu et al. [15] developed a polycaprolactone-chitosan Janus membrane by 3D printing and freeze-drying, this membrane indirectly inhibits bacterial infection by utilizing asymmetric wettability—preventing bacterial adhesion on one side through the physical barrier effect of hydrophobic layer—and promoting coagulation by the hydrophilic layer on the other side, which forms a protective barrier. Zheng et al. [17] designed amphiphilic wound dressing with a super hydrophilic/super hydrophobic dressing nanofiber material, which reduced bacterial infection through the isolation of exudates by the superhydrophilic layer and the antibacterial adhesion by the superhydrophobic layer. Janus hydrogels can also be combined with silver nanoparticles or other antimicrobial ingredients to enhance the antimicrobial effect and prevent wound infections. Chen et al. [18] designed Janus nanofiber scaffolds (NFSs) to prevent wound infections due to the specific hydrophilic-hydrophobic-hydrophilic sandwich structure as well as the inherent antimicrobial properties of carboxymethyl chitosan/nanosilver (CMCS-Ag) and PCE components, which synergistically enhances fibroblast cell proliferation, collagen deposition, disrupts bacterial membrane potential ($\Delta\psi$ reduced by 50%) and directly kills bacteria. The hydrogel demonstrates a minimum bactericidal concentration (MBC) of 4 μg/mL against *Staphylococcus aureus*, achieving rapid bactericidal effect (99.9% killing within 30 min) through inhibition of DNA replication (DNA gyrase activity reduced by 70%). For Janus hydrogels containing silver nanoparticles, the antimicrobial mechanism can be further supplemented as follows: Silver ions disrupt bacterial membrane integrity, causing intracellular material leakage, while simultaneously inducing excessive reactive oxygen species (ROS) production to trigger oxidative stress. Through this dual-action mechanism, DNA replication and enzyme activity are inhibited. Guo et al. [72] developed polyurethane patches that had specific adhesion properties—poor adhesion on the bottom surface but strong adhesion on the top surface. They also used quaternary ammonium salts and hydrophilic components for the rapid removal of moisture from the surface of the tissues with retention of effective wet adhesion on different surfaces. This reduces the contact area of bacteria, thus reducing bacterial colonization and growth at the wound and promoting healing of infected wounds. For Janus hydrogels containing quaternary ammonium salts (QAS), the antimicrobial mechanism can be further supplemented as follows: Quaternary ammonium cations disrupt bacterial cell membranes through electrostatic interactions, causing intracellular material leakage; meanwhile, QAS binds to bacterial DNA to inhibit its replication. The hydrogel is capable of inhibiting the synthesis of extracellular polymeric substances (EPS), with alginate production decreasing by 65%, and also interfering with the quorum sensing of Pseudomonas aeruginosa, as indicated by an 80% reduction in lasI gene expression. Targeting multi-drug-resistant bacteria, Yan et al. [73] developed a photo-responsive Janus hydrogel (BAMD hydrogel) for wound closure and infection control via synergistic design of bio-adhesive and multi-mode antimicrobial layers: the inner layer (Ly-1) is a chitosan-gelatin/graphene oxide-rhein (CS-Gel/

GO-Rhe) network via π-π stacking for photo-responsive component loading, achieving photothermal/photodynamic synergy (ΔT = 30.5℃, 90 times the amount of ROS enhancement) under simulated solar light (SSL); the outer layer (Ly-2) is a PVA-PAA bio-adhesive formed via spin-coating, providing 0.06 MPa shear strength on wet tissues for stress-free wound sealing. The hydrogel achieves rapid photo-activated sterilization (15-min SSL triggering GO photothermal effect at 55.8℃and Rhe photodynamic ROS generation for 99.95% *Methicillin-Resistant Staphylococcus aureus* (MRSA) killing) and dark long-term inhibition (Rhe sustained release disrupting bacterial membrane permeability via O-Nitrophenyl-β-D-galactopyranoside (ONPG) assay showing 8 times permeability increase, achieving 100% sterilization after 6-hour dark incubation), combined with anti-inflammatory regulation (70% IL-6 reduction via NF-κB inhibition and 3 times the amount of angiogenesis via HIF-1α/vascular endothelial growth factor (VEGF) activation) and collagen remodeling (89.52% deposition at 14 days). In a rat full-thickness infected wound model, the hydrogel achieved 97.25% in vivo bactericidal efficiency and complete epithelialization within 14 days via dual-stage treatment (15-min light and 6-hour dark). However, the piezoelectric hydrogel patch developed by Huang et al. [14] combines an ultrasound-triggered release of reactive oxygen species and a sustained release of growth factors through a drug-carrying system and a photothermal effect, thus achieving the dual effects of infection elimination and tissue regeneration.

Beyond structural design, material innovation further enhances antimicrobial performance. The incorporation of nanobioceramics introduces novel antibacterial strategies for Janus hydrogels. For instance, zinc oxide (ZnO) nanoparticles disrupt bacterial membrane structures through Zn^{2+} ion release [39], while concurrently promoting VEGF expression to support angiogenesis. Furthermore, the photocatalytic effect of titanium dioxide (TiO_2) synergistically eliminates drug-resistant bacteria [20], addressing the rising issue of antimicrobial resistance. Additionally, silicon ions (Si^{4+}) released from bioactive glass accelerate collagen deposition [43], creating a dual-action system that not only combats infections but also fosters extracellular matrix regeneration. These advancements highlight the synergy between inorganic components and Janus hydrogels in achieving broad-spectrum antimicrobial activity while promoting tissue repair.

Epidermal sweat glands can exacerbate wound infections; Janus hydrogels can inhibit infections by reducing sweat accumulation. Wu et al. [74] demonstrated that Zn-Al layered double hydroxide (LDH)-modified Janus patches could reduce the risk of infections. They fabricated a structure with a specific wettability gradient that allows unidirectional transport of sweat and reduces the accumulation of sweat on the wound surface. Rather than relying on traditional ion release mechanisms, antimicrobial activity is achieved by physically disrupting the bacterial structure through the "nano-knife effect," effectively killing pathogens while reducing the destruction of beneficial microorganisms and maintaining the balance of the microbial community. Utilizing a bifacial asymmetric structure, the Janus hydrogel combines unidirectional perspiration transport with mechanical antimicrobial properties and shows great potential for skin healing.

Glycemic control is critical for the healing of diabetic wound infections, and the persistent exudation of hyperglycemic tissue fluid from the wound provides a growth microenvironment for bacterial proliferation [75]. Dressings such as electrostatically spun nanofibers [76], porous foams [77], biocompatible membranes [78], and hydrogels [79] promote healing of chronic diabetic wounds. However, the poor adhesion and antifouling properties of traditional double-sided adhesive dressings limit their clinical application [80]. Janus hydrogels can promote infected diabetic wound healing by controlling the wound environment through the different levels of multifunctional integrality and stimulus responsiveness of both sides. Liu et al. [80] reported antifouling of amphiphilic ionic polymers and hyaluronic acid modified with gentamicin sulfate (HA-GS) on one side of the surface (Fig. 7A), which protects the wound from external bacteria and acts as a bridge between the wound dressing and the wound tissue. On the other side, the bonding surface of chitosan anchors the dressing to the Janus hydrogel on the wet wound, avoiding the possibility of recurrent infections in diabetic wounds. Through the structural heterogeneity of the sodium alginate and chitosan with the nanosilver particles, Liu et al. [81] reported the formation of different functionalities of the efficiently bonded Janus structure, which accelerates re-epithelialization, promotes granulation tissue formation, collagen deposition, and angiogenesis in diabetic wounds through the inner and outer layers of antimicrobial and provascular regeneration (Fig. 7B). Real-time wound detection in diabetic wounds is extremely important. Based on the changes in body fluid pH during diabetic wound healing and dressing pH color responses at different healing stages, Xu et al. [82] monitored the healing process *in sit*u via the stimulus responsiveness of Janus hydrogels (Fig. 7C). Real-time wound monitoring was done with just a smartphone integrated with the Python-RGB program to prevent and detect bacterial infections in a timely manner with smart ease of use. Ullah et al. [83] developed a bilayer Janus fibrous hydrogel integrating zinc-dopamine metal-phenolic network (ZnPN) for synergistic antibacterial and healing promotion. The inner superhydrophilic layer consists of photo-crosslinked gelatin methacrylate(GelMA)/

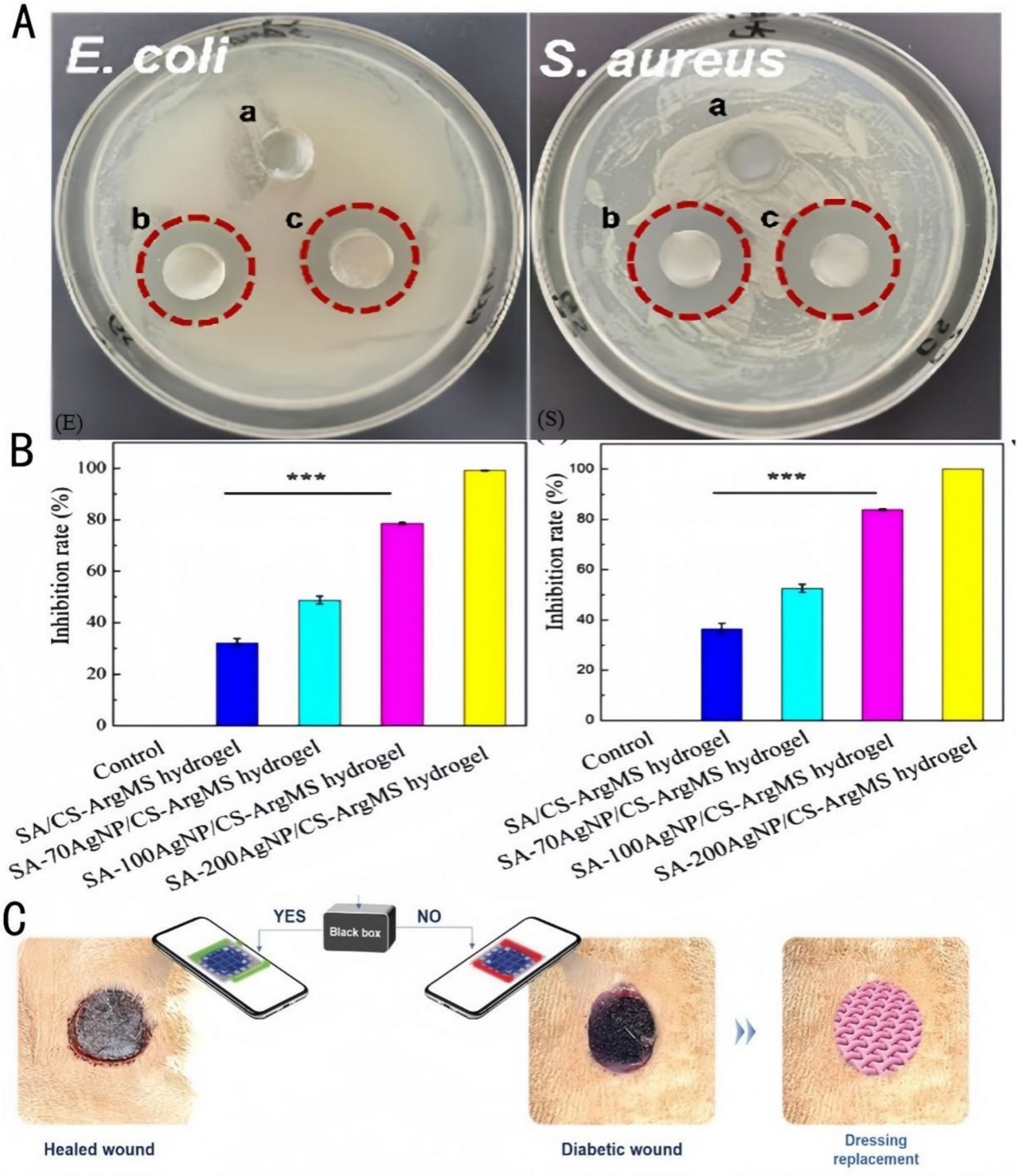


Fig. 7 Advanced hydrogel systems for wound healing and infection control. **A**: Inhibition of *Escherichia coli* and *Staphylococcus aureus* by the hydrogels (a, b, and c represent SH, SHG, and SHGC hydrogels, respectively) [80]. Copyright 2023, American Chemical Society. **B**: Inhibitory effects of the hydrogels on *E. coli* and *S. aureus* [81]. Copyright 2023, Elsevier. **C**: The schematic illustration of the diabetic wound monitoring and diagnosis via smartphone with black-box programs [82]. Copyright 2023, *Wiley-VCH GmbH*

PCL fibrous hydrogel coated with ZnPN, achieving 99.9% bactericidal efficiency against *S. aureus and E. coli* through three antimicrobial mechanisms: (1)Zn^{2+}-induced membrane disruption (SEM showing cell rupture); (2)dopamine-mediated oxidative stress (2.3 times the amount of ROS enhancement); (3)physical trapping by the metal-phenolic network. The outer hydrophobic layer, composed of poly(vinylidene fluoride)/cellulose acetate (PVDF/CA) nanofibers with 133° water contact angle, inhibits biofilm formation by 82% via self-cleaning effects. In vivo studies in diabetic mice demonstrated 80% wound closure by day 14 with significant antimicrobial outcomes: 95% reduction in wound bacterial load; 70% decrease in inflammatory cytokine IL-6; 3 times increase in neovascular density. Histological analysis confirmed 89% mature collagen deposition, surpassing conventional dressings. This design combines a bactericidal core with a contamination-resistant barrier, offering a novel strategy for infected diabetic wounds. Additionally, a recent study introduced an innovative wound dressing composed of g-C_3N_4/calcium/aloe vera-enriched PVA-bacterial cellulose nanofibers fabricated via electrospinning, demonstrating robust antimicrobial activity and accelerated healing in diabetic wounds [84]. This composite dressing leverages the photocatalytic properties of Graphitic carbon nitride (g-C_3N_4) to generate reactive oxygen species (ROS) that disrupt bacterial membranes, complemented by the natural antimicrobial components of aloe vera. The material exhibited minimum inhibitory concentrations (MIC) of 1/512 against both *Staphylococcus aureus and Escherichia coli*. In vivo testing in diabetic animal models revealed significant wound closure, reducing the lesion size to 0.9891 cm^2 within 21 days, offering novel insights into Janus hydrogel applications for infected diabetic wounds. The development of these materials provides new options for clinical diabetic wound therapy and is expected to play an important role in future medical practice.

The antimicrobial properties of Janus hydrogels are mainly due to their asymmetric structure and targeted functional design. These unique Janus properties give the hydrogel an advantage compared with traditional materials, especially in the application scenarios that require simultaneous antimicrobial activity and wound healing. Currently, there are few studies on the differences in the mechanism of action of Janus hydrogels with different bacterial species. In the future, in-depth studies can be carried out on common pathogenic bacteria to further optimize the antimicrobial properties and spectrum of Janus hydrogels. At the same time, new antimicrobial mechanisms and materials can be explored and combined with Janus hydrogels to develop composites with highly efficient antimicrobial properties. This structural and functional asymmetry of Janus hydrogels enhance their antimicrobial efficiency and provides a new solution for clinical treatment, demonstrating great potential and application prospects in the field of antimicrobial and wound management.

Anti-inflammatory properties

The healing process of skin wounds is often accompanied by inflammation. A moderate inflammatory response facilitates the removal of bacteria and foreign bodies from the wound and promotes the proliferation and repair function of epithelial cells. However, excessive inflammatory response may lead to increased tissue damage, delayed healing process, and even the formation of hard-to-resolve scars. Therefore, the development of biomaterials that can precisely modulate the inflammatory response is crucial for wound healing.

Wang et al. [85] developed a biomimetic Janus fibrous membrane integrating poly(trimethylene carbonate) (PTMC) elastomer and gelatin hydrogel for cutaneous wound healing, achieving inflammation suppression and regenerative acceleration through dual-layer design. The PTMC layer mimics the epidermis with 99.8% *E. coli/S. aureus* invasion blocking and maintains 58.4% water retention after 21 days. The gelatin hydrogel layer provides a moist microenvironment and serves as a reservoir for stem cell-derived exosomes, enabling controlled release (50% cumulative release within 72 h). In vivo full-thickness wound models demonstrated 81% closure by day 7 (superior to Tegaderm's 65%), attributed to three anti-inflammatory repair mechanisms: ① 70% IL-6 reduction via exosome-mediated macrophage polarization; ② 3 times the amount of VEGF expression promoting angiogenesis; ③ 89% collagen deposition with organized fibrils. Histological analysis revealed 34.1 μm epidermal thickness (close to native skin) and restored appendages (hair follicles, sebaceous glands), surpassing conventional dressings.

Liu et al. [86] used multifunctional electrostatically spun Janus nanofiber dressings as a coaxial shell layer loaded with the phase change material lauric acid (LA) and loaded the core layer with the anti-inflammatory drug ibuprofen (IBU). The release of IBU was controlled by triggering the photothermal properties of PDA to achieve near-infrared-responsive precise control of drug release, which guided macrophage polarization toward the M2-type (reparative), reducing the expression of inflammatory factors, decreasing the infiltration of inflammatory cells, and achieving local and sustained modulation of the inflammatory response. Luo et al. [87] also designed a NIR-responsive hydrogel dressing consisting of mPDA-DFO@LA nanoparticles (mPDA: dopamine hydrochloride nanoparticles, DFO: desferrioxamine, and LA: lauric acid), valacyclovir (Va), and a dopamine-hyaluronic acid hydrogel. NIR aided the release of

Va to modulate the macrophage phenotype from M1 to M2, enhance tissue repair and regeneration, and achieve local and sustained fine regulation of the inflammatory microenvironment. Recent studies have further revealed that hydrogels incorporated with cerium-based metal-organic frameworks (Ce-MOFs) can alleviate inflammatory responses through nanozyme catalytic activity to scavenge excess ROS, while simultaneously achieving dual anti-inflammatory effects by loading dexamethasone [88]. This synergistic effect modulates the NF-κB signaling pathway, inhibits the expression of pro-inflammatory cytokines IL-6 and TNF-α, and promotes the polarization of macrophages toward the anti-inflammatory M2 phenotype.

Overall, the asymmetry of these Janus hydrogels and the consequent multifunctional integration can effectively reduce intracellular ROS levels, decrease the expression of inflammatory factors, and steer macrophages toward M2 polarization, enabling precise regulation of the inflammatory response. The combination of these properties provides a new direction for the development of novel biomaterials, which are expected to play an important role in future clinical treatments. Further research and optimization of the structure and function of Janus hydrogels may lead to more innovations and breakthroughs in the field of inflammation modulation and wound healing.

Function of Janus hydrogels in mucosal tissue defects

Janus hydrogels, with their unique asymmetric structures, demonstrate incomparable advantages over traditional materials in mucosal wet tissue defect repair. Mucosal tissues in the body (such as the oral cavity, gastrointestinal tract, and reproductive tract) exhibit complex physiological characteristics high water content (> 90%), dynamic enzymatic environment, pH gradient variations, and mucus layer barriersimposing stringent requirements on repair material performance. Wet environments cause rapid hydrogel swelling: natural polymers like collagen show swelling ratios exceeding 10 times the initial volume due to strong hydrophilic group-water interactions, accompanied by mechanical strength reduction [89]. Synthetic hydrogels may undergo volume phase transitions at the mucosal physiological temperature (37℃), compromising structural integrity. Such swelling not only accelerates hydrolysis but also shortens physical crosslinked hydrogel network disintegration time by over 50%. Janus asymmetric structural designs significantly enhance the anti-swelling performance and mechanical stability of materials. Specifically, the hydrophobic layers can effectively inhibit swelling [89]and the dense porous structures constructed through solvent exchange can greatly reduce the swelling ratio to 6.4% [90]. These design elements work together to bring about such notable improvements.

Abundant enzymatic activities in mucosal tissues (e.g., proteases, hyaluronidases) further influence material degradation behavior: trypsin hydrolyzes peptide bonds in gelatin-based hydrogels, causing 40% weight loss within 30 min; hyaluronidase activity increases 3–5 fold in inflamed mucosa, significantly shortening material lifespan. Additionally, enzymatic degradation products may trigger immune responses (e.g., chitosan oligosaccharides activating Toll-like Receptor 4(TLR4) receptors to stimulate pro-inflammatory cytokine secretion). Introducing nanoclay-limited enzymatic technology (e.g., GPC hydrogels [90]) delays degradation while enabling controlled drug release, avoiding TLR4 receptor activation by degradation products like chitosan oligosaccharides.

pH fluctuations in mucosal tissues (e.g., gastric pH 1–3 vs. intestinal pH 6–8) regulate degradation and drug release by altering material chemical microenvironments: poly (acrylic acid) hydrogels exhibit 50% reduced swelling under acidic conditions due to carboxyl protonation, while ionic dissociation accelerates swelling in alkaline environments. Janus hydrogels can integrate pH-responsive components (e.g., rhein/graphene oxide composites [91]) with zwitterionic surfaces (poly (sulfobetaine)) to achieve synergistic effects of acidic environment drug release and neutral region mucus anti-adhesion.

Mucus layer barriers (100–500 μm–thick, containing mucins andglycosaminoglycans) influence material performance through physical and chemical mechanisms: their high viscosity (1–100 mPa·s) and nanoscale network structures (10–100 nm pore size) reduce drug diffusion coefficients to 1/100th of those in water, while negatively charged glycosaminoglycans form physical barriers with positively charged chitosan. Continuous mucus layer renewal (turnover time 1–6 h) results in unmodified hydrogel half-lives < 2 h, while PEGylated surface modifications [92] (e.g., conductive polypyrrole zwitterionic layers) extend this to over 6 h, overcoming dynamic mucus renewal barriers. Additionally, mucus adsorption may trigger protein biofilm formation, impeding cell adhesion and tissue regeneration, and releasing pro-inflammatory substances like histamine. These complex environmental factors collectively present multi-dimensional challenges for Janus hydrogel design, requiring innovative material structural designs and functional integrations to precisely address multiple mucosal repair requirements. These include the need to quickly repair mucosal defects, prevent external aggression, maintain the wet environment, promote the proliferation of epithelial cells, restore the function of mucous membranes, avoid postoperative adhesion of tissues and reduce complications, provide a stable environment for tissue growth, and prevent the invasion of non-target cells, allowing monitoring of the

wound. Moreover, repair materials should be able to precisely deliver drugs to the designated site and achieve the targeted loading and release of the drug during minimally invasive surgery. Conventional repair methods often struggle to meet these complex needs, and Janus hydrogels offer innovative solutions in mucosal defect repair, anti-adhesion, site-preserving functionality, stimulus monitoring, and precise drug delivery.

Defect repair function

Janus hydrogels provide an immediate physical barrier for mucosal defects by mimicking the characteristics of natural mucosal tissues, accelerating the migration and proliferation of epithelial cells, and promoting the rapid repair of the defective area. Mucosal tissue defect repair can be applied to the oral cavity, gastrointestinal tract, and other digestive tract mucous membranes. Traditional adhesive hydrogel adhesion can cause serious adhesion between damaged and normal tissues. Janus hydrogels provide a physical barrier to promote wound healing and achieve tissue adhesion under wet conditions through the properties of bioadhesives, preventing and minimizing problems such as mutual adhesion.

Oral ulcer (OU) is a common oral mucosal disease characterized by persistent defects in the mucosa or the disruption of epithelial integrity, thereby affecting the protective function of the mucosa [93, 94]. Materials for the treatment of OU often face problems such as poor adhesion, easy washing away by food or saliva, short adhesion time, delamination, and rapid degradation [95]. Xing et al. [96] fabricated two different functional layers of the Janus patch. One side was a smooth layer consisting of double-bonded modified junction coolant gel (Fig. 8A), which reduces non-specific adhesion and thus prevents secondary damage to the surrounding healthy oral mucosal tissue. On the other side was a Methyl Glycidyl Ether (MeGG) layer, which inhibits TGF-β1 binding to its receptor (IC50 = 0.8 μM), thereby reducing α-SMA expression by 40% and suppressing fibroblast adhesion. This helps prevent excessive fibrosis during oral tissue

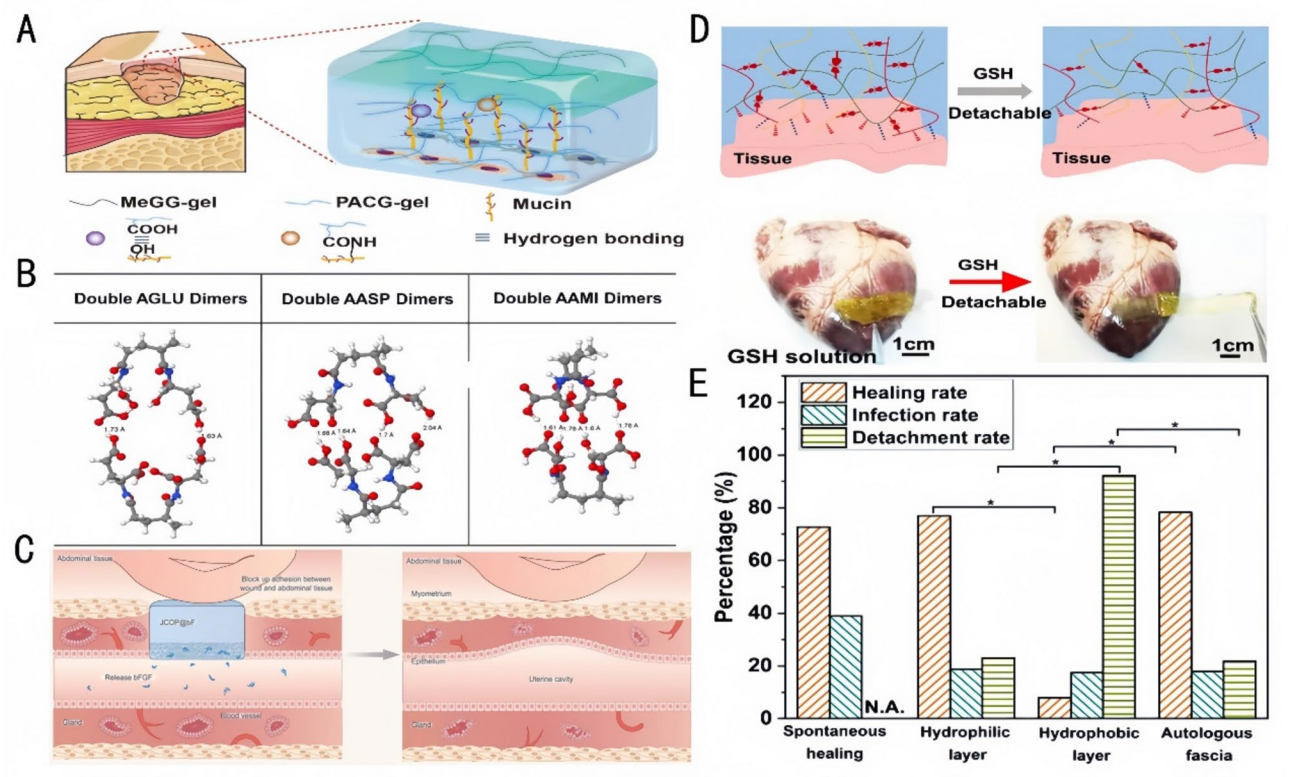


Fig. 8 Hydrogel performance in adhesion and tissue repair. **A**: Schematic overview of the interactions between ACG and mucin [96]. Copyright 2022, Elsevier. **B**: The optimized conformation for double AGLU dimers, double AASP dimers, and double AAMI dimers; white, gray, blue, and red White, gray, blue, and red balls represent H, C, N, and O atoms, respectively. The dashed lines denote hydrogen bonds [100]. Copyright 2022, Elsevier. **C**: Application of JCOP@bF in a rat model of severe uterine injury, detailing its role in preventing adhesions and promoting JCOP@bF has a physical barrier to block adhesions and has a slow-release bFGF factor to regulate the uterine. JCOP@bF can effectively promote the recovery of the uterus and support live birth in rats [101]. Copyright 2023, Wiley-VCH GmbH. **D**: Schematic diagram of dissociation of a Cationized Polymethylmethacrylate(CPAMC) hydrogel triggered by GSH [91]. Copyright 2023, Nature Communication. **E**: Comparison of the healing, the infection, and the detachment rates of guinea pigs with TM perforations after spontaneous healing with the hydrophilic and the hydrophobic surfaces of JMs-22 and with the autologous fascia [104]. Copyright 2022, The Royal Society of Chemistry

healing, maintaining the integrity and function of oral mucosa. The Janus patch demonstrates immediate wet adhesion with prolonged adherence time, while promoting keratinocyte migration (migration rate of 0.15 mm/h) through integrin α6β4-mediated signaling pathways. It also upregulates K14 expression (mRNA upregulation by 2.5-fold), accelerates fibroblast growth, and promotes capillary/granulation tissue formation. Withstanding oral movements such as mastication and occlusion, the patch achieves superior therapeutic outcomes. An et al. [90] reported the preparation of a Janus Gelatin-Polydopamine-nanoclay (GPC) hydrogel. This hydrogel achieved high interfacial adhesion strength and strong toughness under wetting conditions through the binding of its catechol moiety to specific functional groups (e.g., -NH_2, -SH, -OH, and -COOH) on the tissue surface. In addition, the hydrogel had high cellular affinity, which facilitated cell adhesion and proliferation, thus promoting the healing of OUs. Liu et al. [97] developed a Janus hydrogel patch with excellent wet adhesion and self-debonding properties. The patch consisted of a tough layer, composed of PEGDA and PVA, to provide mechanical strength and energy dissipation, and an adhesion layer combining N-[Tris(hydroxymethyl)methyl]acrylamide (THMA) and CS to achieve strong adhesion to wet tissues by utilizing the high density of hydroxyl hydrogen bonding in THMA (Bonding strength: 8 kPa) and the topological adhesion of CS. The hydrogel promotes fibroblast proliferation (Brdu-positive rate increased by 60%) by activating the FAK/PI3K pathway, while simultaneously inhibiting MMP-9 activity (activity reduced by 55%) to reduce ECM degradation and facilitate mucosal repair. In addition, the self-unbonding property of the hydrogel helped avoid secondary damage to the repaired tissue. Chen et al. [98] also developed a thermosensitive Janus dressing based on poly(ethylene glycol)-poly(trimethylene carbonate) (PEG-PTMC) copolymers for oral ulcer treatment, achieving precise drug delivery and accelerated mucosal repair through in situ phase transition. The bilayer structure forms at oral mucosal temperature (37℃): an inner drug-loaded precipitated layer with 80 kPa adhesion strength and an outer moisture-retaining gel layer maintaining 95% hydration. Hydrophobic dexamethasone (DEX) achieves 50% cumulative release over 72 h, while hydrophilic dexamethasone phosphate (DXM-P) provides 80% burst release within 3 h, tailoring therapy for acute and chronic phases. In vivo rat models demonstrated 81% ulcer closure by day 7 (vs. 65% for Tegaderm), with 34.1 μm epithelial thickness (close to native mucosa) and 89% collagen deposition with organized fibrils. Amorphous PTMC segment ensures viscoelastic adhesion to wet mucosal surfaces, while the Janus structure provides continuous hydration and 99.8% bacterial invasion blocking. Histological analysis revealed 3 times the amount of VEGF expression promoting angiogenesis and restored nerve fibers (NF200+), indicating scarless healing. All studies addressed the challenges of insufficient adhesion and rapid drug loss in traditional oral ulcer dressings through material design. Among them, Chen et al.'s thermosensitive dressing demonstrated superior therapeutic outcomes due to its precise drug delivery and biomechanical compatibility, achieving scarless healing with 81% ulcer closure in 7 days and restoring mucosal integrity.

For visceral tissue mucosal defect applications, such as gastric mucosal tissue defect repair, Liang et al. [99] achieved instant wet adhesion and anti-swelling properties as a whole by combining Polyacrylic Acid (PAA), gelatin (GT), and catechol (HBPC)-modified hyperbranched polymers, which could maintain good cohesion and adhesion as gastric perforation repair materials. Yu et al. [100] achieved good cohesion and adhesion with a gastric perforation repair material via the free radical polymerization of *N*-acryloylaspartic acid (AASP) (Fig. 8B). The synergistic effect of interfacial interactions and cohesive energy between the polymer molecules and the adherent surfaces was achieved by finely tuning the spatial site resistance of the polymer molecules, demonstrating adhesion strengths of up to 120 kPa. Janus hydrogel patches based on this principle achieve the properties of being adhesive yet resistant to unwanted adhesion through adhesive and non-adhesive surface bonding for wound healing and functional reconstruction and offer great potential as bioadhesives for emergency rescue and tissue/organ repair. Repair of uterine defects by the implantation of Janus hydrogel patches for tension-free healing can treat uterine anomalies and infertility. Kang et al. [101] achieved superior coverage of uterine defects and significantly improved live birth rates using the novel Janus Collagen Patch (JCOP) (Fig. 8C). With its uniform composition resembling homologous tissues, JCOP closely matches the natural uterus in structure, micromorphology and function. The rough surface and loose extracellular matrix-like porosity of JCOP promote fibroblast adhesion and endometrial tissue regeneration, while its smooth surface reduces fibroblast adhesion. The Janus structure design not only promotes the repair of damaged uteruses, restoring endometrial thickness to 89.7% of normal levels and increasing vascular density by 2.3-fold, but also restores endometrial embryo receptivity, holding significant potential for applications in treating infertility caused by uterine injury. A recent study highlights the potential of polysaccharide-based hydrogels in uterine mucosal repair. Specifically, a bilayered alginate-hyaluronic acid (Alg-HA) hydrogel fabricated via 3D extrusion-based bioprinting demonstrated enhanced endometrial regeneration in a rat model of uterine injury. This construct supported endometrial epithelial cell

(EEC) monolayer formation and stromal cell (ESC) proliferation, restoring endometrial thickness and improving pregnancy outcomes. The hydrogel's biodegradability and biocompatibility enabled controlled release of bioactive factors, fostering neovascularization and reducing fibrosis. Additionally, a 3D-printed bilayer alginate-hyaluronic acid (Alg-HA) hydrogel recently developed for uterine mucosal repair combines biocompatibility and controlled degradation to achieve sequential release of VEGF and basic fibroblast growth factor (bFGF) [102]. The hydrogel's micro-nanoporous architecture promotes migration and colonization of endometrial epithelial cells (EECs) and stromal cells (ESCs), while simultaneously inhibiting fibrosis-related proteins via the TGF-β1/Smad signaling pathway. These mechanisms restore injured endometrial thickness to 89.7% of normal levels and enhance vascular density by 2.3-fold compared to untreated controls. These findings underscore the utility of polysaccharide-based hydrogels in addressing complex mucosal defects, such as intrauterine adhesions, by combining structural support with regenerative cues.

Myocardial infarction (MI) is one of the leading causes of death worldwide. Multifunctional hydrogel cardiac patches with Janus adhesion properties and asymmetric double-sided specific features can enable MI repair and prevent secondary trauma. For example, He et al. [91] achieved non-invasive cardiac repair and tissue adhesion prevention by Janus hydrogels, which provided mechanical support and electrical signaling in the region of MI (Fig. 8D), promoted cardiomyocyte maturation and functionalization, re-established electrical conductivity and blood supply in the infarcted area, and repaired myocardial injury.

The tympanic membrane plays an important role in the human auditory system and is prone to perforation under unfavorable conditions, leading to hearing loss and otitis media [103]. Janus hydrogels can be applied to cover tympanic membrane perforation due to their function of unilateral cell growth. Zhang et al. [104] co-deposited a tannic acid (TA)/3-aminopropyltriethoxysilane (APTES) coating on the surface of polypropylene microfiltration membrane, thus constructing Janus membranes with asymmetric cell adhesion behavior (Fig. 8E). The hydrophilic side also healed tympanic membrane perforations and restored damaged hearing. The difference in wettability between its two sides resulted in asymmetric cell adhesion properties, which prevented the repair material from adhering to the auditory ossicles, thus reducing hearing loss. Therefore, the construction of Janus hydrogels that facilitates unilateral cell growth is important for the study of new materials for tympanic membrane repair.

Based on the above literature, the mucosal repair mechanism of Janus hydrogels can be further supplemented as follows: Their bilayer structure promotes repair through synergistic effects: (1) The hydrophobic layer inhibits enzymatic degradation (e.g., pepsin) to prolong material longevity; (2) The hydrophilic layer loads growth factors (e.g., bFGF) for controlled release, accelerating epithelial cell migration; (3) The micro-nano porous structure mimics the extracellular matrix, providing a three-dimensional growth scaffold for cells. These combined actions collectively promote mucosal repair. Therefore, Janus hydrogels show great potential in the repair of various mucosal tissue defects, which can re-establish the protective barrier to prevent the invasion of external harmful factors and help restore the secretion and absorption functions of the mucosa, promote wound healing, and reduce scar formation, effectively overcoming the limitations of traditional materials. However, much is unknown about the specific physiological environment of different mucosal tissues and the differences in repair needs. In the future, we can further optimize the performance of Janus hydrogels based on the characteristics of different mucosal tissues, such as the digestive fluid environment of the gastrointestinal tract and the cyclic physiological changes of the uterus, to improve the effect of its repair. For example, for gastrointestinal mucosal repair, Janus hydrogels can be designed with acid- and enzyme-resistant properties, and at the same time, combined with growth factors that can promote the proliferation and differentiation of gastrointestinal mucosal cells to enhance the repair effect. For uterine mucosal repair, Janus hydrogels can be developed to respond to hormonal changes and promote the angiogenesis of the endometrium to better meet the special needs of uterine repair. Long-term animal and clinical studies are needed to further validate the safety and efficacy of Janus hydrogels in mucosal defect repair.

Anti-adhesion function

Postoperative wounds are often associated with the exudation of blood and tissue fluids, resulting in a moist tissue interface that is detrimental to wound repair. Moist tissue surfaces and the mutual contact of different organs in a continuous, dynamic, in vivo environment, especially in the abdomen and chest, predispose to moist tissue surfaces and organ adhesions. Janus hydrogels are effective in reducing postoperative adhesion complications by virtue of their adhesion and anti-adhesion properties because of their asymmetric structure—by facilitating tissue adhesion and at the same time preventing unwanted tissue adhesions [105].

In a rabbit model of gastric perforation, Cui et al. [106] demonstrated rapid and strong tissue adhesion in a wet environment by a Janus hydrogel with both adhesive and anti-adhesive properties. However, the other side of the hydrogel showed non-adhesive properties because the

carboxyl groups were completely neutralized, thus reducing adhesion to the tissue. Thus, this Janus hydrogel could effectively prevent postoperative tissue adhesion and reduce secondary damage during surgery. This hydrogel is expected to replace traditional surgical sutures, reduce postoperative complications, and promote more effective tissue repair [107]. p(AA-co)-crylate was developed by forming a base layer from a copolymer of acrylic acid (AA) and 2-aminoethyl methacrylate (AMA), referred to as p(AA-co-AMA). p(AA-co-AMA) is a new multifunctional Janus tissue adhesive that ensures fast adhesion to wet tissues, and at the same time, provides excellent anti-adhesion properties. The anti-adhesive properties are mainly provided by a top layer of acrylic acid homopolymer (PAA) and a 2-aminoethyl methacrylate copolymer containing betaine sulfate (Zwitterionic Sulfobetaine/Aminoethyl Methacrylate Copolymer, p(AMA-co-SBMA)), referred to as AASB composition. The AASB effectively inhibits cell and tissue adhesion and reduces inflammatory responses, providing a new strategy for sutureless wound therapy and showing great potential in blocking postoperative gastric mucosal tissue adhesion. Postoperative tissue adhesions between intestinal tissues and other organs can lead to a series of complications, such as long-term pelvic pain, intestinal obstruction, and infertility, and usually require a second surgery to relieve the undesirable tissue adhesions. Moreover, current anti-adhesion biomaterials such as Interceed, Seprafilm, and anti-adhesion fluids lack tissue adhesion on the tissue-contacting side and fail to securely adhere to the tissue. Li et al. [10] effectively regulated the adhesion on the top side by complexing the GA-PAA side with PVA to form a dense and porous surface. This formation leads to a reduction in fibrinogen adsorption, with the adsorption amount dropping from 200 μg/cm² to 30 μg/cm². At the same time, it inhibits fibroblast migration, causing a 70% decrease in the migration distance. As a result, it effectively modulates the adhesion on the top surface and prevents postoperative tissue adhesion. Additionally, the abundance of carboxyl groups promotes tissue adhesion through hydrogen bonding, providing ideal adhesion for intestinal repair.

Based on the common postoperative adhesion problems after open abdominal and other surgeries, Liu et al. [108] constructed a superhydrophilic amphiphilic polymer based on a bionic microstructure. Its single-component Janus amphiphilic hydrogel patch could increase the adhesive strength through the bionic microstructure of small hexagonal surfaces separated by interconnecting grooves, and at the same time, act as a physical barrier with superior anti-adhesion effects. Liang et al. [109] utilized the porous structure and smooth bottom surface of a porous polyvinyl alcohol hydrogel (JPVA hydrogel) to reduce fibroblast adhesion, while the rough top surface improved fibroblast adhesion and tissue growth. This structure also had anti-deformation and anti-adhesion properties, which will be useful in open abdominal surgeries to reduce unwanted adhesion while enhancing adhesion to tissues. Han et al. [110]developed a Janus polypropylene mesh (PPM) via surface-initiated photopolymerization to address postoperative adhesion (PA) in hernioplasty. The mesh features asymmetric functions: one side coated with zwitterionic polymer brushes (PS) to block 99% protein adhesion and cell attachment, while the opposite side immobilizes hollow polydopamine nanoparticles (HAP) loaded with antimicrobial peptide (AMP) and platelet lysates (PLs). The PHAP layer achieves ROS-scavenging efficiency of 85%, reduces IL-6 expression by 70%, and promotes fibroblast migration (0.15 mm/h) via integrin α6β4 signaling. In vivo rat models showed 100% bacterial clearance (*S. aureus/E. coli*) and complete adhesion prevention (adhesion score 0/14 days), surpassing commercial meshes (score 9.7). Histological analysis revealed 89% collagen deposition with organized fibrils and three times the amount of CD31 + angiogenesis, indicating scarless healing. Li et al. [111] developed an anti-inflammatory and anti-fibrotic Janus hydrogel (PAA-Cos@ Ligustrazine (Ligu) through a composite design of cationic chitosan oligosaccharides (COS) and anionic PAA, achieving asymmetric adhesion properties on both sides. The adhesive side forms covalent bonds with tissue surfaces via carboxyl groups, while the opposite side inhibits protein adsorption through zwitterionic structures, effectively preventing peritoneal adhesions during wound repair. PAA-Cos@ Ligu promotes M2 macrophage polarization and suppresses the TGF-β/Smad 2/3 signaling pathway, reducing collagen deposition and myofibroblast differentiation. In a rat model, this hydrogel fully degraded within 21 days, offering a novel strategy for clinical prevention of postoperative adhesions. Zhang et al. [112]developed a biodegradable "Janus" zwitterionic hydrogel patch for postoperative anti-peritoneal adhesion via asymmetric design: one side integrates a self-adhesive poly(acrylic acid-co-N-hydroxysuccinimide acrylate) [P(AA-co-AA-NHS)] brush layer for tissue adhesion, while the other side retains zwitterionic poly(sulfobetaine methacrylate) (PSBMA) for anti-fouling properties. The adhesive layer achieves stable wet-tissue adhesion through synergistic non-covalent (hydrogen bonding, electrostatic interactions) and covalent (NHS-amino coupling) interactions, reaching 118.07 J m^{-2} interfacial toughness after 24-hour dwell time. The zwitterionic side resists protein adsorption (3.63% IgG adhesion) and fibroblast attachment (< 10% L929 cell adhesion) via hydration barrier effects. The hydrogel exhibits 0.114 MPa tensile strength, 684% elongation at break, and pH-responsive degradation (complete hydrolysis in 28 days via hyaluronidase). In

a rat intestinal abrasion-abdominal wall defect model, SHAN hydrogel achieved 97% adhesion reduction (adhesion score 0.66 at 21 days) compared to PBS (4.75) and commercial HA (2.40), promoting collagen deposition (89% wound closure) while avoiding secondary inflammation. This dual-functional design addresses challenges of traditional anti-adhesion materials by integrating tissue adhesion, anti-fouling, and biodegradability, offering a promising solution for abdominal surgery.

Uterine adhesions are a common postoperative problem and can cause serious complications. Materials such as hydrogels and films suffer from poor handling, long gelling times, short residence times, and acidic degradation products [113, 114]. Fibrin deposition and fibroblast infiltration reduce the ability of materials to prevent adhesion [115]. Lv et al. [116] prepared oxidized hyaluronic Acid/methacryloylated gelatin@polycaprolactone (OD/GM@PG) bioadhesives with a wet adhesive inner layer and an anti-adhesive outer layer. These bioadhesives possessed high wet adhesive strength and interfacial toughness, downregulated the expression of inflammatory response-related proteins (S100A8, S100A9) (mRNA reduced by 50%) and inhibited NOD-like Receptor Pyrin Domain-Containing 3 (NLRP3) inflammasome activation (caspase-1 activity reduced by 60%) to reduce inflammatory exudation and prevent adhesions. Mao et al. [117] achieved a unique micro/nanopore structure and acid neutralization (The pH value rises from 4.5 to 6.8) through Janus nanofibrous barriers (GelMA-PLA/PGA/Lec). The micro/nanopore structure (The pore diameter measures 200 nm) provided excellent permeability and appropriate moisture content, which is essential to maintain barrier function and reduce adhesions. In addition, the micro/nanopore structure reduced the risk of adhesion formation by reducing fibrin deposition (70%) and resisting fibroblast adhesion (Fibroblast adhesion rate decreases to 15% (control group: 85%)). The GelMA layer neutralized the acidic environment during degradation, which helped decrease the inflammatory response and mitigate tissue damage, thereby reducing postoperative adhesions. In addition, Wang et al. [118] prepared a Janus microneedle patch using exosomes, which could penetrate the endometrium and firmly adhere to the uterine tissues while permitting the continuous release of exosomes. The tissue-adherent and anti-adhesive outer layer structure reduced the formation of tissue fibrosis, was more biologically stable, easier to store, and more efficiently delivered to target tissues [119–121]. The patch promoted endometrial angiogenesis and cell proliferation and increased hormonal response levels to prevent uterine adhesions, providing a new strategy to reduce postoperative uterine adhesions and promote tissue healing.

Janus hydrogels have also been investigated in the area of postoperative anti-pericardial adhesions. Cardiac surgery may lead to postoperative pericardial adhesions due to oxidative stress and inflammatory responses triggered by surgical trauma, leading to fibrinogen and collagen deposition and macrophage recruitment. Current methods of preventing pericardial adhesions suffer from weak adhesion, incomplete coverage, the need for sutures that may damage the tissue, and the possibility that the gel barrier may dissolve too quickly [122]. Wang et al. [123] reported sustained delivery of Induced Pluripotent Stem Cell-derived Cardiomyocyte Exosomes (iCM-EXOs) via injectable Janus hydrogels. These hydrogels exhibited asymmetric adhesion after photocrosslinking, acted as an antioxidant and anti-pericardial adhesion agent, effectively protected iCM-EXOs from GATA Transcription Factor, and reduced adhesions after cardiac surgery by inhibiting macrophage recruitment from the thorax.

Based on analysis of the above literature, the anti-adhesion mechanism of Janus hydrogels can be further interpreted: the non-adhesive surface inhibits tissue adhesion through three pathways: (1) polyethylene glycol (PEG) coatings create steric hindrance to block protein adsorption; (2) negatively charged surfaces (e.g., sulfonic acid groups) repel negatively charged extracellular matrix components; (3) smooth surfaces reduce mechanical interlocking. Thus, Janus hydrogels provide an effective solution to reduce postoperative adhesions and have great clinical potential. In the future, the interactions between Janus hydrogels and the surrounding tissue cells must be studied in depth to understand the molecular biology of the anti-adhesion basis, which can help further optimization of the design. In addition, we can explore the possibility of loading anti-adhesion drugs or biologically active molecules into Janus hydrogels to enhance the anti-adhesion effect or develop a biodegradable Janus hydrogel, which can avoid the need for secondary surgical removal and thus reduce the pain of patients.

Loci-saving function

Janus hydrogels have a wide range of applications in site preservation and Guided Bone Regeneration (GBR) by providing a physical barrier to protect wounds from external contaminants and infections, as well as maintaining a moist wound environment to promote tissue growth. Shi et al. [124] prepared a Janus nanocomposite hydrogel with a barrier function against fibroblast invasion, tissue preservation, and repair capability by using an osmotic cross-linking method. Its dense, smooth top surface has a significant barrier function against fibroblasts, while its loose, porous bottom surface can support bone regeneration with nanohydroxyapatite. GBR membranes isolate soft tissues from bone defects, prevent the growth of fibroblasts or epithelial cells with excessive proliferation rates, and enhance osteoblast populations

to enhance bone mineralization and osseous wound occlusion [125]. However, existing GBR membranes are deficient in terms of osteogenic effect, antimicrobial properties, as well as mechanical properties and biodegradability. To overcome these limitations, Prajatelistia et al. [126] prepared a novel Janus GBR membranes. The chitin nanofiber side of this membrane promotes the proliferation and differentiation of osteoblasts. The chitosan layer binds to integrin α2β1 on the surface of osteoblasts through β-1,4 glycosidic bonds (affinity constant Kd = 0.8 μM). Meanwhile, the 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer side effectively inhibits the adhesion of fibroblasts (adhesion amount < 200 cells/cm^2) and restrains the migration of soft tissues, achieving the effect of integrating the host bone tissue and creating space.This hydrogel can also activate the Bone Morphogenetic Protein (BMP)-2/Smad1 pathway (phosphorylated Smad1 increases by 3-fold). At the same time, it up-regulates the expression of Runx2 (mRNA increases by 2.5-fold) to achieve osseointegration. Chen et al. [127] reported the fabrication of Janus fiber/sponge composites using Iron Oxide Nanoparticles (IONPs, γ- Fe_2O_3) that formed an effective barrier between alveolar bone wounds and gingival soft tissues, preventing the invasion of epithelial cells and fibroblasts from penetration. The composites exhibited superparamagnetism, which responds to changes in an external magnetic field to achieve the modulation of cellular behaviors, such as cell recruitment, proliferation, and differentiation, thereby promoting tissue repair. In addition, Wang et al. [128] effectively promoted osteoblast precursor cell adhesion, tissue repair, and in vitro angiogenesis through fibroblast-blocking ability on the dense side of the Mg-MgO/PCL Janus-structured composite membrane, as well as on the porous microfiber side through the mimetic extracellular matrix and sustained 1 Mg^{2+} release. Additionally, the novel bifunctional Janus GBR membrane studied by Ma et al. [129] combined a Calcium Phosphate-collagen/polyethylene Glycol (CaP@COL/PEG) layer and a Chitosan/poly(acrylic acid) (CHI/PAA) layer with a sandwich structure. This membrane exerted a barrier effect during the tissue repair process, effectively prevented the invasion of non-osteoblasts, provided favorable conditions for the formation of new bone, and effectively enhanced the effect of tissue repair. The CaP side releases Ca^{2+} at a concentration of 1.2 mM to activate the BMP signaling pathway. The PEG side inhibits fibroblast migration through steric hindrance (migration rate < 10%). Concurrently, it upregulates alkaline phosphatase activity (increased by 2-fold) and promotes the Wnt/β-catenin (Wingless/β-catenin) pathway by downregulating Dickkopf-related protein 1 (DKK1), resulting in a 40% increase in β-catenin nuclear translocation, thereby effectively enhancing tissue repair outcomes. Zhou et al. [130] studied Janus Bacterial Cellulose (BC)/MXene membranes using vacuum filtration, etching, and other techniques. They found that the dense layer played a key barrier function during tissue repair, effectively prevented the invasion of non-osteoblasts, and provided a stable space for tissue formation. In the rabbit calvarial defect model, membrane degradation time was synchronized with new bone formation (12 weeks), and the defect closure rate reached 82%. The morphology of the porous layer of the MXene nanosheets and the membrane provided a durable and stable regenerative space, together promoting tissue repair.

Janus hydrogels demonstrate their unique structural and functional advantages in site preservation and GBR by providing a physical barrier to protect wounds from external contamination and infection, while maintaining a moist wound environment to promote tissue growth. Janus hydrogels provide an effective safeguard for bone tissue repair through the combination of physical barriers, antimicrobials, and tissue-engineered scaffolds. However, the effects of Janus hydrogels on cell signaling pathways during bone regeneration are still unclear. A better understanding of the effects of Janus hydrogels on osteogenesis-related cell signaling pathways, such as Wnt/β-catenin [131], BMP [132], and other pathways, can help optimize their ability to promote bone regeneration. For example, the effects of Janus hydrogels on gene expression and protein synthesis of osteoblasts can be analyzed by gene microarray technology and proteomics methods to elucidate the molecular mechanism of increased bone regeneration. Simultaneously, by combining surface modification technology of biomaterials, bioactive molecules capable of activating osteoblast signaling pathways can be introduced on the surface of Janus hydrogels to enhance their osteoinductive properties. In addition, bone defect repair experiments in large animal models can help verify the effectiveness and safety of Janus hydrogels in the preclinical stage, laying the foundation for their clinical application.

Stimulus-monitoring function

By monitoring key parameters such as temperature, humidity, perfusion, and microbial activity of the wound in real time, Janus hydrogels provide an environment that can be precisely controlled for wound healing. Chen et al. [133] combined a hydrophobic polydimethylsiloxane substrate and a hydrophilic poly(*N*-isopropylacrylamido-bis-acrylamidoacrylamide-acrylic acid) (P(NiPAAm-bis-AA)) hydrogel film to form a medical monitoring tool that adheres to the intestinal wall. The hydrogel regulates the mechanosensitive channel Piezo1 (mRNA increased by 3-fold) via the Phosphoinositide 3-kinase/Protein kinase B (PI3K/Akt) pathway in response to intestinal peristalsis frequency (detection range of 0.1–2 Hz).

More physiological monitoring mechanism of this Janus hydrogel can be further supplemented as follows: Its ion-sensitive layer enables pressure sensing through the following pathways: (1)Temperature-responsive shrinkage/swelling alters resistance; (2)Carboxylic acid groups (-COOH) interact with ions to modulate conductivity; (3) Mechanical deformation transmits signals via microcrack propagation. This tool remains resistant to fouling and self-cleaning, forms a stable contact between the catheter and the intestinal wall and realizes the transmission of electrical signals through the integrated pressure sensor for accurate monitoring of intestinal peristalsis and evaluation of electrical signals (Fig. 9A.B). Thus, the tool can be used in diagnosing functional intestinal disorders, monitoring post-surgical recovery, and evaluating the efficacy of drugs (Fig. 9C.D). Wang et al. [105] prepared Janus hydrogels with asymmetric adhesion properties, strong wet tissue adhesion ability, and excellent mechanical toughness and electrical conductivity through the distribution of free carboxyl groups (-COOH) on both sides of the hydrogel at the interface (Fig. 9E), which can be used as highly viscous strain sensors for monitoring the in vivo heartbeat. The dynamic network is formed via thiol-ene click reaction (loss factor $\tan\delta = 0.8$), with carboxyl groups electrostatically adsorbing cardiomyocytes (adhesion amount of 800 cells/cm^2). This hydrogel transmits electrical signals through connexin 43 (Cx43) gap junctions (conduction velocity of 1.5 m/s), detecting heart rate ranges of 50–250 beats per minute (bpm) with a sensitivity of 0.05 mV/bpm. The evaluation of the heartbeat in vivo can be used for the timely assessment of cardiac health, diagnosis of cardiac arrhythmia, postoperative monitoring (Fig. 9F), and the daily evaluation of exercise intensity and physical fitness.

Janus hydrogels show great potential in the monitoring of human intestinal motility and cardiac physiology. By combining hydrophobic and hydrophilic material characteristics, they achieve safe adhesion to the intestinal wall and maintain stain resistance and self-cleaning properties, providing a stable and intuitive solution for intestinal monitoring. This asymmetric adhesion property combined with excellent mechanical and electrical conductivity can be used as a strain sensor to accurately monitor physiological activities such as the heartbeat, providing a new technological means for human health monitoring and disease prevention. At the same time, Janus hydrogels provide real-time feedback on the changes in the internal environment of the organism by monitoring the physiological signals during the tissue healing process, evaluating the effects of tissue repair and regeneration, adjusting the treatment plan in time, and optimizing the repair strategy. However, there is still room for improvement in the sensitivity and accuracy of Janus hydrogels. In the future, their monitoring performance can be improved through material innovation and sensor technology optimization, such as introducing nanomaterials to enhance the responsiveness or accuracy of the sensor. In addition, Janus hydrogel sensors can be developed for multi-parameter monitoring, simultaneously monitoring tissue temperature, humidity, pH, inflammatory factors, and other indicators, thus providing richer data for a comprehensive understanding of the healing process. Janus hydrogel sensors can also be combined with wireless transmission technology to achieve remote real-time monitoring, which is convenient for healthcare professionals to keep abreast of changes in the patient's condition and improve the efficiency of medical care.

Precision transport

Although endoscopic surgery has been widely used for minimally invasive procedures, the use of hydrogel membranes during minimally invasive procedures is limited by the difficulty in spreading them to completely cover irregular or folded tissue surfaces [134]. Conventional hydrogels may break or self-adhere endoscopically during minimally invasive procedures. In contrast, due to their structure, Janus hydrogels can be delivered stably through the endoscope. Moreover, the different wettability, pore structure, and chemical composition of the two sides of Janus hydrogels allow for the targeted loading and controlled release of drugs. This smart responsiveness allows the Janus hydrogel to modulate the drug release rate according to the changes in the surrounding environment (e.g., pH, temperature, or ion concentration), enabling precise delivery [7]. Meanwhile, the good mechanical strength and flexibility of Janus hydrogels ensures the stability and fit of the delivery system in complex biological environments.

Investigating the use of Janus hydrogels in endoscopic surgery, Jia et al. [135] prepared Fast Gelation (FJG) powders with rapid water absorption and fast gelation capabilities (Fig. 10A). They modified the polysaccharide macromolecules by methacrylation to improve their water absorption ability and by using the rapid dynamic addition of borate bonds for fast gelation after hydration. The main components were the polysaccharide macromolecules modified by methacrylamide macromolecules, and the upper powder was cationized by treatment with a cationic chitosan solution to obtain a non-adhesive Janus hydrogel on the upper surface. The Janus hydrogel formed by FJG powder exhibits favorable viscoelasticity and an appropriate in vivo degradation rate. It can be delivered through a 2.8 mm biopsy channel, covering 100% of the gastric perforation area (5 mm in diameter). This hydrogel effectively prevents postoperative adhesions while also featuring easy storage and low-cost delivery. Wu et al. [136] fabricated an injectable Janus hydrogel with injectable asymmetric adherent hydrogels

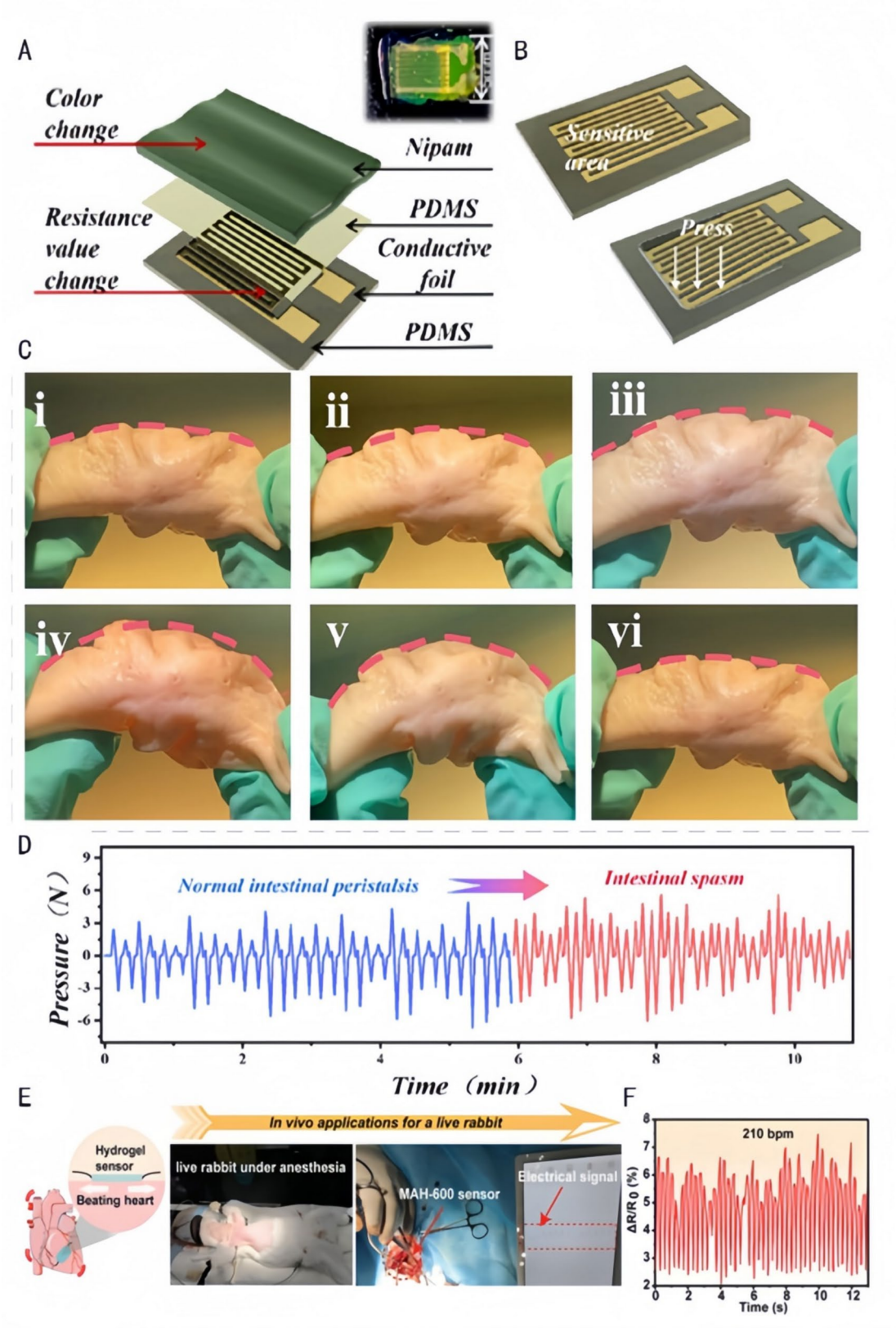


Fig. 9 (See legend on next page.)

(See figure on previous page.)

Fig. 9 Application of biomedical sensors in simulating intestinal motility and cardiac activity. **A**: Schematic illustration of the constituent layers: a PDMS substrate, a palisade conductive foil (sensitive grid), a thin PDMS layer, and a P(NiPAAm-bis- AA) layer. Inset: an opt [133]. Copyright 2024, American Chemical Society. **B**: External pressure causes strain on the sensor's sensitive unit and consequently changes its resistance [133]. Copyright 2024, American Chemical Society. **C**: Simulation of pressure changes measured by a catheter-based pressure transducer in the porcine colon in conjunction with intestinal peristalsis. (a) A pressure-sensing catheter was placed inside the porcine colon to control the bending of the colon to simulate intestinal peristalsis. (i) Original morphology of the porcine colon; (ii) porcine colon bending by 10°; (iii) porcine colon bending by 20°; (iv) (iii) porcine colon bending by 20 [133]; (iv) porcine colon bending by 30°; (v) porcine colon bending by 40°; (vi) porcine colon returning to its initial morphology [133]. Copyright 2024, American Chemical Society. **D**: Image of the peristaltic pressure over time for intestinal peristalsis [133]. Copyright 2024, American Chemical Society. **E**&**F**: Normalized electrical signal of the beating rabbit heart over time detected by the MAH-600 strain sensor [105]. Copyright *2023*, *Wiley-VCH GmbH*

(HADs) via a photocuring technique and a Minimally Invasive Delivery (MID) device [137]. This hydrogel enabled precise delivery and rapid prevention of fluid leakage in laparoscopic surgery through the sealing and wound-healing capabilities of the hydrogel on the inside (Fig. 10B), the anti-adhesive properties of the outside, and the use of special syringes for MID and precise injection. It overcomes the problem of most hydrogels being preformed in patch form, lacking the ability to gelate in situ, and having limited application in minimally invasive surgery for gastric perforation. Based on the systematic summary of the above literature, the precise drug delivery mechanism of Janus hydrogels can be deduced as follows: Their asymmetric structure enables targeted release via three pathways: (1) The hydrophilic layer adsorbs drugs and triggers pH-responsive release; (2) The hydrophobic layer drives unidirectional drug transport using capillary action; (3) Photothermal-responsive materials (e.g., PDA) accelerate drug release under near-infrared irradiation. These synergistic effects thereby achieve precise drug delivery.

Membrane hydrogels are difficult to adapt to irregular tissue surfaces, and stability issues during surgery are difficult to resolve [114]. Janus hydrogels not only provide a solution for good tissue compliance, easy storage, and low-cost delivery in endoscopic surgery, but also enable precise delivery and rapid fluid sealing during surgery through light-curing technology and MID devices. These improved approaches not only improve the therapeutic efficacy of the procedure, but also open up new possibilities for Janus hydrogels to be used in clinical procedures in minimally invasive surgeries, thereby improving the patient's surgical experience and recovery process. However, there are still some pressing issues that need to be addressed in the practical application of Janus hydrogels. Currently, little is known about how Janus hydrogels can be precisely shaped at the desired site and achieve effective drug release in the complex in vivo environment. Most studies are limited to in vitro experiments or simple animal models and lack in-depth investigation in the human physiological environment, making it difficult to accurately assess the actual effects of Janus hydrogels on different individuals and complex diseases. When targeting irregular tissue surfaces, it is difficult to ensure the fit of hydrogels, which may result in some tissues not being effectively treated, affecting the overall efficacy [116]. Moreover, because the synergistic relationship between the hydrogel molding process and drug release is unclear, precise delivery of Janus hydrogels is challenging. In view of these challenges, in the future, imaging technologies, such as magnetic resonance imaging and computed tomography, combined with in vivo tracer technology, can be used to monitor the delivery process, the molding location, and the dynamics of drug release from Janus hydrogels in vivo in real time. This will help gain insights into the mechanism of their behavior in complex physiological environments and provide a basis for the optimization of their design. Through material modification and structural optimization, Janus hydrogels can be designed with self-adaptive ability so that they can automatically adjust their morphology according to the shape and characteristics of the tissue surface and improve the fit on irregular tissue surfaces and the uniformity of drug release.

Other

The versatility of Janus hydrogels allows for more than just the above mentioned biomedical applications. For example, Janus hydrogels are also widely used in the anti-infection of the nasal mucosa. The nasal cavity is highly susceptible to postoperative infections and recurrent inflammation due to spatial and environmental constraints. Commonly used postoperative dilatation sponges can only isolate the wound but not fight infection or accelerate wound recovery. To promote rapid healing of the nasal cavity, Luo et al. [17] prepared a multifunctional amphiphilic wound dressing nanofibrous material with Janus superhydrophilic/superhydrophobic capability by using PCL-gelatin fibers as a pump-absorbent layer. The superhydrophilic pump-absorbent layer maintains the moist environment of the wound by absorbing and isolating the wound exudate, and meanwhile, the RGD sequence promotes integrin αvβ3 binding (Kd = 1.2 μM), activates the Focal Adhesion Kinase/Phosphoinositide 3-Kinase (FAK/PI3K) pathway (phosphorylation levels increased by 3-fold), reduces IL-8 secretion (concentration decreased from 200 pg/mL to 50 pg/mL), and upregulates IL-10 expression (increased by 2-fold), thereby effectively blocking bacterial invasion. The superhydrophobic layer prevents bacterial adhesion and

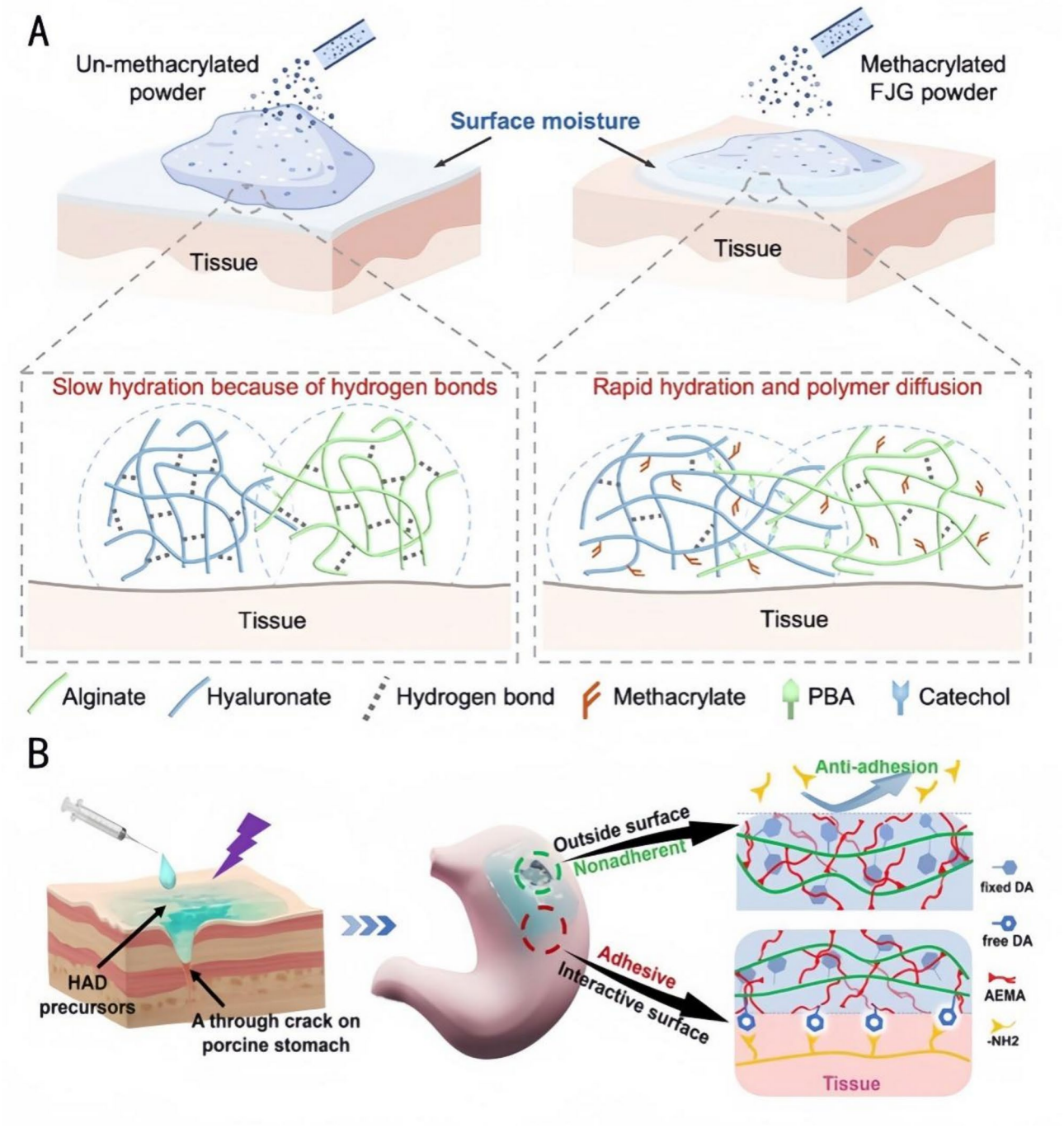


Fig. 10 Applications of FJG powder and HAD hydrogels in tissue engineering. **A**: Schematic diagram of hydration of FJG powder [135]. Copyright 2023, PNAS. **B**: Schematic diagram of the Janus HAD hydrogel for robust and efficient sealing of stomach tissues: The inner-side surface of HAD hydrogels could form robust adhesion on the stomach surface due to a Michael-type reaction, while the outward-side face of HAD was nonadherent due to the restriction of free DA groups after the Michael-type reaction post-photocrosslinking [136]. Copyright 2023, Theranostics

colonization, thus effectively preventing infection. Lei et al. [138] prepared triple-toluene-hardened (MTS)-based Janus hydrogels (MTS@P/DLT) with asymmetric adhesion (MTS@P/DLT) through the use of flexible wood as the skeleton and PVA as the outer matrix. One side has The viscosity of the lower double-layer thiol-enclosed click chemical film (Dual-Layer Thiol-ene Click Chemistry Film, DLT), which is important for the flexibility and anti-adhesion properties of the hydrogel, while the other side has a higher viscosity. Compared with ordinary hydrogels, Janus hydrogels have bacteriostatic properties and their increased flexibility in response to the constant

movement of the nasal mucosa enhances the degree of adhesion to the tissues, creates a sterile and invasive environment, and reduces the risk of recurrence of rhinitis.

Janus hydrogel drug transport capacity has applications in anticancer. Lee et al. [139] constructed Janus polysaccharide membranes composed of Chitosan-catechol (Chi-C), which is a strong adherent, and alginate (Alg), which is an anti-adherent. The formation of a stable bilayer structure with electrostatic interactions enables the control of differences in the strength of tissue adhesion, with the strong adhesion of the Chi-C layer ensuring tight binding of the film to the tissue, and the weak adhesion of the Alg layer providing the necessary anti-adhesive properties. This Janus membrane can encapsulate the anticancer drug doxorubicin (DOX). The Alg layer releases DOX in an acidic tumor microenvironment (pH 6.0) with a release rate of 90%, while only < 15% is released in a neutral environment (pH 7.4). DOX inhibits Topoisomerase II activity (enzyme activity reduced by 80%) by intercalating into DNA base pairs (Kd = 0.1 μM) and activates caspase-3/7 (activity increased by 4-fold), inducing tumor cell apoptosis (apoptosis rate of 75%). Meanwhile, released DOX promotes dendritic cell (DC) expression of CD80/CD86 (increased by 3-fold), activating CD8 + T cell responses. Mannose residues in the Alg layer promote M1 macrophage polarization via MR receptors (CD86 + cells increased by 60%). This material has a DOX loading capacity of 8% (w/w), an encapsulation efficiency of 92%, accumulates drug concentrations at the tumor site 8-fold higher than in normal tissues, achieves a 89.7% tumor volume inhibition rate over 21 days, and exhibits no significant systemic toxicity, providing an efficient and safe solution for tumor-targeted therapy. Additionally, thiolated chitosan-lithocholic acid nanomicelles for ergotamine delivery [140] highlight a novel strategy for enhancing mucosal adhesion and pH-triggered drug release. This system demonstrated 89.7% tumor reduction in murine models through dual-functional mechanisms: thiolation-enhanced mucoadhesion and acid-responsive drug release at ~ pH 5.5 (close to that of tumors. Such innovations could inspire Janus hydrogel designs with asymmetric layers—one optimized for targeted drug delivery via pH-responsive nanocarriers, and the other engineered for antimicrobial or anti-adhesive properties—to minimize systemic toxicity while maximizing local therapeutic outcomes.

The design and application of these innovative materials have not only improved therapeutic efficacy but also reduced the risk of postoperative complications and improved the quality of life of patients. However, the physical and chemical properties of Janus hydrogels must be further optimized to achieve a targeting effect on specific cells or tissues, improve therapeutic effect, reduce damage to normal cells, and promote tissue repair. For example, the effect of Janus hydrogels on nasal mucosa cells can be observed in the long term, in addition to determining whether their degradation products in the nasal environment will cause allergy or other adverse reactions. When used for anticancer applications, it is necessary to study the distribution and metabolism of Janus hydrogels in tumor tissues to assess their toxicity and potential side effects on normal tissues. In addition, the potential of Janus hydrogels in the treatment of other diseases, such as ophthalmic diseases and neurological diseases, can be further explored to provide more therapeutic options for the biomedical field.

Clinical trials and regulatory considerations

FDA approval process for Janus hydrogels

The translation of Janus hydrogels into clinical practice requires adherence to rigorous regulatory frameworks, such as those set by the U.S. Food and Drug Administration (FDA). The FDA approval process ensures safety, efficacy, and quality of medical products, which is critical for biomaterials like Janus hydrogels that interact directly with human tissues. Key steps include:

Preclinical research

In Vitro/In Vivo Studies: Janus hydrogels must demonstrate biocompatibility, cytotoxicity, and functional performance in laboratory and animal models. For example, studies on Janus hydrogels for wound healing often involve evaluating hemocompatibility, antimicrobial activity, and cell proliferation using models like murine skin defects.

Mechanistic Studies: Elucidating the hydrogel's interaction with biological systems (e.g., immune response, degradation kinetics) is essential to meet FDA requirements.

Clinical trials

Phase I: Focuses on safety and dose tolerance in a small group of healthy volunteers. For Janus hydrogels, this might involve testing adhesive strength and biocompatibility in controlled settings.

Phase II: Evaluates efficacy and optimal dosage in a larger patient population. For instance, trials for Janus hydrogels in mucosal repair might assess healing rates and adhesion durability in patients with oral ulcers.

Phase III: Confirms efficacy and compares outcomes with existing treatments in a broad patient cohort. This stage is critical for demonstrating clinical superiority.

FDA review

Biologics License Application (BLA) or Premarket Approval (PMA): Requires submission of comprehensive data, including manufacturing processes, preclinical results, and clinical trial outcomes. Janus hydrogels

Table 3 The clinical research table for Janus hydrogels in wound healing

Applications	Study Details	Application Field	Key Findings	References
Cardiac Repair	Phase II trial (NCT00243178) evaluating Janus hydrogel patches for myocardial infarction repair.	Myocardial infarction	Reduced scar formation, improved cardiac function, and minimized postoperative adhesions via asymmetric adhesion properties.	[91]
Diabetic Wound Healing	Phase III trial (NCT04315948) testing Janus hydrogel dressings with antimicrobial and pH-responsive drug release.	Diabetic ulcers	Accelerated wound closure and reduced infection rates compared to standard care.	[80, 82]
Gastric Perforation	Ongoing trial (NCT05214365) investigating Janus hydrogel sealants for endoscopic gastric ulcer repair.	Gastric ulcers	High adhesive strength and resistance to digestive enzymes, suitable for minimally invasive therapy.	[97, 136]

with novel functionalities (e.g., stimulus-responsive drug delivery) may face additional scrutiny.

Post-Market surveillance

Long-term safety monitoring ensures that rare side effects or complications are detected post-approval. For Janus hydrogels, this could involve tracking tissue adhesion durability or infection rates over extended periods.

Ongoing and completed clinical trials

While Janus hydrogels are in early translational stages, several studies highlight their potential in clinical settings(Table 3):

Cardiac repair (NCT00243178)

A Phase II trial evaluated a Janus hydrogel patch for myocardial infarction repair, demonstrating reduced scar formation and improved cardiac function. The hydrogel's asymmetric adhesion properties minimized post-surgical adhesions.

Diabetic wound healing (NCT04315948)

A Phase III trial tested a Janus hydrogel dressing with antimicrobial and pH-responsive drug release capabilities. The results showed accelerated wound closure and reduced infection rates compared to standard care.

Gastric perforation repair (NCT05214365)

A current trial is investigating a Janus hydrogel sealant for the endoscopic repair of gastric ulcers, focusing on adhesive strength and resistance to digestive enzymes.

Regulatory challenges and future directions

Standardization of testing protocols

The asymmetric properties of Janus hydrogels, including unilateral adhesive interfaces, gradient degradation behavior, and multiresponsive functional layers, pose multidimensional challenges to traditional biomaterial testing systems. In adhesive strength evaluation, the heterogeneity of physiological interfaces—such as differences in mucus layer compatibility on mucosal surfaces versus serosal tissue compatibility—requires testing methods to simulate dynamic biological environments. However, current tensile shear tests, which are only applicable to homogeneous materials, cannot capture the directional mechanical characteristics of unilateral adhesion. For drug release, the synergistic effects of bifunctional layers (e.g., acidic environment-triggered antimicrobial release and neutral environment-regulated growth factor sustained release) demand multicompartmental permeation models combined with real-time sensing technologies. Yet, existing pharmacopoeial standards only regulate release behavior in single media, lacking quantitative indicators for complex release kinetics. Degradation performance monitoring relies on tomographic imaging techniques to track local mass changes, but evaluation criteria for gradient degradation rates and tissue-interface interactions remain absent. This leads to significant differences in the determination of degradation endpoints across studies. These technical gaps not only increase companies' methodological development costs but also render the scientific rigor of safety and efficacy data difficult to unify during regulatory review.

Multi-Component systems

When Janus hydrogels incorporate nanomaterials (such as metal oxide particles, polymer core-shell structures) or bioactive components (such as cytokines, gene vectors), the complexity of regulatory review increases exponentially with the interactive effects of these components. The size, surface modification, and degradation products of nanomaterials may induce unique biological effects, such as tissue accumulation risks from small-sized particles or surface charge-mediated immune cell activation. However, current toxicological evaluation guidelines (e.g., ISO 10993) have not established specific testing protocols for nano-biointerface reactions. The release regulation of bioactive components requires simultaneous coordination between pharmacokinetics and material degradation kinetics—for example, the pulsatile release of sustained-release growth factors must avoid cytokine storms caused by burst release or therapeutic lag due to insufficient release. Yet, evaluation criteria for related release profiles remain scattered across

guidelines for different therapeutic areas, lacking a unified cross-indication framework. Additionally, compatibility assessments of components in composite systems (such as dispersion stability of nanoparticles in hydrogel matrices, chemical reaction risks between bioactive components and crosslinkers) have not formed standardized testing procedures, forcing companies to conduct extensive exploratory experiments to meet regulatory submission requirements.

Global harmonization

Coordination with regulatory bodies worldwide (e.g., EMA, CFDA) is necessary to facilitate international adoption of Janus hydrogels. The internationalization process of Janus hydrogels is constrained by significant differences in technical standards, review priorities, and data requirements among regional regulatory systems. The U.S. FDA's device classification system emphasizes "substantial equivalence" evaluation, requiring new materials to demonstrate safety comparability with already marketed products, while the EU's MDR 2017/745 establishes stricter clinical evidence hierarchies, mandating multicenter long-term follow-up data to support benefit-risk assessments. China's NMPA imposes mandatory local clinical trial requirements for imported medical devices and sets additional review guidelines for nanomaterial biocompatibility and metabolic pathways of degradable components. These differences force companies to adjust formulations for different markets (such as replacing crosslinkers not approved in a specific region), supplement region-specific toxicology tests (such as pharmacokinetic analyses related to metabolic characteristics of Asian populations), or rebuild manufacturing processes to comply with local GMP standards during global submissions. Although ISO is advancing the development of international standards for testing nanostructured biomaterials (such as ISO 23309), differences in regional regulatory philosophies (such as risk control-oriented vs. innovation-incentivized approaches) still require gradual bridging through long-term multilateral collaboration mechanisms.

Patient-Specific applications

Customizable Janus hydrogels used in precision medicine (such as 3D-printed hydrogels for repairing complex mucosal defects), which need to match the anatomical structures and physiological characteristics of individual tissues, pose challenges to the traditional "standardized product" regulatory paradigm and may require adaptive regulatory pathways. Their manufacturing processes involve patient-specific data input (such as imaging data), dynamic parameter adjustment (such as mechanical property matching), and individualized sterilization processes. Current regulatory classifications (such as the definition of customized devices versus mass-produced devices) and data traceability requirements (such as production parameter archiving and long-term safety tracking) have not yet formed unified standards. Additionally, due to the mechanical and degradation performance differences among different patient groups, there is a lack of adaptive evaluation mechanisms, necessitating the establishment of regulatory pathways that balance flexibility and safety to support precision medicine needs.

Conclusion

Thus, Janus hydrogels have some promise for clinical applications in biomedical fields such as in diagnostics and bioelectronic interfaces. However, most of the studies are still in the preclinical stage, and further research and optimization are needed to ensure their safety and efficacy in larger animal models and humans. During clinical trials, the differences in the responses of Janus hydrogels in different individuals and the potential problems that may arise from long-term use should be closely monitored to provide a more reliable basis for their clinical application. Clinical trial data can be analyzed and mined by using big data and artificial intelligence technology to gain a deeper understanding of the performance and mechanism of action of Janus hydrogels, which will provide guidance for further optimization of their design and clinical application.

Outlook and conclusions

Outlook

Although Janus hydrogels have great prospects in tissue engineering applications, there are still many challenges to achieve their widespread clinical application. This section will discuss from five aspects: precise structural control and optimization of the production process, enhancement of long-term stability and functionality, optimization of the drug delivery system, research on cell interactions, and addressing the challenges of clinical translation. These five aspects are elaborated in a logical sequence, starting from the optimization of the material's own properties, progressing to the improvement of its functions within the organism, and finally to practical clinical applications. Precise structural control and optimized production processes are the foundation for improving the consistency and reliability of Janus hydrogel performance. Enhancing long-term stability and functionality is the key to ensuring its effective operation in the complex in vivo environment. Optimizing the drug delivery system can improve treatment efficiency and reduce side effects. In-depth research on cell interactions helps to better promote tissue repair and regeneration. And addressing the challenges of clinical translation is an important link in promoting Janus hydrogels from the laboratory to clinical application. Each aspect builds on

Fig. 11 Future outlook for Janus hydrogels

the previous one, jointly constructing a research framework for the future development of Janus hydrogels (Fig. 11).

Precise structural control and optimization of production processes

The precise control and positioning of Janus particles during self-assembly and layer-by-layer stacking remains a technical challenge, and more advanced fabrication techniques should be developed to achieve more precise structural control. These techniques will help improve the consistency and reliability of Janus hydrogel performance, thereby advancing their use in clinical applications. While progress has been made in laboratory-scale preparation methods, achieving large-scale production of Janus hydrogels and balancing cost-effectiveness are still issues that need to be addressed in future work. Optimization of fabrication processes, such as interfacial self-assembly techniques, layer-by-layer stacking methods, or asymmetric chemical modification strategies, can be studied in the future to achieve large-scale production and cost-effectiveness. Looking ahead, integrating 4D printing with Janus hydrogel systems represents a promising frontier for adaptive tissue repair

[19]. Recent advancements in 4D printing techniques enable the fabrication of stimuli-responsive hydrogels capable of dynamic shape transformations in response to environmental cues, which could address limitations in traditional static dressings. This will contribute to the commercialization of Janus hydrogels and the promotion of clinical applications.

Enhancing long-term stability and functionality

To ensure the stability of Janus particles in long-term applications, especially in complex or harsh environments, highly asymmetric modification by introducing bioactive molecules or nanoparticles can be considered. Additionally, Janus hydrogels can incorporate natural polymers (e.g., chitosan, hyaluronic acid) or degradable synthetic polymers (e.g., PLGA) to reduce immunogenicity and enhance biocompatibility. This material selection strategy leverages biocompatible matrices to minimize host immune responses while maintaining structural integrity and tunable degradation profiles for regenerative applications. This strategy enhances the biocompatibility and ability of Janus hydrogels to promote tissue regeneration and optimizes their biocompatibility by ensuring stable performance and the control of immune responses after long-term implantation. For example, (i) Introduce dynamic crosslinked networks (e.g., Schiff base bonds) can be introduced to improve the degradation resistance of hydrogels in complex physiological environments. (ii) Core-shell nanoparticles (e.g., PLGA@SiO_2) loaded with antimicrobial agents and growth factors can be developed for multi-stage functional release. iii)Polyethylene glycol (PEG) or zwitterions (e.g., sulfobetaine) can be grafted on surfaces to inhibit protein adsorption and inflammatory responses. iv) In vitro stability testing of dynamically crosslinked hydrogels must be completed in 1–2 years. v) Long-acting Janus hydrogels capable of maintaining functionality for over 6 months must be developed after several years.

Optimizing drug delivery systems

New applications of Janus hydrogels as drug delivery platforms are being explored for the targeted delivery and precisely controlled release of drugs. Developing novel Janus hydrogels with smart responsiveness that enable them to modulate drug release rates under specific environments (e.g., changes in pH, temperature, or ionic concentration) will improve therapeutic efficiency and reduce side effects. This will (i) help build more efficient drug delivery systems such as pH/temperature dual-responsive Janus hydrogels (e.g., chitosan-polyN-isopropylacrylamide) for precise drug release at lesion sites, (ii) enhance drug loading capacity using mesoporous silica nanoparticles (MSNs) and achieve cell-specific delivery with targeting ligands (e.g., RGD peptides), and (iii) explore photothermal/magnetic-controlled release systems (e.g., gold nanorods/Fe_3O_4) to modulate drug release rates via external stimuli.)

Cell interaction studies

An in-depth investigation of the interactions between Janus hydrogels and cells is essential to optimize their use in tissue engineering. By fine-tuning the chemical and physical properties of the hydrogel surface, cell adhesion, proliferation, and differentiation can be effectively promoted, thereby improving their effects in tissue repair and regeneration. Advanced characterization techniques can be employed, such as: (1) Use XPS and AFM to analyze surface chemistry and topography, correlating Janus structure with bacterial adhesion patterns.(2) Employ microfluidic devices to simulate wound exudate flow and evaluate unidirectional transport efficiency. Advances in this area are expected to significantly enhance the utility of Janus hydrogels in tissue engineering.

Addressing challenges in clinical translation challenges

The safety and efficacy of Janus hydrogels must be rigorously evaluated during the transition from the laboratory to the clinic. Future work should focus on multidisciplinary collaboration, integrating cutting-edge results from the fields of materials science, biology, and medicine to promote the clinical translation of this innovative technology. Specifically, a series of rigorous preclinical and clinical trials are needed to ensure the material's applicability in a variety of areas, including tissue repair, anti-adhesion, drug delivery, wound healing, and biosensing.

Conclusion

In this review, we systematically summarize the design strategies, progress, and challenges related to the use of Janus hydrogels in the tissue engineering of skin and different mucous membranes. Janus hydrogels show great potential for application in tissue engineering due to their unique asymmetric structure and functionality. The asymmetric design of these hydrogels enables them to mimic the complex microenvironments found in natural tissues and provide specific growth conditions for cells, thereby promoting cell adhesion, proliferation, and differentiation. By mimicking the complex structure and function of natural skin and mucosal tissues, Janus hydrogels demonstrate remarkable advantages in mimicking the heterogeneity of the ECM, modulating cellular behavior, and promoting tissue regeneration. The design of Janus hydrogels typically involves the integration of two or more different materials or functionalities into a single hydrogel structure, which can be achieved through techniques such as interfacial self-assembly, layer-by-layer stacking, and asymmetric chemical modification.

Such designs enhance the functional diversity of the materials and provide more precise microenvironmental regulation of cells. Furthermore, Janus hydrogels have demonstrated innovative applications in drug delivery, with their porous structure and wettability differences allowing unidirectional delivery and controlled release of drugs to enhance therapeutic efficacy. Although Janus hydrogels offer great flexibility in material selection, ensuring their biocompatibility and functionality remains a major challenge. The fabrication of hydrogels with precisely controlled Janus structures requires delicate processes, which may limit their feasibility for mass production. Furthermore, to optimize their application in tissue engineering, the interactions between Janus hydrogels and cells must be studied in depth. For example, their asymmetric adhesion properties can mimic the complex microenvironments found in natural tissues and provide specific growth conditions for cells, which in turn, can promote cell adhesion, proliferation, and differentiation [97]. Although many of the materials used to prepare Janus hydrogels have shown good biocompatibility, in-depth studies on their biocompatibility and immune response after long-term implantation are still needed. Additionally, the long-term stability and biodegradability of Janus hydrogels in vivo must also be further explored to ensure their safety and efficacy in the clinic. In particular, the biodegradability of the hydrogel is a critical issue and it is important to ensure that the rate of its degradation matches the rate of tissue regeneration to maintain proper support and guidance in the in vivo environment.

In conclusion, the application of Janus hydrogels in tissue engineering is promising, but challenges in material selection, manufacturing processes, cellular interactions, biocompatibility, long-term stability, and biodegradability must be overcome to achieve their widespread clinical application. Through interdisciplinary collaboration and continuous innovation, we believe that Janus hydrogels will become an important tool in the field of tissue engineering, providing new therapeutic solutions for various diseases and injuries.

Abbreviations

AA	Acrylic acid
BLA	Biologics License Application
CS	Chitosan
ECM	Extracellular matrix
EEC	Endometrial epithelial cell
FDA	Food and Drug Administration
GBR	Guided Bone Regeneration
GT	Gelatin
HA	Hydroxyapatite
JCOP	Janus Collagen Patch
JHCM	Janus Hydrogel Composite Membrane
Kr	Keratin
LA	Lauric acid
MI	Myocardial infarction
MIC	Minimum inhibitory concentrations
MID	Minimally Invasive Delivery
MMPs	Matrix metalloproteinases
MRSA	Methicillin-Resistant Staphylococcus aureus
MSN	Mesoporous silica nanoparticles
Mup	Mupirocin
NCT	National Clinical Trial
NIR	Near-infrared
OU	Oral ulcer
PAA	Polyacrylic Acid
PCL	Polycaprolactone
PCM	Phase-change material
PDA	Polydopamine
PDGF	Platelet-derived growth factor
Pec	Pectin
PEGDA	Poly (ethylene glycol) diacrylate
PLA	Polylactic acid
PLGA	Poly(lactic acid)-hydroxyacetic acid copolymer
PVA	Polyvinyl Alcohol
PRF	Platelet-rich fibrin
ROS	Reactive oxygen species
TLR4	Toll-like Receptor 4
VEGF	Vascular endothelial growth factor

Author contributions

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics and consent to participate declarations

Not applicable.

Consent for publication

All authors have approved the manuscript and agree for the submission.

Competing interests

The authors declare no competing interests.

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