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Research on the Adhesion Mechanism and Application of Typical Bioadhesives

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Abstract. Bioadhesives, inspired by natural adhesion strategies, rely on key molecular interactions such as hydrogen bonding, electrostatic forces, and covalent crosslinking to achieve strong and durable attachment. Incorporating green chemistry principles, such as using biodegradable polymers and natural polymer-based systems, provides pathways to reduce environmental impact without compromising adhesive performance. The study uses mussel-inspired adhesives and chitosan-based bioadhesives as examples to exemplify how natural polymer chemistry can be leveraged to create effective and biocompatible adhesion systems. In addition to discussing the underlying adhesion mechanisms, this paper highlights practical applications in tissue repair, wound healing, and wearable electronics, demonstrating how molecular design translates into real-world functionality. Traditional wound closure methods can cause secondary tissue damage and complications. Research on bioadhesives offers a promising alternative by providing rapid, strong adhesion, maintaining a favorable microenvironment, and enabling functional modifications such as antimicrobial. These features accelerate tissue repair, reduce trauma, and expand potential applications in regenerative medicine.

Keywords: Bioadhesive, Green Chemistry, Mussel-inspired bioadhesive, Chitosan- based adhesive

1. Introduction

Bioadhesives are polymeric materials that can adhere to biological tissues, serving as an alternative to conventional methods like sutures. While traditional methods are not only time-consuming but also may lead to inflammation and leave some stitch marks on people's skin, but bioadhesives greatly alleviate these issues. As a result, bioadhesives have attracted increasing attention.

Conventional bioadhesives are usually based on some natural materials such as gelatin, natural resin, or even unmodified chitosan. These natural materials often have some problems, such as low biocompatibility, unstable performance, and poor environmental friendliness. In contrast, the development of green bioadhesives has addressed many of these limitations. The green bioadhesives are more friendly to the human body, because the materials for them are less likely to cause allergy such as polypeptide and modified chitosan. Furthermore, new materials for bioadhesives could also improve the adhesive performance. For example, the introduction of dynamic covalent bonds between specific functional groups significantly enhances self-healing properties, as these bonds can

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break and reform under certain conditions. Moreover, dynamic covalent bonds enable controlled degradation, allowing the materials to safely break down in the body and be absorbed at an appropriate rate. Although no specific research has evaluated green bioadhesives against all twelve green chemistry principles defined by Anastas and Warner, the material design, including the use of renewable biopolymers, avoidance of hazardous solvents, and production of biodegradable final products, which aligns closely with key green chemistry principles such as less hazardous synthesis, safer solvents, energy efficiency and design for degradation [1].

This paper will employ two representative systems, mussel-inspired adhesives and chitosan-based adhesives, as examples, combined with green modified synthetic bioadhesives, to systematically explore the application value of bioadhesives.

2. Literature review

Zhang et al. demonstrated that the formation of DHI significantly enhances adhesive performance, offering critical mechanistic insights into mussel-inspired chemistry [2]. However, their results were derived from controlled polymerization systems rather than complex physiological environments, and questions remain regarding the long-term stability and practical translatability of DHI-based adhesion systems.

Rana et al. developed a soft tissue adhesive based on aldehyde sodium alginate and chitosan cross-linked via Schiff base chemistry, achieving rapid gelation (7–10 s), biodegradability (~79% mass loss by day 9), and favorable in vivo adhesion in a murine skin incision model [3]. However, their evaluation was restricted to small animal experiments, and the adhesive's mechanical durability under dynamic physiological conditions was not comprehensively assessed. He et al. developed a conductive self-healing nanocomposite hydrogel based on chitosan and polyvinylpyrrolidone for photothermal therapy of infected full-thickness skin wounds [4]. The hydrogel exhibited good electrical conductivity, self-healing ability, and photothermal performance, promoting wound healing in vitro and in vivo. However, these studies ignore assessing the hydrogel's long-term in vivo stability and performance.

3. Mussel-inspired bioadhesives

3.1. Mussel foot proteins: the core role of 3,4-dihydroxyphenylalanine

3.1.1. The central role of DOPA

The primary structure of mussel foot proteins (Mfps) contains a high proportion of 3,4-dihydroxyphenylalanine (DOPA), a catecholic amino acid that plays a key role in adhesion. The catecholic side chain of DOPA enables diverse chemical interactions and crosslinking reactions, thereby allowing Mfps to adhere strongly to a wide range of surface substrates.

3.1.2. Basic binding forces: non-covalent interactions and coordination

The catechol group participates in diverse chemical interactions, enabling adhesion to both organic and inorganic surfaces via reversible non-covalent bonds or irreversible covalent linkages. The two hydroxyl groups of catechol enable the formation of strong hydrogen bonds, while its aromatic ring can participate in π–π stacking with other aromatic systems and engage in cation–π interactions with positively charged species—one of the strongest non-covalent interactions in aqueous environments [5].

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3.1.3. Key mechanism of strong adhesion: oxidation and crosslinking

Apart from non-covalent cation–π interactions, the dihydroxy structure of catechol enables it to act as a bidentate ligand, effectively chelating a variety of transition and early transition metal ions including Cu^{2+}, Zn^{2+}, Mn^{2+}, Fe^{3+}, V^{3+}, Ti^{3+}, and Ti^{4+} [6]. These interactions are typically highly stable due to the formation of five-membered chelate rings.

Moreover, catechol is known to form coordination complexes with a broader spectrum of metal ions through diverse binding geometries. Besides its ability to coordinate with metal ions, catechol can be oxidized to form semiquinone and quinone by losing one electron and two electrons respectively. Quinone can undergo tautomerization to yield quinone methide, which subsequently rearranges into α,β-dehydro-Dopa, ultimately leading to the dimerization and polymerization of Dopa residues [5].

3.1.4. Environmental limitation: influence of acidic conditions on catechol-based adhesive performance

Finally, quinone can also undergo covalent bonding with various nucleophilic functional groups, such as amino groups present in biological substrates, thereby forming strong interfacial linkages. Furthermore, at acidic pH, nucleophilic functional groups become protonated, which diminishes their capacity for covalent crosslinking and leads to weaker interfacial bonding between catechol-based adhesives and soft tissue surfaces [5]. Such reduced crosslinking efficiency under acidic conditions may limit the use of catechol adhesives on mildly acidic tissues.

3.2. Polydopamine in mussel-inspired adhesives and its adhesion mechanisms

3.2.1. Synthesis and structural features of Polydopamine

Polydopamine (PDA) is synthesized via the oxidation of catechol amines bearing a free primary amine group (e.g., dopamine), leading to intramolecular cyclization and subsequent polymerization through a pathway resembling natural melanin formation. PDA contains a large number of indolic moieties, particularly 5,6-dihydroxyindole (DHI), which arises from intramolecular cyclization.

3.2.2. The role of DHI in strengthening PDA adhesion

The presence of these DHI units enables PDA to form much stronger interactions than catechol groups, supported by molecular-level simulations and previous coating deposition studies. Furthermore, Zhang et al. explored the role of 5,6-dihydroxyindole (DHI) in PDA adhesion [6]. They found that PDA adhesion is largely insensitive to Li^+ and Na^+ but significantly reduced by K^+, consistent with DHI-enabled cation-π interactions being the dominant adhesion mechanism.

4. Chitosan-based adhesives

4.1. Structural characteristics of chitosan and derived functional properties

4.1.1. Chitosan: extraction, structure, and chemical reactivity

Chitosan is a natural polysaccharide derived from the deacetylation of chitin, which is a structural component found in the exoskeletons of crustaceans and the cell walls of certain fungi. Due to the

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abundance and low cost of chitin, shrimp and crab shells are commonly used as the primary raw materials for its extraction. From around 7 tonnes of crab shells, approximately 1 tonne of chitin can be obtained, while the same amount of shrimp shells can yield about 2 tonnes of chitin [7]. Chitin is composed of β-(1→4)-linked 2-amino-2-deoxy-D-glucopyranose and N-acetyl-D-glucosamine unit [8]. Upon deacetylation, it is converted into chitosan, a copolymer consisting of N-acetyl-D-glucosamine. This deacetylation process introduces amino groups along the macromolecular chain, significantly enhancing the reactivity of chitosan. These amino groups enable a variety of chemical modifications, including quaternization, alkylation, and metal chelation [8].

4.1.2. pH-dependent solubility and functional properties of chitosan

The protonation state of the amino groups is highly dependent on pH. At pH values below 6, the amino groups are protonated, with a positive charge to the polymer and rendering chitosan a water-soluble cationic polysaccharide. Conversely, at pH values above 6, deprotonation occurs, causing the macromolecules to lose their charge and become insoluble in water. As a result, chitosan is typically dissolved in dilute acid solutions. Beyond its structural versatility, chitosan exhibits biodegradability, biocompatibility, and antimicrobial properties—making it suitable for applications aligned with green chemistry principles.

4.2. Biodegradable, biocompatibility, and antimicrobial properties

4.2.1. Biodegradability and clinical relevance of chitosan

Degradability is an essential property for tissue adhesives, as permanent adhesion can lead to infection, postoperative secondary injury, and thrombosis [9]. Degradable adhesives offer a promising approach to address these issues. For clinical applications, it is crucial that the degradation products are biocompatible and can be safely eliminated from the body via the respiratory or excretory systems. As an example, chitosan can undergo gelation triggered by heat or pH changes, and is enzymatically degraded in the body by lysozyme and chitosanase [10].

4.2.2. Biocompatibility of chitosan-based adhesives

When bioadhesives contact the human body, both the host response and the material response must remain within a safe range. Moreover, the host immune system may exhibit latent or innate reactions toward the biomaterial, which could impair its intended function. Therefore, it is essential to evaluate and, where necessary, enhance the biocompatibility of the materials used. For chitosan-based dressings, ensuring a thorough biological safety evaluation is critical for successful clinical application. The degree of deacetylation directly influences the biocompatibility of chitosan. Yao et al. reported that increasing the degree of deacetylation enhances chitosan's biocompatibility [11]. Additionally, biocompatibility is not directly related to positive surface charges, but was related to the preferential adsorption of chitosan to fibronectin, which was proved by Qing et al. by measuring the surface potential of chitosan-based membranes under different pH conditions to investigate their interaction with a recombinant fibronectin polypeptide [12]. Li et al. Also demonstrated that in situ cross-linking of oxidized hydroxyethyl starch with modified carboxymethyl chitosan via a Schiff-base reaction eliminates the need for potentially toxic initiators and produces a hydrogel with improved biocompatibility [13]. At present, the mechanisms underlying the biocompatibility of chitosan have not been fully elucidated, indicating that certain challenges remain in this field. It should also be noted that modifications of chitosan with other materials may influence its

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biocompatibility in complex and sometimes unpredictable ways, and the outcomes can vary depending on the specific modification strategy and application context.

4.2.3. Antimicrobial properties of chitosan-based adhesives

For effective wound healing, bioadhesives should possess antimicrobial properties to prevent infection. The bacteriostatic effect of chitosan is influenced by factors such as solvent pH, degree of deacetylation, and the presence of metal ions. The incorporation of metal ions can diminish the inherent antimicrobial activity of chitosan. However, it may enhance the overall antibacterial performance of chitosan-based dressings through metal-chelating synergy [14]. Moreover, a higher degree of deacetylation in chitosan has been associated with reduced antibacterial efficacy [8]. Chitosan exhibits stronger antibacterial activity in solvents with a pH around six compared to other pH conditions [5]. In conclusion, the antimicrobial behavior of chitosan results from a balance between its chemical structure, environmental conditions, and possible modifications, which should be carefully tailored for biomedical applications.

4.3. Adhesion mechanisms of chitosan-based adhesives

4.3.1. Non-covalent adhesion mechanisms of chitosan-based adhesive

Chitosan-based adhesives exhibit their remarkable adhesion properties through a complex interplay of multiple molecular interactions. At the fundamental level, hydrogen bonding plays a crucial role, as the abundant amino and hydroxyl groups on the chitosan chains readily form strong hydrogen bonds with complementary functional groups on biological substrates. These interactions contribute significantly to the initial attachment and stabilization of the adhesive interface. Electrostatic interactions, driven by the protonation of amino groups under physiological conditions, facilitate strong ionic attractions with negatively charged surfaces, enhancing adhesion strength. Hydrophobic interactions can also influence adhesion by promoting localized aggregation and phase separation that improve contact intimacy.

4.3.2. Covalent crosslinking and reinforcement effects in chitosan-based adhesives

Beyond these non-covalent intermolecular forces, covalent linkages such as imine (azomethine) groups formed via Schiff-base reactions (a type of dynamic covalent bond) further reinforce the adhesive interface, providing enhanced stability and durability. For example, Rana et al. developed a soft tissue-adhesive hydrogel composed of chitosan and aldehyde sodium alginate for promoting skin wound healing in mouse models [3]. In this system, adhesion is achieved through Schiff base reactions between the hydrogel and amine groups present in skin tissue. Similarly, He et al. developed a self-healing, conductive hydrogel-based bioadhesive designed for skin wound dressing, incorporating benzaldehyde-terminated Pluronic, N-carboxyethyl chitosan, and carbon nanotubes [4]. The exceptional adhesive performance of this hydrogel primarily arises from Schiff base linkages formed between the aldehyde groups of benzaldehyde-terminated Pluronic and the amine groups in porcine skin. This covalent bonding is further reinforced by hydrogen bonding interactions between the tissue and the hydrogel matrix. The combined effect of these intermolecular forces and covalent linkages creates a versatile adhesion platform, capable of adapting to diverse environments and substrates. A thorough understanding of these diverse adhesion mechanisms is crucial for the effective development of chitosan-based adhesives, enabling the design of formulations with precise control over adhesion strength.

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5. Applications of bioadhesives

Building upon these diverse adhesion mechanisms and material designs, bioadhesives have found utility across a wide spectrum of biomedical and technological fields. Their tunable mechanical properties, intrinsic biocompatibility, and potential for biodegradability enable tailored solutions for applications ranging from clinical therapeutics such as wound closure, tissue sealing and drug delivery, to emerging technologies like flexible electronics and biosensors. The integration of sustainable synthesis strategies and degradable polymer systems further enhances their alignment with green chemistry principles, reducing environmental impact while expanding their applicability. As research continues to bridge molecular-level understanding with scalable manufacturing, bioadhesives are poised to play an increasingly pivotal role in addressing both medical challenges and the demand for environmentally responsible materials in advanced engineering domains.

5.1. Wound healing

Traditional wound dressings such as gauze, cotton pads, and synthetic fibers often suffer from limitations, including poor air permeability and a limited ability to promote wound healing. In the field of wound healing, mussel-inspired and chitosan-based bioadhesives have shown remarkable potential. Hydrogels based on mussel adhesive proteins or polydopamine, for example, can achieve firm adhesion on moist wound surfaces while providing a favorable microenvironment for tissue repair. These bioadhesive hydrogels are also biodegradable, allowing them to degrade naturally after healing without the need for secondary removal.

In contrast, hydrogel-based dressings can maintain a moist wound environment while offering good biocompatibility and inherent adhesion, making them a promising new generation of wound care materials. In cases of trauma, rapid hemostasis is essential, as uncontrolled bleeding can lead to shock or even death from excessive blood loss. This challenge is particularly critical during surgery and after severe injuries. Bioadhesive hydrogels that can rapidly polymerize at the wound site help minimize blood loss while facilitating the accumulation of clotting factors and platelets necessary for hemostasis [14].

Porous hydrogels are especially effective in this role: their dense pore network can absorb serum water, locally concentrating clotting factors, red blood cells, and platelets, thereby accelerating clot formation [14]. Stable adhesion to the wound surface is also a prerequisite for effective healing. To achieve this, researchers have drawn inspiration from adhesive organisms in nature, such as mussels, whose adhesive proteins provide strong bonding even under wet conditions. Additionally, the use of biocompatible hydrogels further enhances adhesion and tissue compatibility. For instance, glycoproteins, which are crucial components of the extracellular matrix, are known to promote tissue repair. Inspired by this, hydrogels with chemical compositions mimicking natural glycoproteins have been developed, exhibiting excellent biocompatibility and effectively promoting wound healing [8].

5.2. Drug delivery

Chitosan’s inherent bioadhesive properties make it an effective platform for drug delivery, particularly in the context of wound healing. Its strong adhesion to wound surfaces enables localized and sustained release of therapeutic agents such as antimicrobial compounds, growth factors, and anti-inflammatory drugs--that act directly at the injury site, thereby improving treatment efficacy. Conjugation of chitosan with polyethylene glycol enhances its solubility in neutral aqueous media,

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broadening its applicability as a tissue sealant for wound repair. Furthermore, incorporating recombinant human epidermal growth factor into a glycidyl methacrylate modified chitooligosaccharide hydrogel has been shown to slow its release rate, thereby extending its therapeutic effect in promoting skin wound healing in animal models [15].

5.3. Tissue repair

Mussel-inspired and chitosan-based bioadhesives have been applied for repairing cartilage, bone, and skin. Mussel-inspired adhesives adhere firmly to wet tissues, providing a favorable microenvironment for healing, while chitosan-based adhesives combine biodegradability, biocompatibility, and antimicrobial properties, making them suitable for skin grafts and surgical applications. Formulating these bioadhesives as hydrogels further enhances their conformability to irregular tissue surfaces and maintains strong adhesion under moist conditions.

Furthermore, bioadhesives hold particular promise in tissue repair due to their ability to form rapid, strong, and conformal bonds with wet, irregular biological surfaces. Unlike traditional sutures or staples, they minimize mechanical trauma and reduce operation time. Recent advances in bioinspired and biodegradable designs have further enhanced their biocompatibility, enabling them to not only physically close wounds but also actively participate in the repair process through localized drug delivery or cell recruitment. These multifunctional capabilities position bioadhesives as a critical component in the next generation of regenerative medicine strategies.

Hydrogels are prevalent in cartilage tissue repair. Catecholamines, especially polydopamine, are known for their strong and long-lasting surface adhesion. Plant-derived phenolic compounds, such as caffeic acid, often offer advantages over dopamine. For instance, a nanoclay-organic hydrogel bone sealant with exceptional adhesive performance has been developed by grafting phytochemicals onto chitosan and combining them with nanosilicates. The catechol groups in the phytochemicals enable robust bonding, while the composite structure promotes bone regeneration [16]. Although hydrogel adhesives hold great promise for tissue repair, challenges remain—particularly in achieving strong adhesion to wet human tissues. To address this, researchers have designed various bioadhesive hydrogels specifically for wet-tissue bonding. These hydrogels are often functionalized with adhesive moieties and engineered with optimized network structures to improve performance in moist environments. For example, a catechol-modified hyaluronic acid hydrogel has been shown to adhere effectively to a wide range of surfaces, including wet tissue, and can be applied in minimally invasive cell therapies [17].

5.4. Wearable sensors based on chitosan bioadhesives

Chitosan can serve as a sensitive material for wearable sensors, offering not only excellent adhesion but also the ability to respond to environmental changes, enabling real-time monitoring of physiological parameters in the human body. While wearable sensors have become essential tools for personalized healthcare, clinical diagnostics, and continuous physical monitoring. In contrast, wearable sensors have become essential tools for personalized healthcare, clinical diagnostics, and continuous physical monitoring, traditional strain sensors made from metal and semiconductor films often suffer from brittleness, rigidity, limited stretchability, and high modulus. These drawbacks hinder their ability to conform and adhere seamlessly to human tissue surfaces. To overcome these limitations, biopolymer-based hydrogels have been developed as flexible and sustainable components for wearable sensors, offering inherent adhesion and self-healing properties. Porous hydrogels are especially effective in this role: their dense pore network can absorb serum water [14].

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Despite these advances, many sensors still rely on external tapes or bandages for skin attachment. In this context, bioadhesives provide a promising solution by enabling strong, durable adhesion directly on the skin, improving sensor stability and user comfort.

6. Conclusion

In summary, bioadhesives represent a versatile and rapidly advancing class of materials with applications spanning wound healing, drug delivery, tissue regeneration, and wearable electronics. Their diverse adhesion mechanisms, ranging from covalent and non-covalent interactions to biomimetic functionalization, have enabled the development of materials with tunable mechanical strength, biocompatibility, and, increasingly, biodegradability. While this paper focused on two conventional bioadhesives, it discussed their adhesion mechanisms and the processes that exploit their unique properties. Additionally, it highlighted the application areas of these materials.

Despite providing a detailed overview of two representative bioadhesives, this study has certain limitations. For instance, the performance of these adhesives under extreme environmental conditions has not been thoroughly discussed. Additionally, dynamic adhesion processes, such as time-dependent bonding or reversible interactions, were not explored. Addressing these aspects in future studies could provide a more comprehensive understanding of bioadhesive behavior and expand their potential applications.

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