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Progress in Drug-Release Characteristics and Applications of Biodegradable Drug-Loaded Hydrogels

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Abstract. Biodegradable drug-loaded hydrogels possess high water content, excellent biocompatibility and in-situ formability, which enables them to achieve localized targeted drug delivery. Thanks to these outstanding material properties, they have become core biomaterials supporting precise regional drug delivery in biomedical practice. These hydrogels have gone through noticeable functional evolution and are no longer simple passive-diffusion-based carriers; instead, they have developed into intelligent therapeutic platforms capable of adapting to tissue microenvironments. This paper systematically sorts out the core regulatory mechanisms behind drug release of biodegradable drug-loaded hydrogels, and analyzes how intrinsic material properties and in-vivo physiological environments affect drug-release behaviors from four dimensions: cross-linking structure, pore structure, pH responsiveness, and temperature responsiveness. This review further sorts out application progress of such hydrogels across four typical clinical scenarios, including cutaneous wound repair, local myocardial infarction treatment, interventional targeted tumor therapy, and bone-defect regeneration. It also summarizes key industrial bottlenecks hindering their clinical translation, such as insufficient suppression of burst drug release, high technical barriers for fabricating integrated multifunctional hydrogels, as well as translational difficulties in large-scale production and clinical approval. At the same time, this paper puts forward several key directions for follow-up research, covering multi-stimuli-responsive delivery systems, sequential multi-drug co-delivery strategies, composite hydrogels with tissue-matching mechanical properties, and the construction of standardized in-vivo evaluation systems. This study offers comprehensive theoretical references for structural optimization, performance improvement and clinical translation of biomedical biodegradable drug-loaded hydrogels.

Keywords: Biodegradable, hydrogel, drug-laden, stimulation response

1. Introduction

1.1. Research background and global research trends of biodegradable drug-laden hydrogels

Implantation of traditional non-degradable drug carriers requires secondary surgical removal, which easily triggers inflammation, tissue injury and other adverse reactions.

To overcome these drawbacks, drug-loaded degradable hydrogels have been developed.

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Benefiting from high water content, favorable biocompatibility, in-situ formability and tunable degradation cycles, they have become key materials for sustained local drug delivery, and have been widely studied for cutaneous wound repair, myocardial infarction local therapy and localized targeted tumor treatment.Typical examples of such hydrogel systems with varied performances are listed in Table 1.Globally, degradable drug-loaded hydrogels are transforming from passive drug carriers toward active intelligent therapeutic platforms. Overseas research focuses on precision medicine, on-demand drug release, immune regulation and cell reprogramming. Domestic research pays more attention to preventing postoperative recurrence and managing chronic diseases. By taking advantage of natural polymer raw-material resources, domestic studies aim to realize substitution of key biomaterials and promote interdisciplinary integration of medicine and engineering.

Table 1. Performance comparison of several typical natural-polymer-based hydrogel materials

Material system	Material category	Mechanical properties	Advantages for drug-loading
Gelatin hydrogel	Natural polymer	1-100kPa	Poor
PVA	Synthetic polymer	100-5000kPa	Good
PVA/CS	Composite polymer	1-10MPa	Excellent

1.2. Functional evolution of biodegradable drug-laden hydrogels: from concentration-gradient diffusion to intelligent release modulation

Early biodegradable drug-loaded hydrogels relied purely on concentration-gradient passive diffusion for drug delivery. Their release rate was controlled by hydrogel pore size and encapsulated drug molecular weight. Such systems suffered obvious limitations: serious initial burst release, insufficient late-stage drug supply, and poor adaptability to dynamic pathological changes. They could only meet basic requirements for local administration in simple wound repair, with highly limited drug-release regulation strategies.Researchers optimized passive-diffusion systems via adjusting cross-linking density and constructing layered composite structures to mitigate burst release. Even so, these modified hydrogels still lacked stimulus-responsive capacity and could not achieve intelligent release control.With further research progress, stimuli-responsive biodegradable hydrogels emerged. By introducing dynamic covalent bonds or responsive substrates into hydrogel networks, specific endogenous biological signals can trigger precise drug release and improve the accuracy of local drug delivery. Current research targets microenvironment-adaptive strategies, which can real-time adjust drug-release flux according to pathological signal intensity. Nevertheless, long-term stability of responsive feedback systems and biosafety issues remain major bottlenecks restricting clinical translation of these intelligent hydrogel platforms.This evolutionary process is illustrated in Fig. 1.

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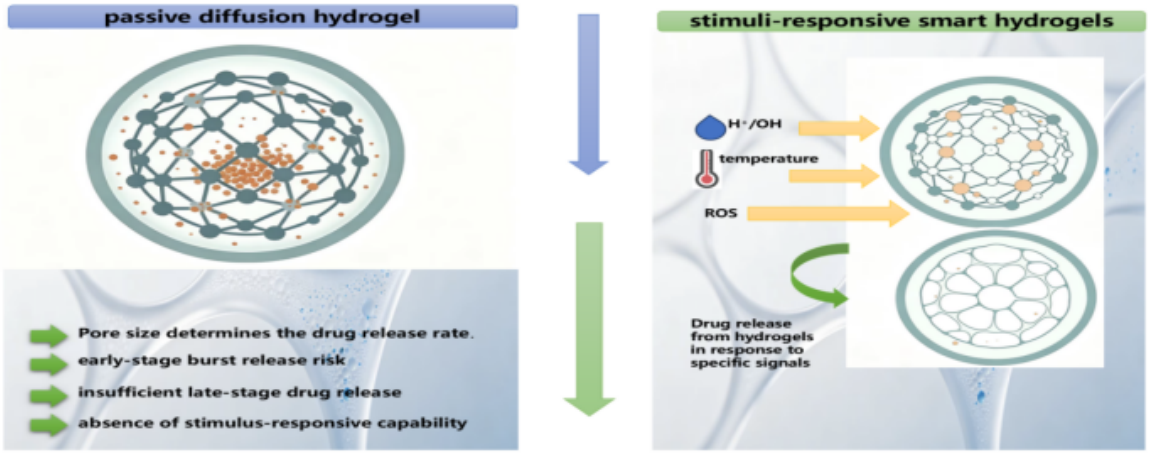

Figure 1. Functional evolution of biodegradable drug-laden hydrogels

2. The effects mechanism of controllable drug release

2.1. Effects of material structure on drug release performance

Crosslinking density serves as a core regulatory factor dominating the drug release profiles of biodegradable stimuli-responsive hydrogels. It manipulates hydrogel mesh structure, swelling behavior, as well as matrix degradation and erosion mechanisms, thereby generating diversified drug release behaviors. In a study reported by Laquerbe et al. [1], Fe-tpy complex-based crosslinking was verified to rapidly form stable structures comparable to permanent covalent bonds, endowing hydrogels with superior mechanical performance and excellent fatigue resistance. Notably, such coordination crosslinking can be reversibly cleaved by oxidants, enabling controllable sol-gel transition of hydrogel matrices. This structural design balances stimuli-responsive capability and mechanical robustness, effectively overcoming the inherent limitations of traditional chemically crosslinked hydrogels and conventional weak supramolecular hydrogels. Lee et al. [2] constructed hierarchical dual-crosslinking architectures to optimize hydrogel performance. This strategy effectively addresses the issues of continuous crosslink dissociation and premature scaffold collapse that commonly occur in conventional dynamic covalent hydrogels under physiological fluid environments. The optimized dual-crosslinking system achieves prolonged drug release duration and improved cell retention capability, exhibiting superior comprehensive performance compared with purely covalent crosslinked or single dynamic crosslinked hydrogels. Collectively, rational modulation of crosslinking density tailored to specific functional requirements is crucial for improving the responsive and sustained release performance of biodegradable hydrogels.

Furthermore, hydrogel pore structure directly governs drug release profiles by mediating medium permeation and drug diffusion kinetics. Excessively large pores tend to cause severe initial burst release, whereas overly compact pore architectures hinder the infiltration of physiological fluids, resulting in inadequate matrix degradation, incomplete drug release, and unnecessarily prolonged delivery cycles. To address such limitations, Siboro et al. [3] developed porous alginate hydrogels with a well-defined multiscale pore synergistic diffusion system. In this design, microscale pores enable stable mass transport, while nano-crosslinked networks provide long-term drug retention and sustained diffusion resistance. The optimized system achieves steady doxorubicin delivery for up to 35 days with negligible initial burst release. Overall, in-situ gas-generated porous architectures have

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been validated as effective structural designs for achieving long-term, stable drug delivery with suppressed burst release behavior.

2.2. Effects of external microenvironments on hydrogel controlled drug release

The effect of pH on drug release behavior is determined by the difference between the acid dissociation constant (pKa) of responsive functional groups and ambient pH value, which drives swelling or collapse of hydrogel networks. Meanwhile, pH directly catalyzes the hydrolysis rate of acid-labile or base-labile bonds. Drug-release performance is jointly regulated by these two factors. Yin et al. [4] fabricated dual-polysaccharide pH-responsive networks for oral administration by compounding pineapple peel residues, Hericium erinaceus extracts, oxidized hydroxyethyl cellulose and carboxymethyl chitosan. Under acidic gastric conditions, carboxylate groups become protonated, triggering pore shrinkage to sequester loaded drugs. Upon entering the intestinal tract, carboxylate groups undergo deprotonation, enlarged mesh pores facilitate drug liberation. Zhang et al. [5] constructed precise reversible pH-responsive systems based on Schiff-base dynamic covalent bonds. The network disassembles into low-viscosity injectable solutions at $pH < 4.2$ and re-gelates under neutral or weakly-alkaline environments. Unlike most polysaccharide hydrogels with only one-way swelling or shrinkage, this material achieves reversible sol-gel transition and suits minimally invasive injectable administration. In brief, the core principle of pH-responsiveness lies in acid-base-induced hydrogel structural transformation, including mesh contraction-expansion or network disassembly-reconstruction, so as to realize controllable drug release.The core mechanism of temperature-regulated drug-release behavior is the conformational transition of thermosensitive polymer segments, and variation in diffusion coefficient of loaded drugs acts as an auxiliary regulatory factor. The whole drug-release process is co-modulated by these two effects. Zhao et al. [6] constructed dual-reversible ionic networks combining polyelectrolyte ionic cross-linking and bicarbonate weak ionic cross-linking. This system shows high swelling degree at low temperature. Under physiological temperature of 37 °C, network contraction encapsulates drug molecules; drug release accelerates when temperature rises above physiological conditions or the ionic microenvironment changes. The network realizes temperature-tunable drug-release rate for long-term temperature-controlled localized delivery, and supports simple administration for surgical and minimally-invasive scenarios. Zhi et al. [7] prepared a novel injectable thermo-sensitive polymer backbone. It maintains low-viscosity injectable fluid at room temperature and completes in-situ gelation within 10 min at 37 °C. Vancomycin is physically immobilized inside the gel matrix to avoid systemic side-effects from intravenous infusion. Stable hydrogel network forms under physiological temperature and provides a matrix for steady sustained drug release. In brief, thermoresponsive hydrogels can construct local drug depots and achieve long-term controlled release, supplying controllable delivery platforms for minimally-invasive local treatment of infections, tumors and other diseases.These external-stimulus-triggered release processes are summarized in Fig. 2.

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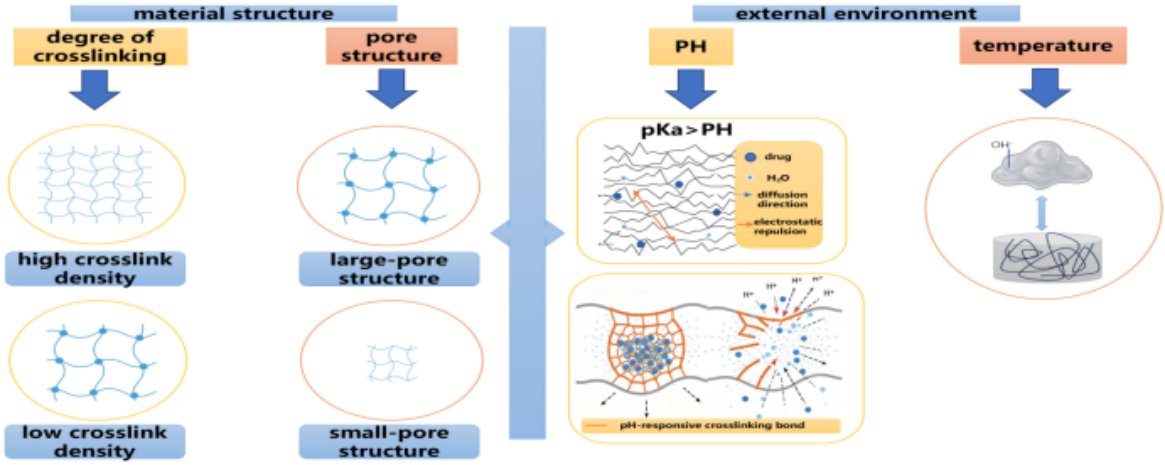

Figure 2. Effects of external stimuli on controlled drug release of biodegradable hydrogels

3. Application scenarios

Hydrogel drug-delivery platforms serve a variety of biomedical uses. Representative applications are illustrated in Fig. 3, and Table 2 lists common hydrogel types together with their drug-release mechanisms.

3.1. Wound repair and skin administration

Biodegradable hydrogels for wound management combine two key functions: forming a moist microenvironment barrier for wound healing and acting as a localized drug reservoir. The hydrogel matrix can effectively absorb wound exudate and accelerate tissue regeneration, while achieving sustained and controllable drug release, extending in-situ retention time at wound sites and improving transdermal drug bioavailability. Owing to these combined advantages, such hydrogels have become advanced active dressings for refractory skin defects including diabetic wounds and burn wounds. Liu et al. [8] developed a dual-functional self-healing hydrogel with in-situ oxygen generation and broad-spectrum antibacterial properties. This material integrates three core functions: continuous oxygen supply, efficient antibacterial performance and autonomous self-repair. It addresses three major obstacles in diabetic wound healing: tissue hypoxia, persistent bacterial infection and poor mechanical stability of traditional dressings, overcoming the functional limitations of conventional wound dressings. Nevertheless, both commercial dressings and laboratory-developed hydrogels still have obvious drawbacks, such as insufficient mechanical strength, uncontrollable matrix erosion, inadequate multi-functional synergistic effects, poor adaptability for minimally invasive filling of irregular wound defects, and low efficiency for clinical translation. Sawadkar et al. [9] systematically summarized research advances of skin-repairing hydrogels from seven dimensions, including wound pathological features, material design strategies and industrial technical bottlenecks, and built a complete logical framework linking fundamental material mechanisms and clinical translation. In general, biodegradable hydrogels possess unique merits in cutaneous wound repair and transdermal controlled drug delivery. Future research will focus on intelligent upgrading and personalized structural customization of hydrogel systems, which is a core direction to promote innovation and clinical transformation of wound-dressing biomaterials.

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3.2. Myocardial infarction

Massive cardiomyocyte necrosis occurs after myocardial infarction (MI), and lesion sites maintain persistent oxidative stress and chronic inflammation. Drug-loaded hydrogels can realize long-term local retention of therapeutic agents in cardiac tissues. Integrating mechanical support and drug-delivery functions, they serve as key carriers for precise local treatment of myocardial infarction [10]. Ding et al. [11] first achieved systematic integration of bioactive components from traditional Chinese medicine with cardiac hydrogel patches. This work fills the research gap of cardiac composite hydrogels loaded with traditional Chinese-medicine ingredients, breaking the limitation of existing reviews that only focus on chemical-drug-loaded hydrogels or pure traditional-Chinese-medicine-based myocardial therapy. Mu et al. [12] originally constructed an integrated conductive composite hydrogel platform with microenvironment-responsive temporally staged delivery. Its outer ROS-responsive conductive hydrogel HGB eliminates early oxidative inflammation, while the inner layer encapsulates Alginate/gelatin (Alg/GT) stem-cell microspheres. These microspheres exert paracrine effects to realize long-term cardiac repair at later pathological stages. This design achieves sequential drug delivery matching the staged pathological progression of myocardial infarction.Taken together, hydrogels for post-infarction cardiac drug delivery have evolved from simple single-function drug carriers to comprehensive platforms combining precise release regulation, formulation innovation, active stimulus-responsiveness and sequential delivery.

3.3. Localized targeted tumor therapy

Drug-loaded hydrogels exhibit unique advantages for minimally-invasive interventional tumor therapy, including modifiable targeting groups, long-term regional tissue retention, multi-drug co-loading capacity, favorable biocompatibility and biodegradability. Guo's research team [13] developed a thermoresponsive-triggered dual-modal therapeutic strategy by constructing injectable interpenetrating polymer network (IPN) hydrogels. This system organically combines tumor starvation therapy and local hyperthermia-mediated tumor cell ablation, exploring a new direction for low-toxicity non-invasive localized anti-tumor treatment. Liang et al. [14] originally fabricated in-situ injectable supramolecular hydrogels with the intrinsic capability to reverse the acidic tumor microenvironment (TME). The hydrogel itself possesses inherent anti-tumor bioactivity. It fundamentally disrupts the acidic pathological microenvironment that promotes tumor proliferation and drug resistance, and realizes dual therapeutic effects: intrinsic tumor suppression from the matrix material and synergistic anti-tumor efficacy of loaded drugs.Taken together, hydrogel research has shifted from simple single-drug encapsulation toward active tumor-microenvironment modulation, and upgraded from single-modal therapy to multi-mechanism synergistic anti-tumor treatment, continuously providing novel strategies for localized tumor interventional therapy.

3.4. Precision bone tissue regeneration

Precision bone tissue regeneration mainly targets three kinds of bone defects: traumatic bone loss, infectious bone lesions, and bone defects after bone-tumor resection. Drug-loaded hydrogels show prominent advantages in this field, owing to good defect-filling adaptability, spatially precise delivery, tunable mechanical properties and microenvironment-regulating capacity. Zhao et al. [15] originally designed two self-assembling supramolecular hydrogels, which are separately tailored to regulate cell proliferation and inflammation-mediated biomineralization to satisfy sequential requirements of bone regeneration. Minimally invasive injection avoids transplantation-related

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complications. The peptide self-assembled nanofiber networks encapsulate and protect osteogenic growth peptide (OGP), reducing administration frequency and improving therapeutic efficacy. Chen et al. [16] fabricated a bilayer dual-network composite hydrogel to meet the divergent regeneration requirements of superficial cartilage and deep subchondral bone in osteochondral lesions. The upper layer is responsible for cartilage regeneration, and the lower layer realizes subchondral-bone restoration. Matching bioactive ingredients from traditional Chinese medicine are loaded in separate regions of the hydrogel matrix. It achieves persistent local drug delivery at target lesion sites and greatly reduces systemic drug exposure.In summary, hydrogels can serve as defect fillers for precision bone tissue regeneration. Meanwhile, they realize active regulation of bone regeneration through spatiotemporally precise drug delivery, thus providing flexible and customizable delivery platforms for clinical treatment of complex bone defects of the above three categories.

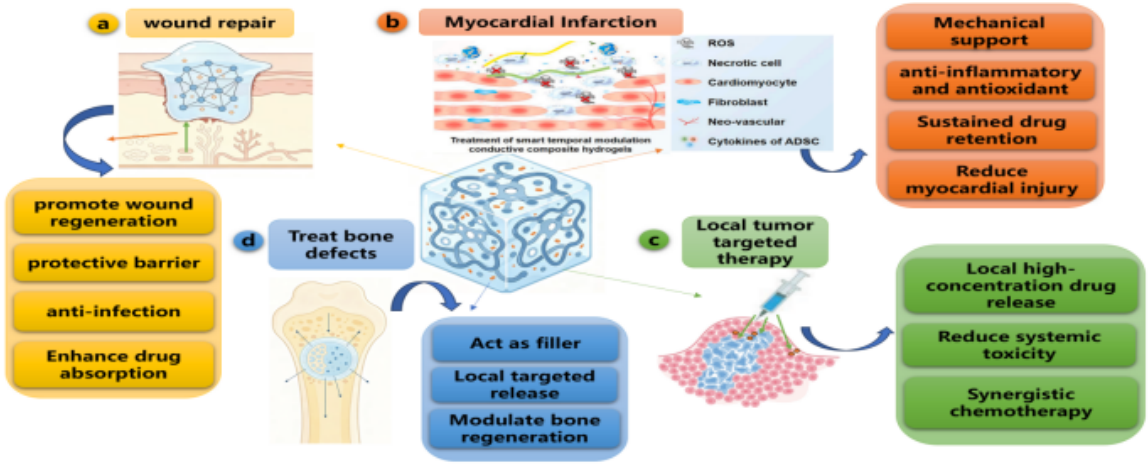

Figure 3. Applications of hydrogels (a)wound repair (b)myocardial infarction [12] (c)Local tumor targeted therapy (d)treat bone defects

Table 2. Categories of hydrogel-based drug delivery carrier materials and corresponding drug release mechanisms

Hydrogel Material Category	Drug Release Mechanism	Application Scenarios
Natural polymer materials	Swelling-diffusion controlled release	Wound dressings and hemostasis
Synthetic polymer materials	Stimuli-responsive swelling-diffusion controlled release	Drug delivery systems
Composite/dual-network materials	Multi-responsive degradation-diffusion synergistic release	Tissue engineering scaffolds

4. Challenges and future perspectives

4.1. Suppression of burst release effect

Biodegradable hydrogels hold unique merits when they act as advanced drug-delivery carriers, yet the burst release effect will remain a dominant bottleneck that restricts their clinical translation. One

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aspect comes from the intrinsic high-water-content and porous matrix of hydrogels; these properties can drive rapid diffusion and premature leakage for encapsulated drugs during the early implantation stage. On another aspect, hydrogel networks will go through gradual hydrolysis and enzymatic degradation after in-vivo administration, and degradation that crosses a critical threshold can trigger abrupt phase transition alongside structural collapse, which further worsens drug burst release. Excessive sensitivity toward environmental triggers for stimuli-responsive hydrogels can also bring about uncontrollable drug leakage. Besides that, mature theoretical models that can precisely simulate drug-release kinetics within complex physiological microenvironments are still hard to obtain, so material optimization work has to rely heavily on trial-and-error attempts.In practical material-development work, we can notice that burst release cannot get fully eliminated through simple structural adjustment alone; even well-optimized hydrogel formulations will still run into risks of unexpected drug leakage when they face dynamically changing in-vivo conditions.Multiple interacting factors can make burst release become the primary obstacle that holds back clinical application of hydrogel-based delivery systems.

4.2. Development of multifunctional composite biodegradable drug-laden hydrogels

Multifunctional composite biodegradable drug-laden hydrogels have experienced a clear evolutionary shift; they have moved away from conventional passive delivery carriers and grown into intelligent, precision-oriented therapeutic platforms. At the material level, the introduction of diverse functional components is able to improve mechanical performance and expand therapeutic capabilities, which can bring effective integration of multiple functions. At the structural level, multi-stage encapsulation together with dual-network architectures can curb premature drug diffusion and relieve the early-stage burst-release phenomenon. Advanced functions including stimulus responsiveness, multi-drug co-delivery and programmable sequential release have also got progressively integrated into hydrogel systems. Such structural and functional innovations make hydrogel platforms flexible enough to match diverse disease types as well as personalized therapeutic demands, and they can provide feasible, efficient strategies that support precise clinical intervention for complex diseases.

We also need to take an objective view toward material fabrication; simply piling up different functional components cannot deliver satisfying comprehensive performance. Excessively complicated component compositions may weaken biocompatibility instead, and they will raise the technical difficulties for subsequent material preparation procedures.

5. Conclusions

5.1. Material design should be matched with biomedical requirements

To acquire optimal therapeutic outcomes, the material design of hydrogels as drug delivery carriers must be closely matched with biomedical practical demands.Firstly, crosslinking density and composite components are required to match the mechanical properties of target host tissues, and degradation kinetics should be coordinated with tissue regeneration or therapeutic cycles. Secondly, the characteristics of host immune response need to be taken into consideration during material design. Inflammatory reactions can be avoided, and even active regulation of immune microenvironment can be realized via rational structural optimization. Furthermore, convenience of clinical operation and feasibility of large-scale manufacturing should also be considered

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comprehensively.Hence, we believe these practical constraints should be weighed carefully throughout the whole material design workflow.

5.2. Existing limitations and future research directions of biodegradable drug-laden hydrogels

Multiple challenges remain in current investigations, including uncontrollable burst release and drug release behavior, insufficient mechanical performance, difficulty in matching degradation rate with tissue regeneration cycles, uncertain immunogenicity and biosafety, obstacles in large-scale manufacturing, and ambiguous pathways for clinical translation.Future research should focus on the development of multiple stimuli-responsive hydrogels. Dynamic drug release can be adapted to pathological progression through such materials. Furthermore, platforms for sequential delivery of multiple drugs should be developed to satisfy the demands of whole-course intervention for complicated diseases.Meanwhile, standardized evaluation systems for drug release need to be established. The maturation of large-scale fabrication technologies and regulatory frameworks should be promoted, which serve as key breakthrough points for the clinical translation of degradable drug-loaded hydrogels.It should also be pointed out that real-world clinical translation still demands joint efforts from both material scientists and clinical practitioners.

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