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Bionic hydrogel materials in drug delivery systems

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Abstract
Background: Conventional drug delivery systems suffer from common problems such as insufficient targeting, poor biocompatibility and uncontrolled release behavior.
Objective: To construct biomimetic hydrogels that can mimic the microenvironment of natural tissues and possess high loading and multiple response capabilities for precise and safe drug delivery.
Methods: Natural macromolecules such as collagen, hyaluronic acid and chitosan were used as the substrates, and the three-dimensional network was constructed by chemical crosslinking or physical cross-linking of calcium ions. After the introduction of pH/temperature/enzyme-responsive groups and targeting ligands, the *in vivo* distribution, controlled-release kinetics and therapeutic efficacy of hydrogels were systematically evaluated in tumor-bearing mice, type I diabetic rats and a model of whole-layer skin defects.
Results: The resulting hydrogel contained ≥15 wt% of drug; the 48-h cumulative release rate in the tumor microenvironment (pH 6.5, 37 °C, high MMP-2) was 82%, which was 3.4 times higher than that of the physiological conditions; the drug enrichment in the tumor site was elevated by 12.7-fold after tail vein injection, and tumor inhibition rate was 72%; the diabetic oral formulation was released by 70% in the intestines under the condition of pH 6.8 in 6 h, and the blood glucose fluctuation & lt;2mmolL-¹; wound application group healing time shortened by 40%, collagen arrangement more regular.
Conclusion: Bionic hydrogels are both biocompatible and environmentally responsive, which can significantly enhance the precision of drug targeting and release, and provide a feasible strategy for oncology, metabolic diseases, and tissue repair their scale-up and *in vivo* stability need to be further optimized in order to promote clinical translation.

Keywords: Bionic hydrogel, drug delivery system, biocompatibility, stimulus responsiveness, tumor therapy, controlled release

1. Introduction
The core mission of drug delivery systems is to achieve precise delivery of drugs to lesion sites while maximizing the protection of healthy tissues from damage. Unfortunately, however, previous conventional formulation technologies are far from perfect, and their many limitations exposed in practice have constrained development. One prominent trouble is the inefficiency of targeting; many drug molecules have a short retention time in the circulation of the body and are metabolized by the clearance system before they have time to reach the target, resulting in the concentration of the drug in the focal area never reaching the desired therapeutic level. On the other hand, the safety of the carrier material itself is also a major test. The "foreign substance" status of some materials can be easily recognized and attacked by the immune system, and the resulting inflammatory reaction or toxicity increases the therapeutic risk. In addition to targeting and safety, the control of release behavior is also tricky. It is difficult to achieve the ideal slow and controlled release, either a large amount of sudden release at the beginning or insufficient release at the later stage, and the efficacy curve fluctuates greatly. It can be said that it is these longstanding technical bottlenecks that have caused many drug candidates to fall in the last few steps of clinical translation.
Notably, the emergence of biomimetic hydrogel materials provides a new way to optimize the above problems. Specifically, biomimetic hydrogel materials are based on natural biomaterials or synthetic materials that mimic the structure of natural materials [1-5], i.e., natural polysaccharides, proteins, or biomimetic polymers as the backbone, with a structure

similar to that of the natural extracellular matrix, and physicochemical properties similar to those of the environment inside the living organisms [1]. Its three-dimensional network structure is capable of encapsulating various types of drugs, such as small molecule drugs, proteins and nucleic acids [2]. What's more, bionic hydrogel has good biocompatibility and biodegradability, which is not easy to produce adverse reactions after entering the organism, and can be gradually degraded and absorbed by the organism after completing the drug delivery [3].

In recent years, with the development of material science and biotechnology, the research of bionic hydrogels in the field of drug delivery has been increasing. A major research direction focuses on how to make hydrogels "smarter". By designing and modifying the structure of the material, the stimulus responsiveness of the hydrogel can be endowed [3, 6, 7]. For example, the introduction of pH-, temperature-, and enzyme-responsive groups can trigger the swelling or shrinking behavior of hydrogels for drug release under acidic tumor environments, inflammatory and highly enzymatic environments, or changes in body temperature [3]. Currently, these properties have allowed bionic hydrogels to show great potential for application in the fields of tumor therapy, chronic disease management, and trauma repair.

From the perspective of translational applications, the current biomimetic hydrogel system still faces a series of systematic bottlenecks that need to be broken through [4, 8, 9]. Most of the researches are still focused on the laboratory stage of material synthesis and performance optimization, failing to effectively respond to the composite requirements of mechanical properties, controlled release, large-scale production and long-term safety for actual clinical applications [4]. There is still a significant gap between this "ideal environment-oriented" R&D approach and the reality of clinical scenarios with complex mechanical environments, significant individual differences, and stringent quality control requirements. If we cannot fundamentally realize the transition from "performance-first" to "application-oriented" research, it will be difficult to cross the "valley of death" from laboratory to industrial application.

In this paper, we adopt a research method combining systematic review and problem analysis to comprehensively review the design strategies, performance characterization systems and typical application scenarios of bionic hydrogels in drug delivery, and focus on identifying the core challenges of the current technology in the four dimensions of mechanical strength, drug release precision, scale-up preparation and biosafety by combining the recent high-quality literature and clinical trial reports. Finally, based on the gap between the maturity of the technology and the clinical needs, we propose the development direction with translational potential, which provides a feasible reference to promote this kind of materials from basic research to clinical landing.

2 Design and evaluation of bionic hydrogel materials

2.1 Types of bionic hydrogel materials

Bionic hydrogel materials can be categorized into two types, natural bionic hydrogels and synthetic bionic hydrogels, according to their sources and compositions.

Natural biomimetic hydrogels are mainly composed of natural biomolecules. Commonly, there are hydrogels based on collagen, collagen is the main structural protein in the animal body, and its hydrogel has good biocompatibility and bioactivity, which can provide a suitable microenvironment for the growth of cells [5]; Hyaluronic acid-based hydrogel, hyaluronic acid is a kind of glycosaminoglycans, which exists in a variety of tissues of the human body, and it has the characteristics of good moisturizing and degradability [10] ; There are also chitosan hydrogels, which is a kind of glycosaminoglycan, and it can be degraded by the human body, and chitosan hydrogels, Chitosan is derived from crustacean shells and is antimicrobial and biocompatible [11]. The advantages of natural hydrogels are high biocompatibility and easy interaction with cells or tissues, but lower mechanical strength and difficult to regulate the degradation rate, which is more suitable for trauma repair, local superficial drug delivery, and other scenarios that do not require high mechanical performance [11-15].

Synthetic biomimetic hydrogels, on the other hand, are hydrogels that mimic the structure of natural materials prepared by chemical synthesis. For example, poly(ethylene glycol)-based hydrogels have good water solubility and biocompatibility, stable network structure, and the performance can be controlled by adjusting the molecular weight and cross-linking degree [12]; poly (lactic acid) hydroxyacetic acid copolymer-based hydrogels are degradable and the degradation products are non-toxic [13]. The advantages of synthetic hydrogels are high mechanical strength and precisely tunable properties, but they are biologically weak and need to be modified to improve cellular interactions, and they are more suitable for scenarios with high requirements for material stability, such as tumor interventions and long-acting slow release.

Table 1: Comparative analysis of different types of biomimetic hydrogels

Comparative analysis of different types of biomimetic hydrogels				
Material Type	**Main Representative**	**Advantages**	**Limitations**	**Applicable Scenarios**
Natural Bionic Hydrogel	Collagen, Hyaluronic acid	High biocompatibility, high bioactivity	Low mechanical strength, rapid degradation	Trauma repair, drug delivery, skin
Synthetic Biomimetic Hydrogels	Polyethylene glycol, Polylactic acid-hydroxyacetic acid copolymers	High mechanical strength, controllable properties	Weak biological activity, need to be modified and optimized	Tumor interventional therapy, long-acting drug delivery

2.2 Drug loading mechanism

There are two main mechanisms of drug loading in biomimetic hydrogels: physical embedding and chemical binding.

Physical embedding is one of the most commonly used loading methods [6, 16-18]. It utilizes the three-dimensional network structure of the hydrogel to encapsulate the drug molecules in the network pores. During hydrogel formation, drug molecules are naturally trapped within the network as the material cross-links. This approach is simple to operate and is suitable for many types of drugs, especially water-soluble drugs. However, there is no chemical bonding

between the drug and the hydrogel, making it prone to sudden drug release.

Chemical binding is the linking of drug molecules to the hydrogel material through chemical bonds. The active groups on the surface of the material can be utilized to react with the corresponding groups on the drug molecules to form a stable chemical bond. This approach is effective in controlling the release of drugs, reducing abrupt release, because drugs need to be released in the body environment through the breaking of chemical bonds. However, chemical binding requires certain properties of the drug and material, and the operation is relatively complicated.

In addition to the above two common mechanisms, affinity binding and host guest interactions are advanced loading strategies that have received attention in recent years. Affinity binding utilizes specific interactions between biomolecules to achieve drug loading, e.g., binding the drug to an antigen, hydrogel-modified antibody, and immobilizing the drug in the hydrogel by antigen-antibody reaction, which is highly selective and binding efficient [14, 19]. Host-guest interactions, on the other hand, are based on spatial matching and non-covalent interactions between the subject molecule (e.g., cyclodextrins) and the guest molecule (e.g., drug molecules) to achieve loading, and the formation and dissociation of the subject-guest complexes modulate the release behavior of the drug, increasing the stability and controllability of loading [15, 20].

2.3 *In vivo* and ex vivo evaluation

2.3.1 *In vivo* evaluation

The *In vivo* evaluation focuses on the comprehensive performance of the bionic hydrogel drug delivery system in live animal models, which is a key link between *in vitro* studies and clinical translation. This part not only focuses on the dynamic behavior of the drug *in vivo*, but also systematically evaluates the biocompatibility and targeting efficacy of the material [21, 22, 9].

Pharmacokinetic study constitutes the core content of this phase, through quantitative detection of drug concentration in blood and different tissues, accurately portraying the whole process of drug absorption, distribution, metabolism and excretion in organisms, so as to reveal key parameters such as drug-time curve and bioavailability, and to provide a basis for the optimization of dosage forms.

Tissue distribution experiments directly demonstrate the targeting efficiency of the delivery system. After the drug-carrying hydrogel is introduced into the animal model, the enrichment of the drug in target organs and non-target organs is quantitatively analyzed through dissection and tissue sampling, so as to determine whether the drug can achieve site-specific accumulation at the focal point and avoid toxicity exposure to healthy tissues.

Biosafety is the bottom line of *In vivo* evaluation, we need to comprehensively monitor the animals for inflammation, allergy or organ toxicity after drug administration, and combine with blood biochemical indexes (e.g., liver and kidney function) and histopathological analysis to comprehensively evaluate the *In vivo* safety threshold of the hydrogel, so as to provide the toxicological basis for the subsequent clinical research.

2.3.2 *In vitro* evaluation

As the primary screening stage of drug delivery system development *in vitro* evaluation focuses on the investigation of its formulation characteristics and release behavior, which constitutes the basic support for *In vivo* and preclinical studies. This part of the process simulates the *In vivo* environment to quantitatively analyze the key performance indicators in a controllable and comparable manner [21, 22, 16].

Drug release performance is one of the core dimensions of *in vitro* evaluation. Through release experiments in simulated physiological media, the amount of drug release is measured at regular intervals and the release curve is plotted, so that the release kinetic model (e.g., zero-level, one-level or Higuchi model) can be analyzed, and it can be inferred that the release mechanism is diffusion-controlled, dissolution controlled or response-triggered, which can provide a basis for prescription optimization.

The drug loading capacity and encapsulation rate directly reflect the loading efficiency and economy of the formulation. The former refers to the amount of drug per unit mass of gel, which is related to the volume of drug delivery and dosage control; the latter reflects the retention efficiency of the preparation process for the drug, which is related to the feasibility and cost-effectiveness of production. Together, they constrain the formulation feasibility of the delivery system.

In addition, the physicochemical properties of hydrogels, such as swelling behavior, gelation time and mechanical modulus, also have a direct impact on their application efficacy. The swelling behavior is related to the drug diffusion path and release rate; the gelation time determines the convenience of clinical operation; and the mechanical strength constrains the morphology retention and long-term stability in different physiological environments (e.g., muscular, subcutaneous, or cavernous), which are the basic attributes for the functionalization of biomimetic hydrogels.

3 Application Examples

3.1 Applications in tumor therapy

Chitosan-gelatin composite hydrogels are commonly used as carriers for localized drug delivery in oncology [7, 23], and their formulations are usually designed with a chitosan-to-gelatin mass ratio controlled between 1:1 and 3:1-a ratio range that balances the material's biocompatibility (with gelatin providing cellular affinity) and mechanical strength (with chitosan enhancing network stability). The researchers loaded the chemotherapeutic drug Adriamycin into this hydrogel by physical encapsulation, and then administered the drug by intra-tumor injection [12]: The hydrogel can be rapidly cured to form a stable structure within 5-10 minutes after injection, and its network pores can effectively encapsulate the drug molecules.

The acidic character of the tumor microenvironment (pH 6.0-6.5) is a key signal that triggers drug release. Glycosidic bonds in chitosan molecules were gradually hydrolyzed under acidic conditions, leading to relaxation of the network structure and subsequent slow release of Adriamycin. *In vitro* release experiments showed that the 24-hour drug release rate of this hydrogel was only about 20% in the simulated normal tissue environment (pH 7.4), whereas the release rate was significantly increased to more than 50% in the simulated tumor microenvironment (pH 6.5), which demonstrated good environmental responsiveness (Figure 1) [21]. Compared with conventional intravenous injection, this system reduces the distribution of Adriamycin to normal organs such as the heart and liver (40-60% lower drug

content), while increasing the drug concentration at the tumor site by 2-3 times, which enhances the antitumor effect and reduces systemic toxicity at the same time.

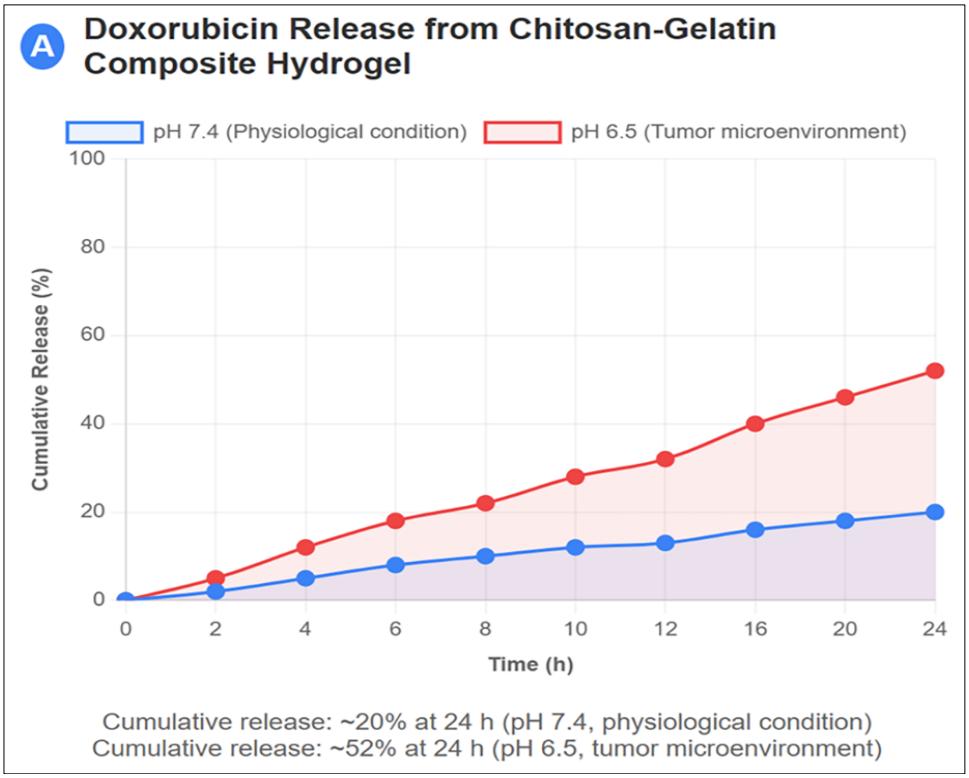

Fig 1: Adriamycin release profile from chitosan-gelatin composite hydrogel

There are also polyethylene glycol and peptide based biomimetic hydrogels for tumor immunotherapy [13, 24, 25]. The molecular weight of the polyethylene glycol of such hydrogels is usually 10 kDa-20 kDa, and the peptides are selected from RGD peptides or CCL21 peptides that bind to immune cell surface receptors. The hydrogel is loaded with a tumor vaccine (e.g., tumor cell lysate or antigenic peptide) and then entered into the body by subcutaneous injection. The hydrogel is slowly degraded in the body with a degradation cycle of about 2-4 weeks, continuously releasing vaccine components and activating the body's immune system. At the same time, the peptide component in the hydrogel promotes the recruitment and activation of dendritic cells and T cells, and experiments have shown that the number of immune cells at the injection site has increased by 3-5 times compared with that of the control group, which improves the response rate of immunotherapy. In experimental models, the system significantly inhibited tumor metastasis, reducing the number of lung metastatic nodules by more than 70% [26].

3.2 Applications in chronic disease management

In the treatment of diabetes, pH-sensitive alginate hydrogels show promising applications. Alginate is a natural polysaccharide derived from brown algae, and the carboxyl groups in its molecule are protonated or deprotonated in different pH environments, causing the hydrogel to swell or shrink. Researchers encapsulated insulin in alginate hydrogels and formed the gel by adding calcium ions as a crosslinking agent, which is usually at a concentration of 10-50 mM and affects the degree of cross-linking and pH sensitivity of the gel [22].

After making an oral preparation, when the preparation enters the stomach, the acidic environment of the stomach (pH 1.2) protonates the carboxyl groups of alginate, enhances intermolecular hydrogen bonding, and shrinks the hydrogel, reducing the release of insulin, with a release rate of less than 10% within 2 hours, to avoid destruction of insulin by stomach acid. After entering the intestine, the neutral environment of the intestine (pH 6.8) deprotonated the carboxyl groups, increased intermolecular repulsion, hydrogel swelling, expanded the network structure, and released insulin, and the release rate could reach more than 70% in 4-6 hours, which was absorbed into the bloodstream through the intestine to achieve controlled release and regulate the blood glucose level (Figure 2). The above *in vitro*, *in vivo* correlation studies provide an experimental basis for oral insulin delivery [22, 27].

For the treatment of rheumatoid arthritis, hyaluronic acid-based biomimetic hydrogels can be used for articular cavity delivery [28-31]. Hyaluronic acid is the main component of joint fluid, with molecular weight selection of 100 kDa-500 kDa, similar to the natural hyaluronic acid in joint fluid. Its hydrogel fuses with the joint fluid after injection into the joint cavity and slowly releases anti-inflammatory agents (e.g., methotrexate or dexamethasone). The degradation rate of the hydrogel can be regulated by the degree of cross-linking and is usually designed to match the drug release cycle at 2-4 weeks. The drug acts locally in the joint, and the concentration of the drug in the blood is only 1/10-1/5 that of systemic administration, reducing the side effects of systemic medication (e.g., gastrointestinal reactions, liver damage). At the same time, hydrogel can also play a role in lubricating joints and protecting cartilage, and experiments have shown that the coefficient of friction of joints has been reduced by 30%, and the degree of cartilage damage has been reduced [28].

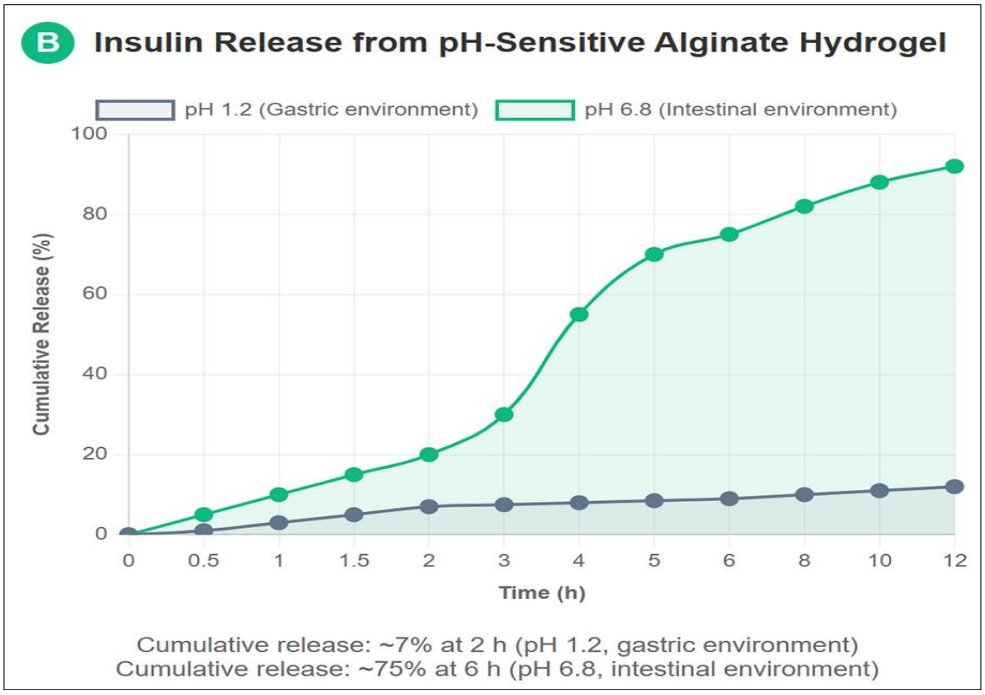

Fig 2: Insulin release profile of pH-sensitive alginate hydrogels

3.3 Applications in trauma repair

Collagen-hyaluronic acid composite hydrogels are commonly used for skin wound repair and are formulated with a ratio of collagen to hyaluronic acid ranging from 2:1 to 5:1 [32-39], which gives the hydrogel a similar modulus of elasticity (10-50 kPa) and moisturizing properties to skin tissue. This hydrogel provides a continuous moisturizing environment for the wound, reduces crust formation, and creates a suitable microenvironment for cell migration and proliferation [40, 41]. These hydrogels are often co-located with growth factors (e.g., EGF to promote epithelial regeneration, bFGF to stimulate granulation tissue formation) and antimicrobial agents (e.g., gentamicin, silver nanoparticles). After covering the wound, the hydrogel is gradually degraded under body temperature (37 °C) and tissue fluid infiltration, with a degradation cycle of about 714 days, which is highly compatible with the natural healing cycle of skin wounds. The drug release showed a "dual-phase characteristic": about 60% of the antibacterial drug was released rapidly in the first 3 days, which could effectively inhibit the early infection of the wound; growth factors were released continuously with the slow degradation of the hydrogel, which could promote the proliferation of fibroblasts and the neovascularization of the wound (Figure 3). The experimental results showed that the wound healing time of using this hydrogel was 30%-40% shorter than that of the control group, the scar area was reduced by more than 50%, and the turgor recovery of the new skin was closer to that of the normal tissue [37, 40].

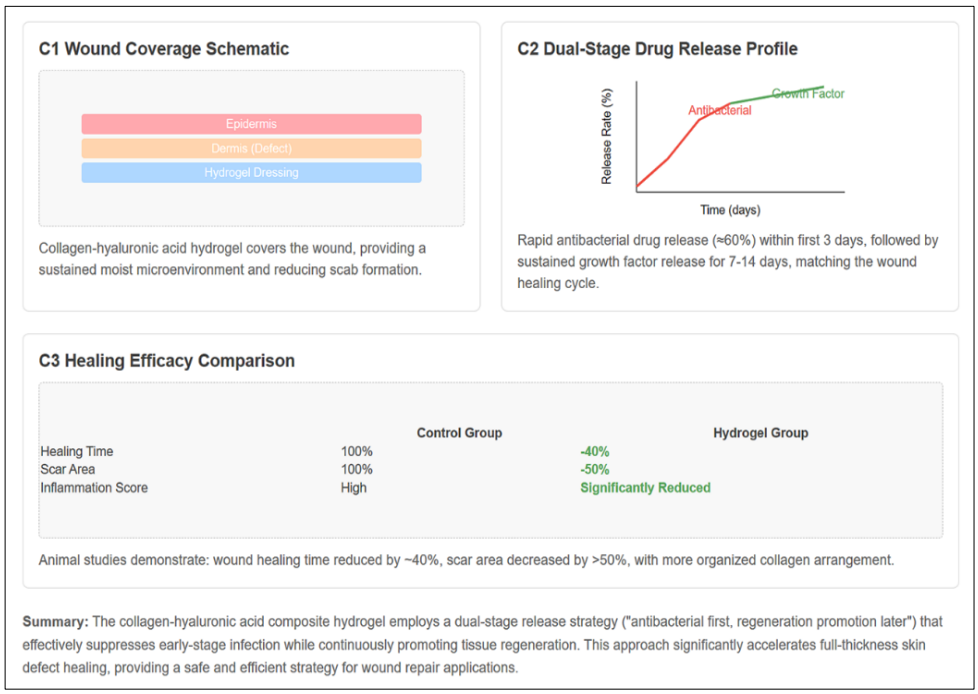

Fig 3: Schematic diagram of collagen-hyaluronic acid composite hydrogel for trauma repair

4 Challenges and Future Prospects

4.1 Challenges

Inadequate material properties are one of the core issues limiting the application of biomimetic hydrogels [41-46]. Although natural hydrogels have excellent biocompatibility, their mechanical strength is generally low, for example, the Young's modulus of pure collagen hydrogels is usually lower than 50 kPa, which is prone to breakage due to friction from daily activities in skin trauma repair, leading to failure of the trauma protective barrier, and affecting the sustained release of drugs and tissue regeneration [47]; At the same time, the degradation rate of natural hydrogels is significantly affected by environmental factors (e.g., local enzyme concentration, temperature), which may lead to the problems of "too fast degradation leading to early release of drugs" or "too slow degradation triggering the reaction of foreign bodies". Although the mechanical properties of synthetic hydrogels can be controlled, they lack natural bioactive sites on the surface. The cell adhesion rate is usually lower than 20%, which may reduce the recruitment efficiency of immune cells (e.g., dendritic cells, T-cells) in scenarios relying on cell-cell interactions, such as tumor immunotherapy, and thus affect the therapeutic response [48].

There are deficiencies in drug release modulation. Most stimuli-responsive hydrogels are only sensitive to a single environmental factor, e.g., only pH or temperature [49-52]. However, the complexity of the *In vivo* environment, such as the gastrointestinal tract with pH gradient changes and digestive enzymes, and the tumor microenvironment with acidity, high enzymes, and hypoxia at the same time, a single response mechanism may lead to release abnormalities [6]. Some hydrogels have the phenomenon of sudden drug release, especially for physically embedded water-soluble drugs, more than 30% of the drug may be released rapidly at the initial stage of hydrogel swelling, which increases the risk of local tissue toxicity [16]. In addition, drug release kinetics are difficult to control precisely and the release rate often decreases with time, preventing the maintenance of stable therapeutic concentrations.

There are also obstacles in the clinical translation process [53-55]. Batches of laboratory-prepared biomimetic hydrogels vary widely, and small changes in raw material purity, cross-linking agent dosage, and reaction time can lead to fluctuations in product performance, making it difficult to standardize production [10]. For example, the difference in drug loading of alginate hydrogels from different batches can be up to 10%-20%, affecting the consistency of therapeutic effects. There is insufficient data on the long-term safety of hydrogels *In vivo*, e.g., prolonged retention in the joint cavity may trigger a foreign body reaction and lead to synovial inflammation, and experiments have shown an increase in the rate of inflammatory cell infiltration around hydrogels that have been retained for a long period of time (more than 6 months) [13]. In addition, hydrogels have expensive equipment for mass production and low production efficiency, leading to higher costs and limiting the popularity of their clinical application.

4.2 Future Prospects

To address the material performance issues, multifunctional composite hydrogels can be developed in the future. Combining the bioactivity of natural materials with the mechanical advantages of synthetic materials, such as introducing nanofiber reinforced structures into collagen hydrogels [17]. Natural macromolecules can also be modified by genetic engineering techniques, e.g., gelatin can be modified to enhance cellular interactions [18].

Drug release modulation techniques need to be further optimized. Multistimulus response mechanisms can be designed, such as developing hydrogels that are sensitive to both pH and temperature [7]. Combined with smart sensing technology, micro-sensors can be embedded in hydrogels to monitor the release in real time, and studies have been conducted to regulate the release of insulin from hydrogels through near-infrared signaling [23]. Promoting clinical translation still requires a multi-pronged approach. On the one hand, establishes a standardized production process, and breaks through the bottleneck of scale-up with standardized and automated production process [8]; on the other hand, it builds a biological evaluation system that covers multiple indicators and a long period of time, and builds up a solid foundation for the application of a long period of time and multi-dimensional safety evaluation system [9]. Despite the challenges, with the upgrading of material technology and evaluation methods, bionic hydrogels are expected to break through the current formulation bottlenecks and grow into the next-generation drug carriers with both efficient delivery and good safety characteristics.

5. Conclusion

Bionic hydrogels have become an important material for the construction of efficient drug delivery systems due to their biocompatibility, structural designability and stimulus responsiveness. By complementing each other's advantages (e.g., the bioactivity of natural materials and the mechanical stability of synthetic materials) and combining various drug-carrying mechanisms such as physical embedding and chemical binding, natural and synthetic hydrogels have achieved clinically significant applications in scenarios such as localized chemotherapy for tumors, intelligent drug delivery for diabetes, and trauma repair, chitosan-gelatin composite hydrogels have achieved targeted drug enrichment at tumor sites, pH-sensitive alginate hydrogels have optimized the oral delivery efficiency of insulin, and collagen-hyaluronic acid hydrogels have significantly accelerated the healing process of skin wounds.

Currently, the field is still facing the "double-edged sword" effect of insufficient strength of natural materials and weak bioactivity of synthetic materials, the difficulty of adapting a single stimulus response mechanism to the complex *In vivo* environment, and the imperfections of standardized production and long-term safety evaluation system. These challenges are expected to be overcome in the future through the research and development of multifunctional composite hydrogels, the optimization of multi-response release technology and the establishment of a systematic evaluation system [56-60]. Overall, bionic hydrogels provide an important idea for the innovation of drug delivery technology. With the integration of interdisciplinary technology, their application in precision medicine and personalized therapy will be more promising, and they are expected to provide support for the innovation of treatment modes of various diseases.

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7. Author Contributions

Wangwang An: Writing, original draft, Writing, review & editing. Shuiping Ou, Writing, review & editing. Sen Wang: Conceptualization, supervision.

8. Conflict of interest

All authors declare that there is no conflict of interest related to this study.

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10. Data Availability Statement: Not applicable.

11. Ethical Compliance Statement

After checking, literature [12, 14] reported only *in vitro*/cellular level experiments and did not involve animal experiments; literature [13, 15-17], if animal experiments were involved, readers are advised to refer to the original literature Methods or Supplementary Materials for information on ethical approvals. No new animal or human experiments were added to this review.

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