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Perspective

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Dynamic bonds enabled hydrogel adhesives: advancing ophthalmic repair and regeneration

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1. Introduction

Dynamic covalent bonds, characterized by their unique combination of chemical stability and reversible cleavage under specific stimuli, have been strategically incorporated into hydrogel networks to develop advanced tissue adhesives. These dynamic-bonded hydrogels exhibit remarkable adaptability to various substrates, including hydrated and topologically complex biological surfaces, through precise modulation of interfacial energy that balances adhesion strength with reversible dissociation. In addressing critical challenges in ocular surface therapy, particularly poor drug bioavailability, fibrotic scarring, persistent inflammation, and suture-related complications, these materials have demonstrated transformative potential.[1–3] Their multifunctional capabilities span: (1) enhanced transcorneal drug permeation, (2) dual functionality as both implantable scaffolds and surface-adherent devices via stimulus-responsive mechanisms, and (3) precise modulation of cellular behavior to promote scar-free regeneration. Recent advances have particularly highlighted the crucial role of hydrogel-tissue interfacial dynamics in orchestrating cellular recruitment, polarization, and directional migration—fundamental processes governing tissue reconstruction. The distinctive value of these adhesives emerges from their synergistic combination of robust tissue integration, spatiotemporally controlled therapeutic delivery, and environmentally responsive degradation. This perspective examines recent breakthroughs in dynamic bond chemistry, analyzes their ophthalmic applications, identifies persistent translational challenges, and proposes innovative design strategies to accelerate clinical implementation of next-generation ocular adhesives.

2. Dynamic bonds in advancing ophthalmic therapy

2.1 Challenges in ophthalmic therapy

The ocular barriers, including corneal barrier (eg, corneal epithelial tight junctions and opposite polarity compared with corneal stromal cells), tear film barrier (eg, dilution and dynamic removal of tears), and blood-ocular barrier, regulate material or drug transport. In addition to this, the pathological processes, such as inflammatory responses, neovascularization, and extracellular matrix (ECM) remodeling during tissue injury progression, as barriers interfere with drug transport and efficacy.[4,5] Collectively, ocular barriers impede drug penetration into deeper tissues, reducing bioavailability and yielding primarily palliative outcomes. The main barrier-like components affect drug delivery during wound healing as follows. (1) Inflammatory mediator: IL-6 and TNF-α accelerate tissue damage and affect drug transport. (2) Neovascularization: VEGF-driven pathological angiogenesis promotes tissue repair, while vascular leakage affects the distribution and retention of drugs; P-glycoprotein overexpression in endothelial cells further potentiates drug efflux. (3) Extracellular matrix: TGF-β-activated myofibroblast transdifferentiation causes aberrant and dense collagen deposition during ocular wound healing, physically obstructing drug diffusion and distribution to compromise function (Figure 1).

Consequently, current ophthalmic delivery relies heavily on frequent dosing, compromising patient compliance. Intravitreal injections enhance efficiency, while the invasiveness risks secondary complications. Novel delivery systems are thus imperative, requiring prolonged retention, stimuli-responsive release, robust tissue adhesion/penetration, and superior biocompatibility. Dynamic covalent bonds offer a potential platform for enabling these functionalities.

2.2 Dynamic bonds redefining ophthalmic therapeutics

Dynamic bonds encompass noncovalent interactions (hydrogen bonding, metal coordination, host–guest complexation, hydrophobic interactions, and ionic interactions) and covalent dynamic bonds (imine bonds, borate esters, disulfide linkages, hydrazone bond, and acylhydrazone bond), defined by reversible kinetics.[6,7] Noncovalent interactions exhibit rapid yet labile dynamics, whereas covalent dynamic bonds demonstrate slower but robust exchange. Crucially, the reactive moieties of dynamic covalent bonds resemble endogenous functional groups in human tissues, enabling transient conjugation with ocular structures to enhance drug utilization.

Hydrogel-based drug carriers significantly enhance bioavailability. Dynamic covalent bonds enable hydrogel fabrication with improved viscoelasticity and robust mucoadhesion. Their reversible breakage–reformation confers self-healing capacity, resisting blinking-induced shear forces while maintaining structural integrity. Multivalent reversible interactions between these hydrogels and ocular mucins markedly prolong drug retention. Physically cross-linked gels serve as carriers for sustained cargo delivery. Their network architectures,

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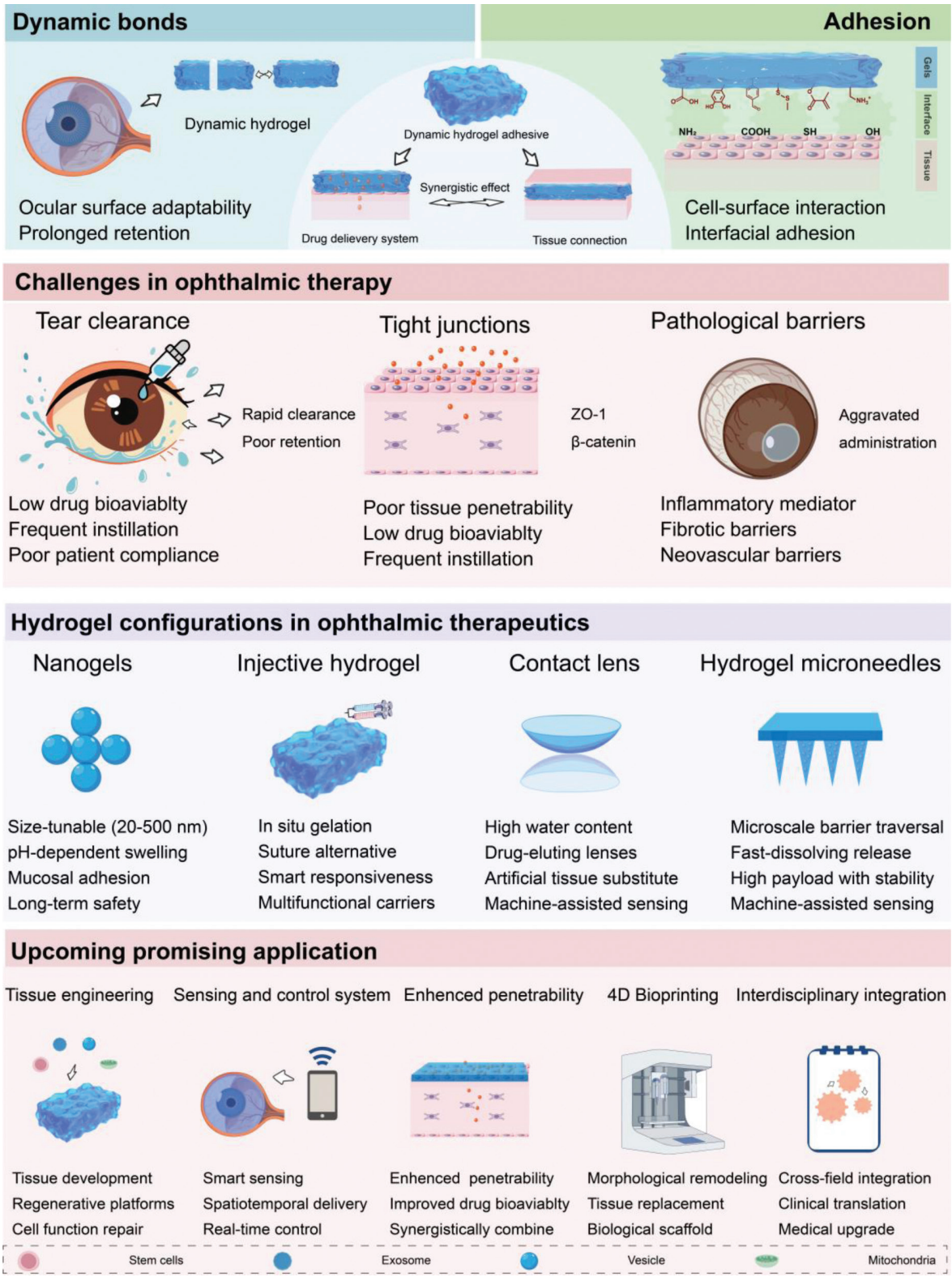

Figure 1. Dynamic bonds in hydrogel adhesives advancing ophthalmic repair and regeneration: challenges, configurations, and upcoming applications.

stabilized by noncovalent interactions, withstand blinking-induced mechanical stress without imposing a burden on ocular tissues.

Hydrogels for repair (e.g., in situ-forming bandage lenses) typically rely on Schiff base or disulfide bonds, as they offer moderate cross-linking kinetics and suitable mechanical strength under physiological pH, facilitating adherence to the wound. In contrast, nanogels for intravitreal therapy preferentially employ boronic ester bonds or host–guest interactions, owing to their responsiveness to specific intraocular biomarkers, reactive oxygen species (ROS), or matrix metalloproteinases (MMPs), enabling intelligent drug release. Dynamic bonds serve a dual

purpose: acting within the internal network of the gel and mediating interactions at the tissue interface. Internally, they enhance drug-loading capacity or enable responsive dissociation, while at the interface, they strengthen adhesion to the tissue, thereby resisting clearance caused by blinking-induced stress.

Dynamic covalent gel networks facilitate stimuli-responsive drug release.[8,9] Drugs conjugated via dynamic covalent bonds or physically entrapped within such networks undergo precise liberation upon pathological microenvironment-triggered bond cleavage. For instance, imine bond-cross-linked hydrogels accelerate drug release in response to localized pH reduction at inflammatory/infectious sites; disulfide bond systems release cargo under elevated inflammatory conditions (eg, dry eye, keratitis, and uveitis); and light-triggered spatiotemporal control is achieved via photoisomerizable moieties (eg, azobenzene). This on-demand release enhances local drug concentration, minimizes off-target effects, and optimizes therapeutic efficacy.

Dynamic covalent bonds also enhance tissue penetration and targeting efficacy. For example, disulfide bond-containing nanoparticles undergo size-shedding via cleavage to penetrate dense barriers (eg, corneal epithelium and mucus layers), followed by postpenetration reconstitution; boronic ester-functionalized materials conjugate sialic acid moieties, enabling active targeting toward inflammatory cells.

3. The adhesion in ophthalmic therapeutics

3.1 The necessity of adhesion

Developing the adhesive properties of hydrogels aims to enhance their interaction with tissues. The ocular microenvironment imposes stringent demands on drug delivery and therapeutic materials. For surface therapies, hydrogels resist blinking-induced shear forces, enabling sustained retention on the dynamic ocular surface.[10,11] This extends treatment intervals from multiple daily doses to once every few days. Simultaneously, the robust yet reversible nature of dynamic covalent bonding minimizes structural compromise to corneal tissues, demonstrating exceptional biocompatibility. This achieves synergistic optimization of mucoadhesion and safety. For extensive tissue defects (e.g., corneal stromal lesions or transplantation), robust interfacial adhesion prevents dislodgement during therapeutic cycles, while balanced dynamic covalent bonding and mucoadhesion ensure modulated degradation kinetics at the injury site.

3.2 The mechanism of adhesion

The ocular tissue surface contains functional groups such as carboxyl, amino, hydroxyl, thiol, and fumarate moieties, exhibiting a net negative charge. Adhesion can thus be achieved via physicochemical interactions. Hydrogel surfaces may be functionalized with polyhydroxyl, polycarboxyl, polyphenolic, phenylboronic acid, aldehyde, or disulfide groups to achieve adhesion.

Alternative adhesion strategies include mechanical interlocking via microneedle arrays and topographic adhesion mediated by chitosan's phase transition and interfacial diffusion under physiological versus acidic conditions. Current research extensively focuses on mussel-inspired adhesion strategies, which rely on polyphenol-enabled multivalent hydrogen bonding and covalent interactions to achieve interfacial tissue integration. Although direct evidence is lacking, the recruitment and migration-promoting effects of specific functional groups suggest that adhesive materials can modulate cellular behavior to some extent, thereby facilitating tissue repair.

3.3 Balance of adhesion and cohesion

The magnitude of adhesion arises from a balance between interfacial adhesive moieties and bulk cohesive strength, both of which must be optimized to achieve robust adhesion. For ocular surface modulation, cohesive contributions can be neglected; however, tissue integration requires careful consideration due to inherent persistence limitations at the tissue interface. The clinically prevalent mode of adhesive failure manifests as cohesive fracture within hydrogels, primarily governed by internal crack propagation mechanisms.

The synergistic integration of strong and weak bonds enables stable hydrogel adhesion, where robust bonds maintain structural integrity while labile bonds dissipate imposed stresses, thus ensuring cohesive stability. This fundamental principle has driven recent advances in dual-network and dual-cross-linking material strategies.

Adhesive failure represents another clinically relevant failure mode, primarily mediated by interfacial hydration layers that compromise tissue-adhesive interactions. Excessive tissue exudation impedes wound healing by inducing edema and facilitating microbial colonization. Hydrogels counter this through their superior hydration capacity, which simultaneously shields the wound bed and exposes engineered reactive sites to enable persistent interfacial integration. For internal tissue integration, hydrogel hydration capacity poses significant clinical risks: swelling-induced volumetric expansion may compress neural structures and elevate intraocular pressure. Thus, modulating hydrogel hydration capacity while preserving adhesive properties necessitates disease-specific trade-offs in clinical implementation.

A particularly distinctive scenario involves unilateral asymmetric adhesion, where anisotropic binding interfaces exclusively facilitate deep-tissue integration while preventing detrimental interfacial binding on nontargeted surfaces. This mechanism operates via 3 distinct pathways: passivation of surface adhesive moieties, integration of nonadhesive interfacial layers, or counter-charge neutralization combined with in situ network polymerization that internally confines adhesive functional groups. The diverse spectrum of adhesion modalities offers unprecedented therapeutic alternatives for ophthalmic applications, enabling disease-specific tailoring of distinctive adhesive hydrogels.

4. Biointegration of dynamic covalent bonds and adhesion

Biointegration leverages reversible, stimuli-responsive chemical bonds to engineer biomaterials capable of intelligent, robust, and enduring adhesion to living tissues. This approach targets the molecular design of stable, functional interfaces between materials and host tissues that resist fibrous encapsulation.[12]

Conventional materials, however, face significant challenges in achieving ideal biointegration, particularly concerning dynamic adaptation to tissue changes, long-term interfacial stability, and on-demand detachment. The integration of dynamic bonds overcomes these limitations by enhancing interfacial cross-linking dynamics and adaptability. Within adhered hydrogels, the dynamic chemical bond-enabled network undergoes adaptive remodeling in response to the local microenvironment (e.g.,

pH, enzymes, and redox state), accommodating tissue morphology and mechanical shifts while mitigating detrimental stress shielding or concentration. Furthermore, this internal dynamic network creates an ECM-like microenvironment conducive to cell infiltration, tissue integration, and the potential guidance of cell behavior and tissue ingrowth. Critically, dynamic bonds facilitate the immobilization of bioactive molecules (growth factors, antibodies, and cell-adhesive peptides), offering a platform for controllable immunomodulation.

At the material–tissue interface, dynamic covalent networks establish stronger, reversible covalent bonds with tissue surface molecules (collagen, fibrin, and cell surface receptors), surpassing the inherent weaknesses of traditional noncovalent interactions and enabling purposeful detachment. This dynamic nature also confers self-healing properties; upon damage (e.g., microfractures), the interface reversibly breaks and reorganizes, restoring structural integrity and adhesion strength. Importantly, the application of specific external stimuli (e.g., pH shift, light exposure, and reducing agents) allows for the on-demand, reversible disruption of the adhesive interface, facilitating noninvasive or minimally invasive device removal.[13,14]

Biointegration of dynamic covalent bonds and adhesion imparts dynamic mechanical properties, facilitates cellular infiltration and vascularization, and enables responsive release of bioactive factors to the tissue microenvironment. Concurrently, it achieves adaptive adhesion to soft tissues, rapidly establishing robust, reversible bonds on hydrated tissue surfaces. This holds significant promise for tissue engineering, implantable devices, adhesive sealing, and intelligent delivery systems.

5. Hydrogel configurations in ophthalmic therapeutics

Based on these core designs, hydrogels exhibit diverse ocular configurations, including nanogels, injectable hydrogels, hydrogel contact lenses, and hydrogel microneedles, designed to overcome conventional therapeutic limitations and enhance efficacy.

5.1 Nanogels

Nanogels refer not to the simplistic integration of nanoscale designs with hydrogels, but rather to nanoscale microstructures fabricated based on gel preparation principles. They possess not only the adhesive properties of hydrogels but also the nanoscale effects of nanomaterials, enabling penetration through biological barriers and prolonged retention at wound sites. This design concurrently integrates macroscopic and microscopic advantages, transcending traditional composite approaches. Such therapeutic strategies optimize treatment efficacy while facilitating scalable applications.

Compared with conventional nanoparticles (poor retention), metallic nanoparticles (weak penetration), lipid nanoparticles (prone to hydrolysis), and mesoporous silica (fibrosis induction), nanogels leverage biomimetic structural design and dynamic network modulation. They offer tunable elastic modulus, mucin-mimetic structures for prolonged retention, integrated multiresponsiveness (temperature/pH/ROS), high swelling ratios (10–50×), and high drug-loading capacity. Additionally, their high-water content and ECM-mimicking composition enhance biocompatibility—reducing inflammation, lubricating surfaces, and enabling controlled degradation—benefiting treatment of delicate ocular tissues. Also, nanogels exhibit superior coloading efficiency for both hydrophilic and hydrophobic drugs, with intelligent release enabled by dynamic bonds. In contrast, liposomes suffer from low drug-loading capacity and insufficient stability. Nanoparticles and micelles demonstrate poor hydrophilic drug encapsulation and are susceptible to premature drug release. Exosomes face challenges in isolation/purification and low drug-loading efficiency. Critically, while all these carriers can utilize thiol-mediated surface interactions for cellular internalization, potentially avoiding lysosomal clearance, nanogels uniquely retain tunable elasticity. This adjustable particle stiffness may better accommodate biomechanical stress transmission in biological systems.

5.2 Injectable hydrogel

Injectable hydrogels gel in situ at lesion sites, conforming to irregular defects and modulating both superficial and deep injuries. Typically, photo-cross-linked or dynamically bonded, they provide sustained hydration protection and controlled release of therapeutic agents for enhanced repair. Classified as surface dressings or internal fillers, their mechanical strength varies, exemplified by weak intravitreal gels versus low-modulus dry eye lubricants. Crucially, grafts and defect-filling designs require adhesion and optical transparency to mitigate detachment risks while preserving visual function.

Beyond superficial drug delivery, hydrogel-tissue engineering coordinates uniform cellular growth across tissue layers, preventing scar formation and functional impairment caused by heterogeneous cell proliferation. For transplants, injectable adhesive hydrogels achieve seamless donor–host integration to mitigate surgical trauma while enabling holistic wound modulation across superficial and deep strata for comprehensive recovery.

5.3 Hydrogel contact lens

Hydrogel contact lenses are fabricated into cornea-mimetic structures with specific curvature and exceptional transparency. They provide mechanical barrier protection for the cornea while enabling customized curvature correction for myopia, hyperopia, and astigmatism. Crucially, their high oxygen permeability prevents hypoxic edema.

Hydrogel contact lenses enable human–digital interfacing, facilitating digitally controlled release of encapsulated therapeutics and transmission of ocular surface pathology via electrical signals for expert computational analysis.

Hydrogel contact lenses may serve as biomimetic ocular prostheses. When suitable donors are unavailable, stable, biocompatible, customized hydrogels can replace ocular structures to preserve viable visual function.

5.4 Hydrogel microneedles

Hydrogel microneedles (400–800 μm in length) penetrate the corneal epithelium (50 μm thick), creating transient micropores (<1 μm in diameter) pain-free. This enables drug bypassing of tear clearance and mucus barriers while establishing adhesive anchoring via microneedle arrays.

Hydrogel microneedles can be engineered for sustained release via calcium chelation or burst release via pH responsiveness, tailored to specific therapeutic agents. Concurrently, the array penetrates corneal epithelial interstices, adsorbs tear inflammatory mediators (e.g., MMP-9, IL-6), enhances detection sensitivity through surface enhancement, continuously monitors

intraocular pressure fluctuations, and wirelessly transmits data to mobile applications.

6. Emerging applications in ophthalmic therapeutics

6.1 Cascade regulation of ocular inflammation

In ocular diseases, inflammatory conditions (e.g., dry eye and alkali burns) constitute a major proportion and may induce pathological structural changes if untreated. While current medical systems manage such conditions, fewer yet more effective drugs remain critical due to concerns regarding ocular toxicity and drug resistance. Drug-adhesive material cascades may address this challenge. Persistent inflammation not only causes discomfort but also promotes scarring and ocular fragility, necessitating multistage biological cascade regulation (e.g., inflammatory and proliferative phases). Prolonged material–tissue interaction with controlled release is essential for such multiphase modulation. Dynamic covalent bonds with tunable kinetics can be designed to sequentially meet distinct repair phase demands, enabling cascade control of inflammatory diseases.

The existing strategy of coloading hydrophilic and hydrophobic drugs for sequential release confronts critical challenges: achieving sequential delivery of dual hydrophobic drugs, ensuring dual-drug carrier stability, and determining whether their therapeutic effects manifest synergy or antagonism—all demanding rigorous investigation.

6.2 Microinvasive therapeutic approaches for corneal disorders

Corneal transplantation presents complex clinical challenges requiring advanced surgical skill and management of potential immune rejection. Conventional suture fixation induces secondary trauma, scar formation, and risks of corneal neovascularization. Dynamic covalent-bonded hydrogel adhesives address these limitations by adaptively bridging donor and recipient tissues through self-adjusting interfacial bonding, eliminating suture-related complications while promoting seamless tissue integration. Critically, the adhesive process concurrently enables drug loading via dynamic covalent bonding, facilitating sustained release of immunosuppressants to circumvent side effects associated with repeated topical administration.

Compared with donor corneal or hydrogel transplantation, focal repair of damaged tissue for localized corneal defects offers greater clinical appeal by avoiding extensive replacement and invasive surgery. In situ-forming transparent hydrogels—combining tissue adhesion with pre-gel fluidity—provide a novel therapeutic alternative. This approach involves applying a pre-gel solution directly to the defect site, followed by gelation to stabilize the wound suture-free, thereby promoting epithelial reformation and stromal regeneration for vision recovery.

6.3 Hydrogel-mediated regulation in ocular tissue engineering

While pharmacotherapy carries inherent toxicity risks, biomaterial-mediated tissue modulation has emerged as a compelling alternative.[15,16] Magnetic materials direct cellular alignment, hydrogel stiffness governs proliferation, and surface properties regulate adhesion, with intravitreal hydrogel injection further maintaining ocular homeostasis. Hydrogels engineered from abundant biocompatible materials exert multiscale bioinfluence: from receptor-level signaling and migratory guidance to functional tissue restoration. Elucidating these mechanisms will pioneer multidimensional strategies for advancing ocular health.

7. Challenges and perspectives

The current research focus lies in unilaterally enhancing material properties such as adhesive capabilities, dynamic exchange capabilities, and intrinsic bioactivities—which can be optimized to exceptional levels—yet fails to consider the overall logic holistically. While dynamically bonded adhesive hydrogels have made significant progress in ocular drug delivery and tissue engineering, several challenges remain. The fundamental issue lies in the inability to achieve highly efficient treatment targeting of lesion sites. Addressing these will have profound implications for future innovations in ophthalmic materials.

A key challenge lies in achieving robust adhesion while maintaining gentle reversibility. The trade-off between adhesion strength and reversibility primarily stems from the kinetic mismatch of dynamic bonds: strong bonds (e.g., catechol-metal coordination) favor adhesion but hinder detachment, while weak bonds (e.g., hydrogen bonds) enable reversibility but compromise stability. Current cross-linking strategies lack spatiotemporal control to synchronize these opposing requirements. Moreover, for ocular applications, the degree of adhesion and adaptability requires quantitative gold standards, determining what levels ensure sufficient handling convenience and stability without compromising tissue interactions. Additionally, while hydrogels possess ECM-like properties, they are still foreign materials. Existing ISO 10993 standards focus on short-term cytotoxicity but neglect dynamic material–tissue interactions. For hydrogel adhesives, key gaps include: (1) no established protocols to evaluate chronic inflammatory responses induced by bond exchange and (2) insufficient correlation between in vitro degradation tests and actual in vivo behavior due to ocular microenvironment complexity. The incorporation of externally-triggered dynamic covalent bonds offers a pathway to reconcile the kinetic dichotomy between strong permanent anchors and weak reversible linkages. Precise spatiotemporal modulation of cross-link density enables optimization of the adhesion-reversibility trade-off through controlled bond lifetime tuning.

The next shortcoming lies in the long-term interactions of biocompatibility. The existing evaluation methods suffer from a short-term perspective in the temporal dimension, primarily assessing the acute cytotoxicity of materials over a few days, while failing to predict potential genotoxicity and ultra-long-term biological responses. These methods are static and incapable of simulating the complex dynamic physiological environment within the body, such as mechanical stresses and biochemical gradient changes. They lack the ability to monitor dynamic, continuously evolving processes, such as real-time fluctuations in inflammatory factors, dynamic variations in oxidative stress levels, and the evolution of the microenvironment at the tissue-material interface. Most critically, current approaches struggle to effectively integrate long-term changes across molecular levels (e.g., gene expression and proteomics), cellular levels, tissue levels, and organ/system levels, thereby hindering a

holistic understanding of the long-term evolution of biocompatibility. Current detection devices can identify electrical signals and glucose changes and perform genetic analysis, but they lack sufficient sensitivity and specificity—specifically, the ability to reliably detect targets at low concentrations and accurately attribute signals to their precise sources. Integrating miniaturized, biocompatible biosensors into implantable devices or as standalone implants enables long-term, real-time, in situ monitoring of key biomarkers, such as inflammatory factors, tissue damage/repair biomarkers, metabolites, drug molecules, and tissue physical parameters. This provides an unprecedented perspective for understanding the dynamics of material–host interactions and offers early warnings of potential long-term complications. However, it requires multidisciplinary functional integration, and multidimensional, multitiered detection capabilities still demand further development.

Another barrier lies in the penetration capacity of hydrogels. Although current hydrogels can achieve nanoscale dimensions, their improved drug efficacy primarily stems from resisting blink-induced clearance. While the interactive nature of dynamic bonds enhances penetration potential, it still falls short of being satisfactory. For posterior segment diseases, microinvasive hydrogel therapies remain limited. Future strategies may involve functional integration to impart nanomotor functionality, thereby increasing penetration power, but this necessitates controllable environmental responsiveness. Externally-directed propulsion-enhanced targeting achieves both deep-tissue penetration and molecular specificity.

The exchange capacity across hydrogel adhesives presents another challenge. For the ocular surface, maintaining gas exchange (particularly oxygen) between the air and ocular tissues is essential to prevent potential hypoxic edema. Within connective tissues, definitive evidence demonstrating comprehensive exchange of growth factors, nutrients, and cellular components across the adhesive interface remains lacking. Machine learning-guided interfacial simulations may provide foundational mechanistic insights for designing hydrogels and optimizing mass transport across biointerfaces.

Translational hurdles present another significant challenge. Sterilization stability, scalable synthesis, spatiotemporally controlled applicability, and multidimensional in vivo efficacy validation all impact progress. Machine-assisted structural design will facilitate the development of novel functional hydrogels capable of meeting application demands within complex in vivo environments.

The 4D-printed hydrogel structures represent a potential future direction. Although 4D printing holds significant promise, its clinical translation primarily depends on resolving the biocompatibility of materials. Future research must focus on developing novel biocompatible cross-linking systems. For instance, exploring initiator-free click chemistry, enzyme-mediated cross-linking, or the use of endogenous cross-linkers could fundamentally eliminate the potential toxicity risks associated with exogenous photoinitiators. Furthermore, the long-term functional stability of 4D structures poses another major challenge. Future designs of smart hydrogels should ensure that their shape-memory effects remain stable under prolonged physiological conditions. Simultaneously, their stimulus-responsive mechanisms should exhibit greater targeting precision and specificity to enable truly on-demand therapeutic interventions. Shape-adaptive hydrogels offer enhanced compatibility with ocular motility. Furthermore, a comprehensive scientific understanding of the mechanical behavior of hydrogels on the ocular surface—including fatigue, stress relaxation, creep, and aging—remains limited. Future bioink designs must prioritize structural and functional congruence with native tissue architectures, actively emulating biological systems through biomimetic engineering.

Finally, hydrogel adhesives should incorporate rapid diagnostic capabilities. By specifically recognizing key pathological features at the lesion site and providing clinicians with detailed data, they could not only shorten diagnostic timelines and reduce costs but also facilitate future medical advancements.

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Conflicts of interests

The authors declare that they have no conflicts of interest.

Author contributions

H.C.: conceived, organized, and wrote the manuscript. B.A.: conceptualization. Z.L.: conceptualization, funding acquisition, project administration, and supervision. J.L.: conceptualization, funding acquisition, investigation, project administration, resources, and supervision. All authors discussed and approved the final manuscript.

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