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Research Progress on Biomedical Self-Healing Polymer Materials

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Abstract: Self-repairing polymer materials have shown broad application prospects in the biomedical field due to their ability to self-repair after damage. They play a key role in extending equipment life, ensuring reduced quality of use, reducing manufacturing costs, and protecting environmental quality. Due to the widespread application of self-healing materials, the limitations of self-healing polymer materials have gradually been magnified, and there are differences and diversity in the research and application of self-healing materials for different polymers. In addition, there are promising development prospects in biomedical applications such as drug delivery systems, medical coatings and implant materials, and flexible bioelectronics.

1. Introduction

Polymer materials are increasingly utilized in the biomedical field for diverse applications such as drug delivery systems, medical coatings, implantable devices, and flexible bioelectronics. A significant challenge, however, is the inevitable degradation or damage these materials experience over long-term service. To address this issue, self-healing polymers have emerged as a highly promising solution. These materials possess the intrinsic ability to autonomously repair damage through physical or chemical mechanisms, thereby restoring their structural integrity and functionality. This self-repair process not only prolongs the service life of the material but also ensures the long-term reliability and safety of the biomedical device. Moreover, the healing mechanisms of these polymers can be precisely tailored by designing their chemical composition and architecture, enabling them to respond to specific environmental triggers or address the unique demands of different biomedical applications. Consequently, self-healing polymer materials have attracted considerable research interest in the biomedical community and hold enormous potential for future advancements.

Self-healing polymers are broadly classified into two categories according to the underlying reversible chemistry: non-covalent dynamic bonds and covalent dynamic bonds. The former category relies on physical interactions such as metal coordination, ionic interactions, and hydrogen bonding. The latter category is exemplified by chemistries including the reversible Diels-Alder (D-A) reaction, disulfide exchange, and boronic ester formation. These systems are collectively referred to as intrinsic self-healing polymers.[1]

This article will introduce self-healing polymer materials from different polymers, and discuss

their self-healing mechanisms from two aspects: covalent self-healing and non-covalent self-healing. We simultaneously survey the state of the art and future potential of biomedical self-healing polymers, and conclude with a forward-looking summary.

2. Self-healing mechanism

2.1 Covalent bond self-healing

Self-healing relies on dynamic covalent bonds that can reversibly break and reform under specific conditions like heat, light, or pH. Common examples include Diels-Alder (D-A) reactions, which are reversible cycloaddition reactions between conjugated dienes and alkenes or alkynes; disulfide bonds that can be reversibly broken in redox environments, making them ideal for biomimetic medical materials; and transesterification, a process that allows for reversible crosslinking and is useful for pH-responsive drug carriers. [2]

2.1.1 Diels-Alder reaction

In the Diels-Alder reaction, the highest occupied molecular orbital (HOMO) of the diene overlaps with the lowest unoccupied molecular orbital (LUMO) of the dienophile, forming a cyclic transition state. Subsequently, electrons flow from the diene's HOMO to the dienophile's LUMO, creating new sigma bonds through a concerted mechanism to ultimately yield a stable six-membered ring product[3]. Simply put, this reaction forms a cyclohexene derivative from a conjugated diene and an alkene or alkyne. Early research by Chen in the field of thermally reversible crosslinked polymers, followed by nearly forty years of in-depth study, has led the scientific community to fully recognize the unique mechanism and application value of the Diels-Alder (D-A) reaction for constructing dynamic covalent crosslinking networks in polymers.[4]

The core characteristics of this reaction can be systematically summarized as follows: (1) Dynamic reversibility: Its thermally reversible covalent bonds can undergo reversible cleavage at specific temperatures, enabling dynamic control of the material's macroscopic properties and autonomous repair of damage. (2) Mild and controllable conditions: The reaction typically proceeds from room temperature to moderate heating, achieving high conversion without metal catalysts or harsh conditions, which makes it suitable for environmentally sensitive systems. (3) Good environmental compatibility and sustainability: The reaction can be performed in aqueous or green solvent systems like ionic liquids. It also features high atom economy, aligning with the principles of green synthesis. Based on these advantages, the D-A reaction has become a key tool for designing self-healing polymers, intelligent soft materials, and recyclable thermosetting resins, continuously driving functional innovation and expanding applications in the field of polymer materials. [5]

The Diels-Alder reaction is also widely used in the medical field. A notable example is Viniglol, a compound first isolated in 1987 from the fermentation broth of the parasitic fungus Virgaria nigra. Viniglol has demonstrated antihypertensive activity [6]; for instance, intravenous injection can lower arterial blood pressure in normal mice. Furthermore, at lower concentrations, it effectively inhibits human platelet aggregation induced by platelet-activating factor and adrenaline.

Viniglol also exhibits antibacterial activity. At a concentration of 10 $mg \cdot mL^{-1}$, it showed slight antibacterial activity against the Gram-positive bacteria Bacillus subtilis and Staphylococcus aureus. However, it had no inhibitory effect on the Gram-negative bacterium Escherichia coli or the fungus Candida albicans at the same concentration. In addition, Viniglol demonstrated cytotoxicity towards the murine leukemia cell line P388 within a concentration range of 10–50 $\mu g \cdot mL^{-1}$, indicating its potential value for the development of anti-leukemia drugs. The synthesis route for a key intermediate of Viniglol is shown in Fig. 1.

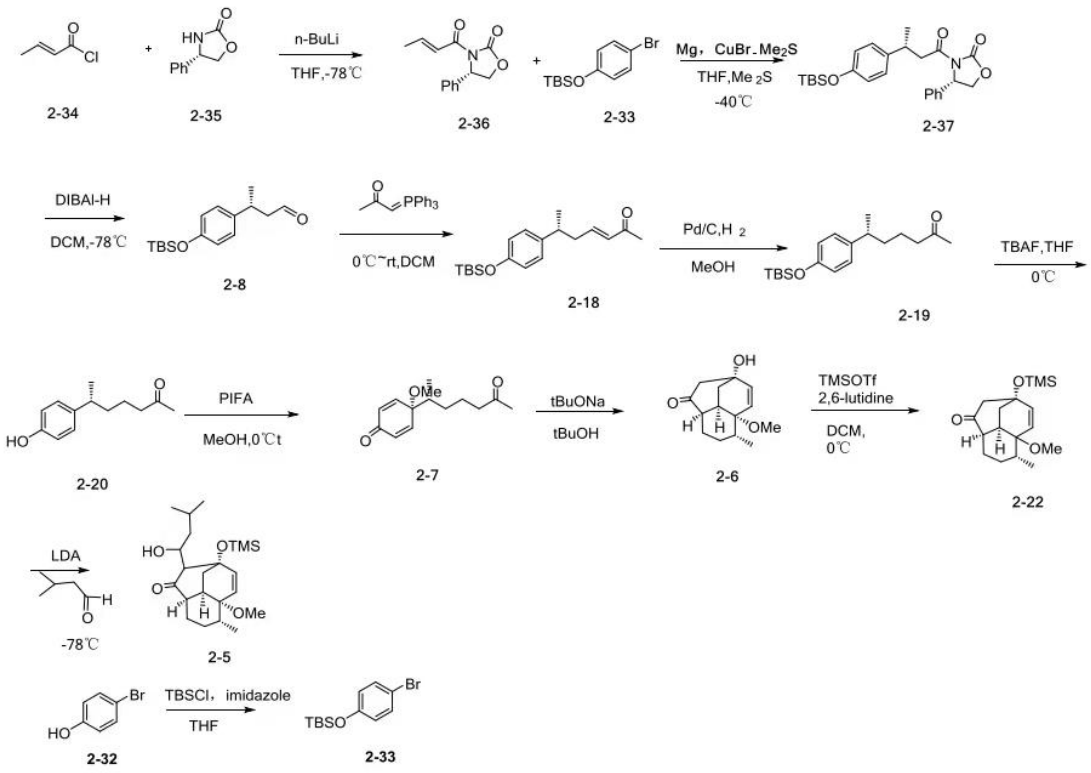

Figure 1 Synthesis route of important intermediates of Viniglol.

2.1.2 Disulfide exchange

Disulfide exchange is a dynamic covalent chemistry process characterized by the reversible cleavage and recombination of disulfide bonds, which can proceed at room temperature. Due to the controllable breaking and reforming of these covalent bonds under external stimuli, disulfide linkages are frequently incorporated into structural self-healing material systems. These systems can autonomously repair damage, thereby significantly extending the material's service life and enhancing its stability [7]. The reaction mechanism is illustrated in Fig. 2 [8].

Figure 2 Schematic diagram of the principle of disulfide bond self-repair performance.

The formation of dynamic reversible covalent bonds relies on the exchange reaction between thiols and disulfide bonds. Such reactions typically proceed with oxidized thiol salts in neutral or weakly alkaline environments. From a mechanistic perspective, this process involves the nucleophilic attack of a thiolate anion (RS^-) on a disulfide bond (S-S). This attack leads to the cleavage of the original disulfide bond and the formation of a new one, while releasing a new thiolate anion [9]. However, thiols in their reduced state exhibit lower reactivity. Therefore, in practice, disulfide bonds are often first cleaved via reduction to generate thiol groups, which are then re-oxidized to form new disulfide

bonds. This pathway achieves reversible crosslinking based on changes in the redox state, rather than through a direct bond exchange mechanism [10].

The alkaline catalytic decomposition method is a simple and efficient strategy for disulfide bond reconstruction. This method usually uses alkali metal hydroxides (such as NaOH, KOH) or organic bases (such as triethylamine, bicyclic amidine, diethylenetriamine, etc.) as catalysts to achieve dynamic exchange of disulfide bonds in homogeneous or two-phase systems. The key to its reaction mechanism lies in the base promoting the generation of thiol salt anions (RS), which can effectively mediate the cleavage and recombination of disulfide bonds. The main advantages of this strategy include lower catalyst costs and easy implementation of experimental processes[11]. However, its shortcomings lie in the difficult control of reaction selectivity in the synthesis of asymmetric disulfide compounds, as well as poor compatibility with some sensitive sensory groups. Fine control of reaction conditions is usually required to achieve satisfactory results.

Disulfide bonds also play a crucial role in the biomedical field, as evidenced in the stability of protein structure and function, drug delivery systems, disease research and treatment, biomedical imaging, and other areas. Xu successfully prepared a disulfide-bridged cyclodextrin hydrogel drug carrier [12]. Initially, two intermediate products, EDA-β-CD and NHS ester functional monomer, were synthesized (as shown in Figs. 3 and 4). Subsequently, stable amide bonds were formed through an electrophilic addition reaction between the NHS ester functional monomer and the nucleophilic reagent EDA-β-CD, resulting in the generation of a polymerizable disulfide-bridged β-CD monomer (MA-SS-β-CD). The structure of the disulfide-bridged β-CD monomer (MA-SS-β-CD) was characterized using nuclear magnetic resonance (NMR) hydrogen spectroscopy, carbon spectroscopy, and Fourier transform infrared spectroscopy, confirming its successful synthesis. Elemental analysis data indicate that the composition of each element in the synthesized monomer is consistent with expectations. The estimated β-CD loading, based on sulfur content, is 77.85%, which is highly consistent with the theoretical value of 78.15%.

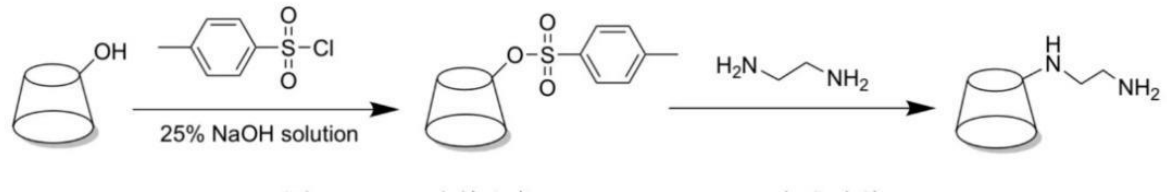

Figure 3 Synthesis route of ethylenediamine mono-substituted -β-CD (EDA-β-CD).

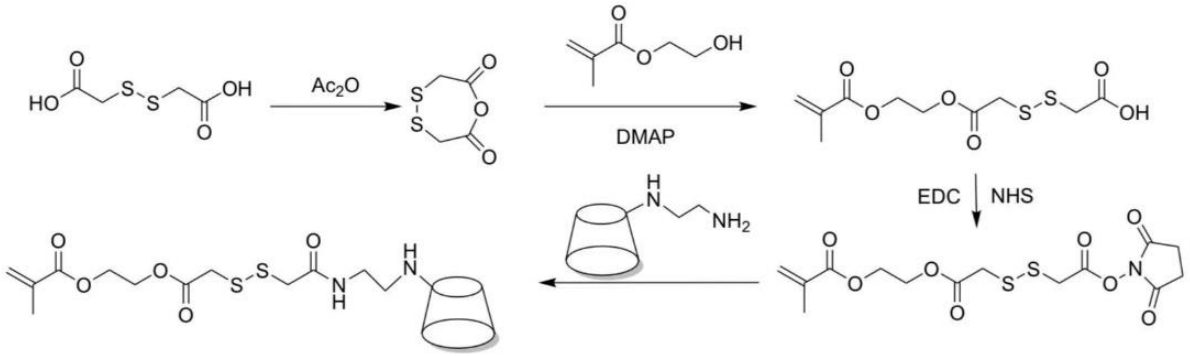

Figure 4 Synthesis route of disulfide bridged β-CD monomer (MA-SS-β-CD).

2.1.3 Transesterification

Boric acid ester bonds are formed through the condensation and coordination between boronic acid compounds and diols (or carboxylic acids) containing adjacent hydroxyl groups in aqueous

media. The reversible breaking and recombination of this dynamic covalent bond endows the material with significant stimulus responsiveness, enabling the regulation of self-healing behavior under external stimuli such as pH, temperature, or specific chemical substances like glucose. In the biomedical field, this chemistry is widely utilized in applications such as self-healing composite hydrogels for drug delivery, tissue engineering, and wound dressings. With ongoing technological advancements, self-healing composite hydrogel electrolytes based on borate ester bonds have been engineered with a variety of enhanced properties. These include low-temperature conductivity, high strength and tensility, tunable characteristics, and high ionic conductivity [13, 14].

Zeng studied the self-healing performance of AR/PVA-B hydrogel. First, cut the hydrogel from the middle, and then make its cross section contact again [15]. After 5 minutes of self-healing at room temperature and without external stimulation, it was observed that the material has completely healed and can achieve large deformation. In order to further investigate its self-healing ability, the mechanical properties of the repaired hydrogel were tested. After the hydrogel is damaged, these dynamic non covalent bonds (such as hydrogen bonds and coordination bonds) can form again and achieve structural recovery. During the process of external force loading, dynamic bonds dissipate energy through fracture and recombination, reestablishing a three-dimensional cross-linked network and effectively restoring the mechanical properties of the material.

2.2 Non-covalent self-healing

Non-covalent interactions, such as hydrogen bonding and metal coordination, endow materials with excellent self-healing properties and biocompatibility. For instance, hydrogen bonding networks in systems like polyurethane (PU) and polyacrylic acid (PAA) can achieve rapid repair under mild conditions. Similarly, the dynamic binding of metal ions, such as Zn^{2+} and Fe^{3+}, to polymer ligands can be utilized in the development of flexible biosensors.

2.2.1 Hydrogen bond

Hydrogen bonds can undergo scission upon material damage to dissipate energy and subsequently re-form, thereby enabling self-healing capabilities. This mechanism significantly enhances the durability, hardness, and toughness of materials. Such properties render hydrogen-bond-based self-healing materials highly promising for biomedical applications, particularly in the design of gene delivery vectors, drug delivery systems, and the development of advanced biomaterials.

In the field of drug delivery, non-ionic delivery systems (TNP) based on hydrogen bonding have achieved efficient loading and charge-independent delivery. For example, Wang prepared TNP-470 nanoparticles with targeted neovascularization characteristics, which demonstrated good therapeutic effects on tumor tissues [16]. TNP-470, a semi-synthetic derivative of aflatoxin, effectively inhibits angiogenesis within the tumor microenvironment.

In this study, we prepared nanoparticles using a single-emulsion method, with TNP-470 as the model drug and Maleimide-PEG-PLA and mPEG-PLA as carrier materials. Based on the high expression of vascular endothelial growth factor receptor (VEGFR) on tumor neovascularization, we coupled the TNP-470-loaded nanoparticles with vascular endothelial growth factor (VEGF). This successfully constructed VEGF-modified, drug-loaded nanoparticles, aiming to endow the nanosystem with active targeting ability and thereby enhance the anti-tumor efficacy of TNP-470[17, 18]. Laser scattering analysis indicated that the average particle size of TNP-470-NPs-VEGF was 130 nm, the average Zeta potential was -14.3 mV, and the polydispersity index (PdI) was 0.270. No significant differences in particle size or surface potential were observed compared with TNP-470-NPs. Both systems presented a light blue, milky appearance, as shown in Fig. 5.

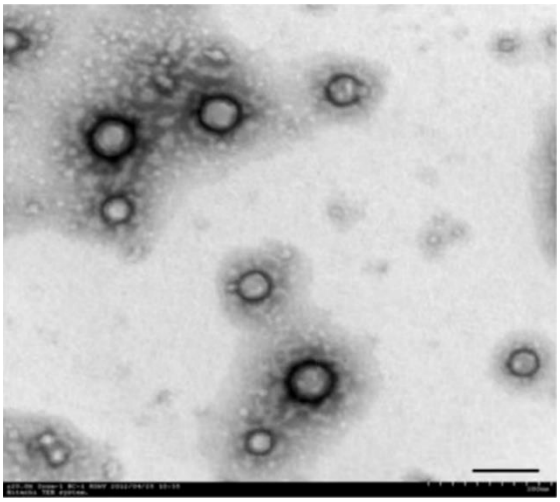

Figure 5 Transmission electron microscope image of TNP-470-NPs-VEGF nanoparticles (scale bar 100 nm)

2.2.2 Metal coordination bonds

High performance self-healing hydrogel is the most widely used field. After being damaged, it only needs to be slightly heated or still to achieve self-healing, which can restore the high mechanical strength of the device. This type of material has broad prospects in fields such as artificial cartilage, tissue engineering scaffolds, wearable sensors, etc.

In metal coordination, transition metal ions exhibit broad selectivity for functional groups containing lone pair electrons. This interaction enables rapid bonding and dissociation under external stimuli, and the process is highly controllable. Currently, construction strategies based on metal coordination have been widely used in the preparation of self-healing composite hydrogels [19]. For instance, taking the work of Xu et al. as an example[20], they constructed the first network using bovine serum albumin grafted with… and the copolymer of sodium acrylate and acrylamide as the second network, successfully developing a conductive, all-physically crosslinked double-network hydrogel with fast self-healing ability.

Relying on the metal coordination between Fe^{3+}, pyrrolidine, and carboxylate groups, the hydrogel exhibits remarkable self-healing performance, achieving a repair rate of 76.42% without any external intervention. Furthermore, the introduction of Fe^{3+} also endows the hydrogel with excellent conductivity and sensing characteristics. This allows it to function as a flexible sensor, effectively monitoring human movement and heart rate changes [21].

3. The application prospects of self-healing materials in biomedical fields

3.1 Drug delivery system

Self-repairing polymer materials can be specifically applied to enhance carrier stability, control drug release, achieve targeted delivery, and repair damaged areas. Luo et al. [22] summarized various preparation methods for self-healing microcapsules, as illustrated in Fig. 6 and Fig. 7 [23, 24]. Microcapsules with pH or enzyme responsiveness can achieve site-specific drug release at lesion sites, thereby improving therapeutic targeting. In a practical application, Yao et al. successfully developed a novel antibacterial, self-healing dental resin [25]. According to the reported research, a new antibacterial, self-healing capsule with good thermal stability and self-healing performance was first successfully synthesized. The hydrophilicity of the resulting dental resin increased with the dosage

of the microcapsules. However, its mechanical properties decreased as the capsule dosage increased.

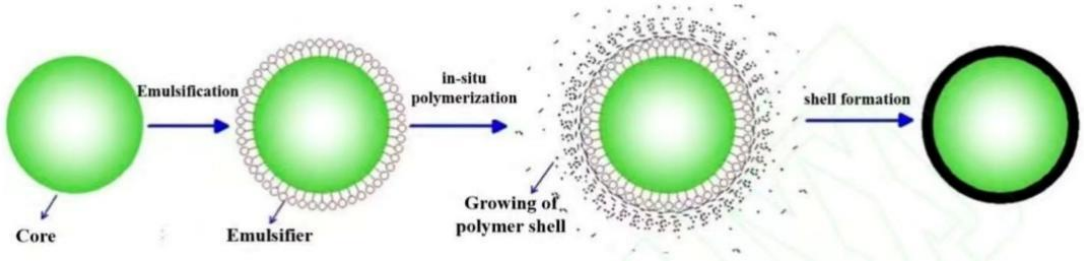

Figure 6 Schematic diagram of in-situ polymerization method for preparing microcapsules.

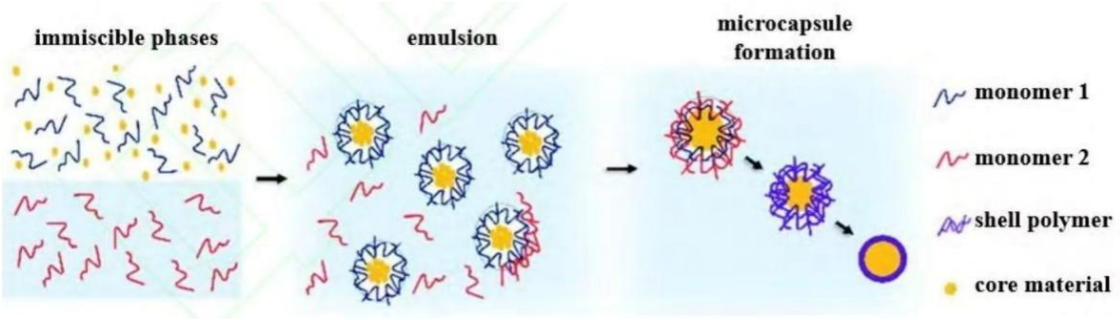

Figure 7 Schematic diagram of preparing microcapsules by interface aggregation method.

3.2 Coatings and implant materials

Self-repairing coatings can effectively prevent the propagation of microcracks in medical implants, increase the service life of implants while reducing the risk of infection, and have a good application environment and development prospects.

Dong et al. first reported the self-healing behavior and mechanism of a coating prepared from dicalcium phosphate dihydrate (DCPD) [26]. They successfully constructed this DCPD coating on a pure magnesium substrate using a chemical conversion method. The research demonstrated that the coating serves a dual function: acting as both a physical barrier and a controllable release carrier for corrosion inhibitors, thereby achieving an integrated design for surface protection and self-healing on medical magnesium. The self-healing mechanism is initiated upon coating damage. The local alkaline microenvironment that forms in the damaged area activates the pH-responsive DCPD material, promoting the directional release of calcium and phosphorus ions. These ions subsequently deposit a new, protective, corrosion-inhibiting layer. Concurrently, the HBSS solution system can supply exogenous corrosion inhibitors, which further accelerates the self-healing process through a synergistic effect between the endogenous and exogenous sources. This material significantly enhances the corrosion resistance of magnesium metal and possesses self-healing properties, which can extend the material's service life and improve its hardness and toughness.

3.3 Flexible bioelectronics

Dielectric elastomer actuators (DEAs), often referred to as artificial muscles, can contract and relax under electrical stimulation and show great promise for applications in soft robotics. Yue et al. proposed a method for preparing self-healing DEAs and discussed its advantages and disadvantages [27]. As intelligent artificial muscle materials, DEAs have demonstrated broad application prospects in biomimetic robots, medical healthcare, and flexible electronics. This review systematically summarizes the actuation mechanisms of DEAs and the design strategies for self-healing variants. Although researchers have made extensive efforts at the molecular, material, and device levels to

achieve large deformation, high energy density, high-frequency response, high output force, and controllable deformation, the practical application of DEAs still faces significant challenges. These include the need to enhance the durability of DE materials, improve the integration of DEA devices, and overcome the difficulties associated with continuous, large-scale production.

4. Conclusion and prospect

This article reviews the recent research progress on polymers with self-healing functions and systematically explains their underlying mechanisms. By utilizing dynamically reversible covalent and non-covalent interactions, these polymers achieve self-healing capabilities, which effectively extends their service lifespan. Owing to these unique properties, such materials show great potential for development and application in the biomedical field.

With the ongoing research and development of self-healing materials, an increasing number of polymer formulations are meeting practical application standards. As a key development direction, self-repairing materials are poised to play a pivotal role in various biomedical fields, including drug delivery, medical coatings, implantable materials, and flexible bioelectronics. By integrating the unique advantages of self-healing materials with the specific demands of biomedicine, this work explores their potential applications and future prospects, thereby providing a roadmap for future research in this interdisciplinary area.

Furthermore, the self-healing mechanisms were discussed, categorizing them into two primary types: covalent and non-covalent. A schematic diagram illustrating the self-healing performance was also presented. Overall, research on self-healing polymers has introduced new paradigms to materials science. Future research in the field is expected to focus on developing “active” materials capable of intelligent environmental responsiveness, multifunctional integration, and biomimetic repair mechanisms. These efforts will significantly promote their widespread application. However, major challenges must be addressed, particularly the need for in-depth exploration of the mechanisms and applications of intrinsic self-healing materials.

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