Adhesive Hydrogels for Oral Ulcer Therapy: A Survey

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Abstract

This survey paper investigates the role of adhesive hydrogels in oral ulcer therapy, highlighting their potential to enhance therapeutic efficacy and patient comfort through improved bioadhesive technology. Adhesive hydrogels, reinforced with polyethylene ultra-thin films, provide strong adhesion to wet mucosal surfaces and enable sustained release of therapeutic agents, offering a significant advancement in the management of oral ulcers. The integration of bioadhesive biomaterials into healthcare applications is recognized as a crucial development, promising to improve patient outcomes by enhancing drug delivery and reducing systemic side effects. This paper also explores the synthesis and structural characteristics of reinforced networks, emphasizing their mechanical strength and adhesion capabilities. Furthermore, the survey addresses the challenges in developing adhesive hydrogels, including issues related to sterilization, biodegradability, and clinical efficacy, and suggests future research directions to optimize these materials for clinical use. The findings underscore the potential of bioadhesives to revolutionize oral therapy and surgical practices, providing safer and less invasive options for wound management. Additionally, the survey highlights the significance of oral lesions as potential early indicators of COVID-19, warranting further investigation into bioadhesive applications in viral-induced conditions. Overall, adhesive hydrogels represent a promising frontier in oral ulcer therapy, with ongoing research poised to advance their application in modern healthcare.

1 Introduction

1.1 Relevance of Adhesive Hydrogels in Oral Ulcer Therapy

Adhesive hydrogels have become essential in treating oral ulcers, offering significant therapeutic advantages due to their unique adherence properties to wet and dynamic tissue surfaces, which is crucial in the challenging mucosal environment [1]. Their capacity to maintain contact with ulcerated tissue ensures targeted delivery of therapeutic agents, thereby enhancing healing.

The high prevalence of oral ulcers, stemming from infections, immune responses, and physical trauma, necessitates innovative treatment modalities [2]. Traditional treatments often lack efficacy, underscoring the need for advanced solutions like adhesive hydrogels that provide sustained drug release and protect ulcerated areas [3]. In cases of oral mucositis, commonly experienced by cancer patients undergoing chemotherapy or radiotherapy, these hydrogels can significantly improve quality of life by alleviating ulcer severity and promoting faster recovery [4].

The integration of polymer-based bioadhesive biomaterials has transformed healthcare applications, offering new strategies for enhancing patient outcomes [5]. These materials provide mechanical support and protection while facilitating sustained therapeutic release, addressing the limitations of conventional drug formulations [6]. Therefore, adhesive hydrogels represent a promising frontier in oral ulcer therapy, merging bioadhesion and advanced drug delivery systems to improve treatment efficacy and patient comfort.

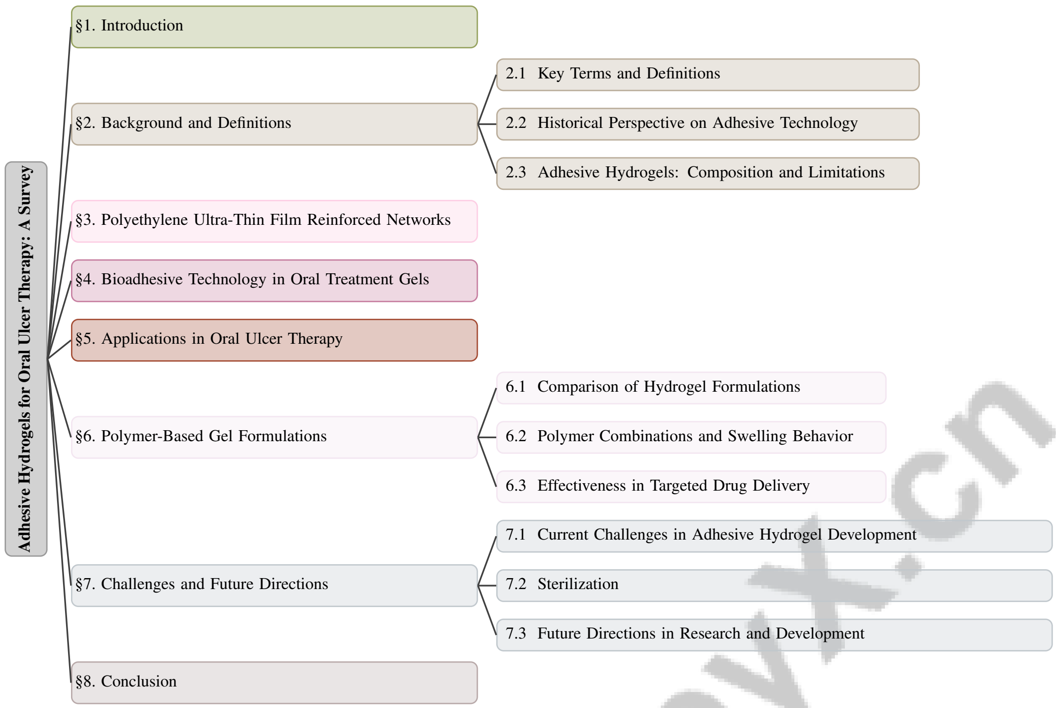

Figure 1: chapter structure

1.2 Importance of Bioadhesive Technology in Medical Applications

Bioadhesive technology has become a pivotal element in advancing medical applications, significantly enhancing healthcare delivery and patient outcomes [5]. By leveraging the natural adhesive properties of specific polymers, bioadhesives form strong bonds with biological tissues, facilitating various clinical applications. These materials are categorized based on adhesion mechanisms, such as electrostatic bonding and chain entanglement, and their applications range from wound healing to drug delivery and leak sealants [7].

The incorporation of bioadhesives into medical treatments signifies a paradigm shift, particularly in drug delivery systems. By ensuring controlled release of therapeutic agents directly at the site of action, bioadhesives enhance therapeutic efficacy while minimizing side effects and improving patient compliance [6]. This is particularly relevant for localized treatments where conventional systemic therapies may be inadequate.

Furthermore, Duan et al. aim to bridge the literature gap by summarizing bioadhesives' clinical applications. While existing research often focuses on the mechanisms of bioadhesion, there is an increasing demand for exploration of their practical applications across various medical fields [8]. Thus, bioadhesive technology not only addresses current medical challenges but also opens new avenues for research and development, promising to revolutionize patient care and treatment methodologies.

1.3 Structure of the Survey

This survey is meticulously structured to provide a comprehensive exploration of adhesive hydrogels in oral ulcer therapy. The paper begins with an **Introduction** that discusses the relevance of adhesive hydrogels and the significance of bioadhesive technology in medical applications. This underscores the essential role of advanced technologies, such as enzymatic gels and composite hydrogels, in improving therapeutic outcomes for oral ulcer patients by promoting tissue repair, enhancing angiogenesis, and facilitating the healing process [9, 10, 11].

Following the introduction, the **Background and Definitions** section delves into core concepts, providing detailed explanations of adhesive hydrogels, polyethylene ultra-thin film reinforced net-

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works, and bioadhesive technology, along with definitions of key terms essential for understanding subsequent discussions.

The survey then progresses to **Polyethylene Ultra-Thin Film Reinforced Networks**, focusing on the role of these films in reinforcing polymer-based gels. This section elucidates the synthesis and structural characteristics of the reinforced networks, comparing the mechanical properties and adhesion of reinforced versus non-reinforced gels.

In **Bioadhesive Technology in Oral Treatment Gels**, the principles of bioadhesive technology are explored, emphasizing its application in oral treatment gels. The section discusses adhesion mechanisms to the oral mucosa and the benefits of sustained therapeutic agent release, while also addressing recent innovations and challenges in the field.

The **Applications in Oral Ulcer Therapy** section examines the practical use of adhesive hydrogels in treating oral ulcers, showcasing therapeutic benefits and presenting case studies of successful treatments. This is followed by an analysis of various **Polymer-Based Gel Formulations**, comparing their properties and effectiveness for clinical applications.

Finally, the survey addresses **Challenges and Future Directions**, identifying current obstacles in developing adhesive hydrogels and suggesting potential research directions. The paper concludes by synthesizing primary findings, highlighting the significant role of advanced technologies, such as bioadhesive biomaterials and innovative hydrogel formulations, in enhancing patient outcomes in oral ulcer therapy. These technologies facilitate effective wound healing by promoting tissue regeneration and angiogenesis, addressing limitations of traditional treatments, ultimately leading to improved recovery times and patient satisfaction [8, 11, 5, 10, 9].The following sections are organized as shown in Figure 1.

2 Background and Definitions

2.1 Key Terms and Definitions

Familiarity with key terms is essential for understanding adhesive hydrogels and oral treatment gels. Bioadhesion refers to the capacity of materials to bond with biological tissues, a fundamental aspect in the design of polymer-based bioadhesive biomaterials for medical applications [5]. These biomaterials are engineered to adhere strongly to tissue surfaces, providing mechanical support and enabling localized drug delivery.

Hydrogels, characterized by hydrophilic polymer networks, can absorb significant volumes of water or biological fluids, making them biocompatible and suitable for drug delivery [6]. Their ability to facilitate controlled, site-specific drug release enhances therapeutic efficacy and reduces systemic side effects [6].

Polymer synthesis involves chemical processes that create hydrogels, allowing customization to achieve desired mechanical and adhesive properties, crucial for enduring the dynamic oral environment and maintaining prolonged contact with ulcerated tissues [6].

Bioadhesives, derived from synthetic and biological materials, are notable for their clinical applications, offering noninvasive alternatives to traditional wound closure methods by providing effective sealing solutions that enhance healing and minimize tissue trauma [7, 1, 8, 5, 10]. Their strong adhesion to living tissues and hemostatic capabilities make them suitable for various medical applications, including tissue adhesives and drug delivery systems.

The potential for SARS-CoV-2 to infect oral keratinocytes and fibroblasts highlights the need for effective treatment strategies incorporating bioadhesive technology [12]. Understanding these terms and their interrelations is critical for advancing adhesive hydrogels in oral treatment.

2.2 Historical Perspective on Adhesive Technology

Adhesive technology has significantly evolved in dental and medical fields, enhancing clinical outcomes. The development of dental adhesives, as detailed by van Meerbeek et al., illustrates a shift from mechanical retention methods to chemical bonding techniques, improving adhesion to enamel and dentin [11]. This evolution, driven by an improved understanding of adhesion mechanisms, has led to the classification of adhesives based on their functional properties and application methods.

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In medicine, bioadhesives are categorized for wound closure, leak sealing, and immobilization [8], demonstrating their versatility in clinical needs from surgical interventions to drug delivery. The integration of bioadhesive technology into medical practice represents a paradigm shift, offering innovative solutions for enhancing patient care.

The COVID-19 pandemic has underscored adhesive technology's role in oral health, emphasizing the need for adhesive-based treatments for oral lesions linked to viral infections [12]. This has spurred interest in bioadhesive materials that create protective barriers and facilitate localized drug delivery for managing such lesions.

Advancements in adhesive technology reflect a commitment to enhancing material properties and application methods. The progression of dental adhesives from Buonocore's acid-etch technique to self-adhering restoratives highlights the complexities of bonding to dentin and the importance of bond stability. Innovations in polymer-based bioadhesives have broadened their healthcare applications, including tissue adhesion and wound closure, integrating insights from various scientific fields to redefine healthcare management and improve therapeutic efficacy [8, 1, 11, 5].

2.3 Adhesive Hydrogels: Composition and Limitations

Adhesive hydrogels, composed of hydrophilic polymer networks, are designed to deliver therapeutic benefits by adapting to the dynamic oral environment and maintaining contact with mucosal surfaces [6]. Bioadhesive components enhance their adhesion to wet tissues, allowing sustained therapeutic agent release at injury sites [3].

A key challenge is the reliance on non-degradable materials that may persist in the body or require removal, posing barriers to clinical application [1]. Ideal hydrogels should degrade safely post-therapy. Current treatments often lack adequate pain relief or effective targeting of mucosal lesions, leading to poor compliance and higher costs [4].

Formulating hydrogels involves addressing bioavailability and solubility issues, critical for therapeutic efficacy [6]. Controlled release mechanisms ensure optimal drug delivery concentrations over time, enhancing healing and minimizing systemic exposure.

The fragility and handling difficulties of materials like human amniotic membrane constrain clinical utility in healing mucosal defects [9]. Hybrid polymer films, incorporating materials like hypromellose and gellan gum, exemplify innovative approaches to overcoming these limitations by facilitating effective therapeutic agent delivery in the oral cavity [3].

The slow healing of traumatic oral ulcers with existing treatments necessitates exploring new formulations for rapid healing and reduced inflammation [2]. Adjuvant treatments like Gelenzyme® highlight the promise of advanced hydrogel compositions in oral surgery [10]. Challenges remain regarding substrate complexity and bond degradation, critical for reliable, long-term outcomes [11]. Addressing these limitations is essential for the continued development of adhesive hydrogels in oral therapy.

In recent years, the development of advanced materials has garnered significant attention in the field of biomedical applications. Among these materials, polyethylene ultra-thin films have emerged as a promising option due to their unique properties. Figure 2 illustrates the hierarchical structure of polyethylene ultra-thin film reinforced networks, detailing their synthesis, mechanical enhancements, and comparative advantages over non-reinforced gels. This figure not only highlights the intricate design of these networks but also underscores their potential for improved performance in various biomedical contexts, thereby enhancing our understanding of their applicability and effectiveness.

3 Polyethylene Ultra-Thin Film Reinforced Networks

3.1 Synthesis and Structure of Reinforced Networks

The development of polyethylene ultra-thin film reinforced networks aims to enhance the mechanical and adhesive properties of polymer-based gels, addressing the limitations of traditional hydrogels in dynamic environments such as the oral cavity [6]. These networks begin with a hydrophilic polymer matrix that absorbs water, allowing the gel to swell and adapt to target tissues. By incorporating ultra-thin polyethylene films, the networks achieve improved performance in biomedical applications

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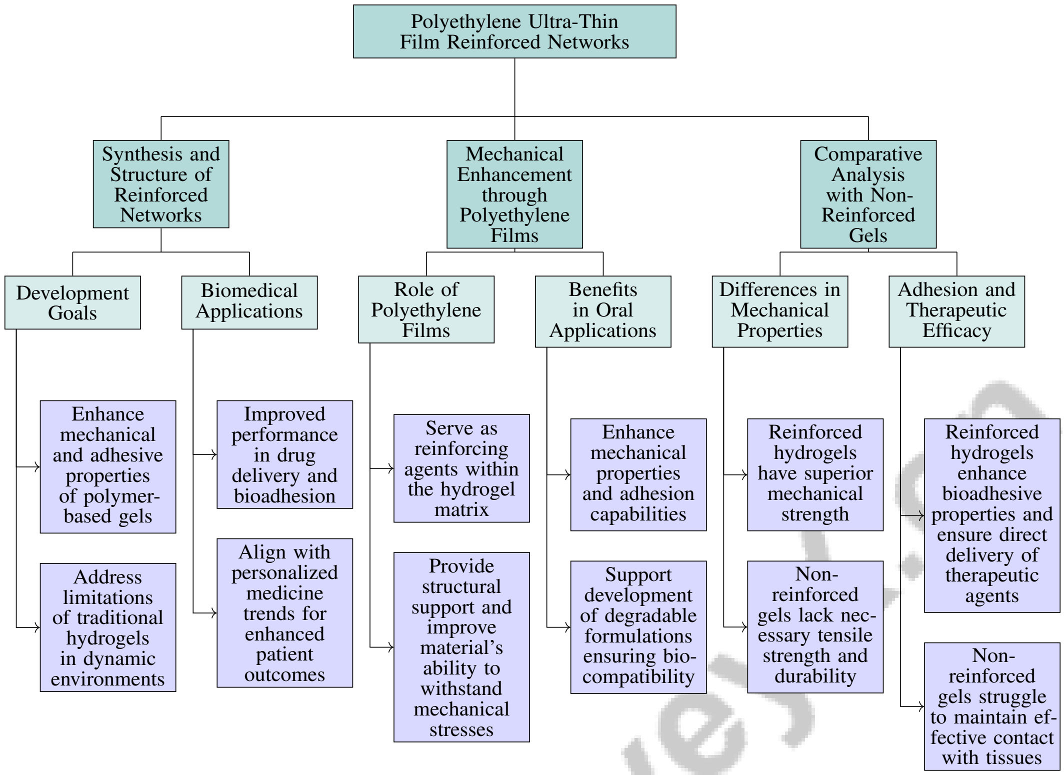

Figure 2: This figure illustrates the hierarchical structure of polyethylene ultra-thin film reinforced networks, detailing their synthesis, mechanical enhancements, and comparative advantages over non-reinforced gels in biomedical applications.

such as drug delivery and bioadhesion, aligning with personalized medicine trends for enhanced patient outcomes [6, 11, 5].

Engineered for high tensile strength and flexibility, polyethylene films withstand mechanical stresses encountered in the oral environment. Their integration with the polymer matrix is facilitated by compatible polymer blends and optimized processing conditions, which enhance interfacial bonding. This multidisciplinary approach, combining insights from engineering, chemistry, and medicine, supports the creation of advanced bioadhesive biomaterials for medical applications. Recent innovations have yielded bioadhesives capable of bonding effectively to challenging substrates like dentin, maintaining biocompatibility and mechanical integrity, and improving patient satisfaction in healthcare settings [1, 11, 5].

These reinforced networks exhibit enhanced mechanical properties, including increased elasticity and durability, crucial for maintaining prolonged contact with mucosal surfaces. Polyethylene films also improve the bioadhesive properties of the gel, facilitating effective adhesion to wet tissues and sustained therapeutic release [6]. This advancement in hydrogel technology enhances mechanical strength and biocompatibility while enabling controlled drug release in response to physiological triggers, crucial for optimizing drug delivery systems in personalized medicine. The integration of these reinforced networks into adhesive hydrogels holds potential for revolutionizing the management of oral ulcers and mucosal lesions, offering more effective and comfortable treatment options [1, 6, 11, 5, 9].

3.2 Mechanical Enhancement through Polyethylene Films

The incorporation of polyethylene ultra-thin films into polymer-based hydrogels significantly enhances their mechanical strength and durability, addressing the limitations of traditional formulations. These films serve as reinforcing agents within the hydrogel matrix, providing structural support and improving the material's ability to withstand mechanical stresses in the oral cavity [6]. Their ultra-thin

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nature allows seamless integration into the hydrogel structure without compromising flexibility or tissue conformability.

Characterized by high tensile strength and elasticity, polyethylene films maintain hydrogel integrity under dynamic oral conditions. They function as scaffolds, evenly distributing mechanical loads and preventing deformation or rupture during application, which is particularly beneficial for oral ulcer therapy where adherence to irregular mucosal surfaces is critical [6].

The interfacial bonding between polyethylene films and the polymer matrix enhances the mechanical stability of the gel. This bonding is facilitated through compatible polymer blends and optimized processing, ensuring effective integration within the hydrogel network. Consequently, reinforced hydrogels exhibit enhanced durability, maintaining adhesive properties and therapeutic efficacy over extended periods [6].

The integration of polyethylene ultra-thin films into adhesive hydrogels represents a notable advancement in oral treatment technologies, enhancing mechanical properties and adhesion capabilities essential for effective bonding to challenging substrates like dentin. This innovation supports the development of degradable formulations that retain adhesive strength while ensuring biocompatibility and patient safety during oral applications [1, 11, 5]. By improving strength and durability, polyethylene films enable the creation of more effective therapeutic formulations, ultimately enhancing patient outcomes in managing oral ulcers and mucosal lesions.

3.3 Comparative Analysis with Non-Reinforced Gels

Comparative analysis between polyethylene ultra-thin film reinforced hydrogels and non-reinforced formulations reveals significant differences in mechanical properties, adhesion capabilities, and therapeutic efficacy. Reinforced hydrogels demonstrate superior mechanical strength due to polyethylene film integration, providing structural support that enhances the gel's ability to withstand the dynamic oral environment [6]. In contrast, non-reinforced gels often lack the necessary tensile strength and durability, leading to potential deformation or rupture during use.

Adhesion to biological tissues further distinguishes reinforced from non-reinforced gels. The inclusion of polyethylene films enhances bioadhesive properties, facilitating stronger adhesion to wet mucosal surfaces [6]. This improved adhesion ensures direct delivery of therapeutic agents to injury sites, enhancing treatment outcomes. Non-reinforced gels may struggle to maintain effective contact with tissues, particularly in the presence of saliva and other oral fluids, compromising therapeutic potential.

Therapeutic efficacy is further augmented in reinforced hydrogels through sustained release of encapsulated agents. The structural integrity provided by polyethylene films allows for controlled and prolonged drug release, optimizing therapeutic concentrations at target sites [6]. Non-reinforced gels may lack this level of control, potentially leading to suboptimal dosing and reduced treatment effectiveness.

The integration of polyethylene ultra-thin films into hydrogel formulations represents a significant advancement over non-reinforced counterparts, offering improved mechanical properties, adhesion, and therapeutic efficacy. Innovations in reinforced hydrogels, particularly those incorporating decellularized human amniotic particles (dHAP) and methacrylated gelatin (GelMA), present a promising approach for managing oral ulcers and mucosal lesions. These composite materials not only enhance mechanical strength and adhesion but also promote rapid angiogenesis, facilitating effective tissue regeneration. Clinical applications have demonstrated their ability to overcome traditional treatment limitations, providing patients with reliable and effective therapeutic solutions for oral mucosal repair [9, 10].

4 Bioadhesive Technology in Oral Treatment Gels

4.1 Adhesion Mechanisms to Oral Mucosa

Bioadhesive gels adhere to oral mucosa through physicochemical interactions and the biological characteristics of mucosal tissues. Adhesion is achieved via hydrogen bonding, van der Waals forces, and mechanical interlocking, ensuring prolonged attachment and effective localization of therapeutic agents [8]. Thermosensitive polymers like poloxamers transition from liquid to semi-solid at body temperature, enhancing adherence to buccal mucosa [4]. The gel's viscoelasticity aids in conforming

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to the mucosa's contours. Bioactive components, such as antioxidants and anti-inflammatory agents, promote tissue repair and regeneration, improving adhesion and therapeutic efficacy while ensuring biocompatibility [2]. Materials like GelMA and dHAP enhance mechanical properties and bioactivity, supporting angiogenesis and tissue repair with low cytotoxicity [9]. These interactions are crucial for oral ulcer therapy, where gels must deliver therapeutic agents directly to injury sites, enhancing healing and reducing complications [12].

4.2 Sustained Therapeutic Agent Release

Bioadhesive gels provide controlled and prolonged release of therapeutic agents, crucial for managing oral ulcers. These gels utilize polymers that swell in saliva, modulating drug release rates [3]. The interaction between the polymer matrix and the biological environment influences drug release, allowing the gel to respond to physiological triggers like pH and temperature, enhancing targeted delivery [1, 6, 5]. Moisture absorption from the oral cavity triggers phase transitions that improve adhesion and controlled drug diffusion, optimizing therapeutic outcomes. Tailored polymer combinations within the gel matrix allow for customized drug release profiles, enhancing efficacy in targeted delivery systems. Advances in formulations, including nano hydrogels, support multi-drug delivery and personalized medicine [6, 5]. Adjusting polymer ratios fine-tunes swelling capacity and drug delivery rates, crucial for precise control in oral ulcer therapy. These gels enhance drug delivery systems, minimizing systemic toxicity while ensuring prolonged contact with mucosal surfaces [4, 6, 3, 5].

4.3 Innovations and Challenges in Bioadhesive Technology

Recent advancements in bioadhesive technology have expanded their medical applications, especially in oral therapy. Innovations include bioadhesives with tunable degradation profiles for on-demand removal, reducing long-term foreign body reactions [1]. These features are vital in oral applications, where materials must maintain efficacy in dynamic environments. Research focuses on developing non-invasive, biocompatible bioadhesives that promote faster healing than traditional methods [7], enhancing patient comfort and outcomes in oral ulcer management. However, challenges remain in exploring new materials to broaden bioadhesive applications and improve understanding of adhesion mechanisms [5]. The oral environment's complexity, including saliva flow, mucosal turnover, and microbiota composition, affects bioadhesive efficacy in clinical applications like wound closure and tissue sealing. Continued research is needed to refine formulations and application techniques, ensuring optimal performance across diverse medical contexts [8, 5].

5 Applications in Oral Ulcer Therapy

5.1 Therapeutic Benefits of Adhesive Hydrogels

Adhesive hydrogels offer significant therapeutic advantages in oral ulcer treatment by ensuring direct delivery of therapeutic agents to injury sites through strong mucosal adhesion. The integration of degradable tough adhesive materials enhances mechanical toughness and biocompatibility, making these formulations well-suited for the dynamic oral environment [1]. Their capacity for controlled release maintains optimal drug concentrations at injury sites over extended periods. For instance, mucoadhesive-thermosensitive gels with metronidazole have proven effective in oral mucositis treatment, enhancing therapeutic outcomes while minimizing systemic side effects and improving patient compliance [4]. Hydrogels like Gelenzyme® have shown reduced healing times and improved patient outcomes compared to traditional treatments [10]. Preclinical models using ANC Gel demonstrate significant advancements in healing traumatic oral ulcers [2], highlighting adhesive hydrogels' potential to accelerate recovery and provide enhanced therapeutic benefits. The improved mucoadhesion and controlled drug release are particularly beneficial for managing oral inflammatory conditions, where effective localization and sustained action are critical [3]. Thus, adhesive hydrogels represent a promising frontier in oral ulcer therapy, offering more effective and comfortable treatment options.

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5.2 Bioadhesive Biomaterials in Oral Healthcare

Bioadhesive biomaterials are revolutionizing oral healthcare by enhancing treatment modalities and patient outcomes through their natural adhesive properties, which enable targeted and sustained delivery of therapeutic agents. These materials have redefined traditional management strategies, opening avenues for improved patient outcomes [5]. Their versatility is evident across various oral health conditions, such as oral ulcers, periodontal diseases, and mucosal lesions, where they ensure controlled release of therapeutic agents at the site of action, enhancing efficacy while minimizing side effects and improving patient compliance [6]. Recent advancements in bioadhesive hydrogels, including those with polyethylene ultra-thin films, have improved mechanical properties and adhesion capabilities, facilitating effective treatment of oral ulcers and other mucosal conditions [6]. These reinforced hydrogels provide structural support and durability, maintaining prolonged contact with mucosal surfaces for sustained therapeutic action. Bioadhesive gels in oral mucositis management have shown significant improvements in patient outcomes, providing better pain relief and faster healing compared to traditional therapies [4]. Incorporating bioactive components such as antioxidants and anti-inflammatory agents enhances their therapeutic potential, promoting tissue repair and regeneration [2]. Bioadhesive biomaterials are emerging as transformative solutions in oral healthcare, addressing challenges like wound closure, tissue adhesion, and drug delivery systems. Their development is supported by interdisciplinary collaboration among engineers, chemists, biologists, and medical professionals, enhancing treatment effectiveness and aligning with the emphasis on value-based healthcare. This advancement paves the way for new research and development opportunities aimed at improving patient outcomes and satisfaction [8, 7, 5].

5.3 Case Studies of Effective Treatments

The efficacy of adhesive hydrogels in oral ulcer therapy is exemplified through various case studies. A notable instance involves Gelenzyme® in treating a traumatic lingual lesion, where rapid healing effects were observed, highlighting its potential as an effective therapeutic agent for oral mucosal injuries [10]. This bioadhesive hydrogel facilitated faster recovery and improved patient comfort by alleviating pain and inflammation associated with the lesion. This case study underscores the substantial benefits of adhesive hydrogels in treating oral lesions, particularly their ability to deliver therapeutic agents directly to injury sites in a sustained manner. Composed of degradable materials, these hydrogels exhibit excellent adhesion to moist tissues, promote rapid tissue repair, and facilitate controlled release of bioactive substances, thereby enhancing healing outcomes and minimizing complications [1, 8, 11, 10, 9]. Their enhanced adhesion properties ensure prolonged contact with mucosal surfaces, optimizing drug delivery and therapeutic efficacy. Incorporating bioactive components within the hydrogel matrix supports tissue repair and regeneration, contributing to treatment success. Encouraging outcomes from this case study align with emerging trends in adhesive hydrogels, which have shown notable advancements in treating oral ulcers and other mucosal disorders. Recent developments in degradable tough adhesive hydrogels, composed of approximately 90% water and engineered with covalently and ionically crosslinked components, exhibit superior mechanical properties and biocompatibility, facilitating effective adhesion to dynamic tissue surfaces. These hydrogels support rapid tissue repair and healing processes, aligning with research emphasizing their potential in clinical applications like wound closure and tissue regeneration, thus enhancing overall patient outcomes [1, 8, 11, 10, 9]. By providing targeted and sustained therapeutic action, adhesive hydrogels represent a valuable tool in oral healthcare, offering more effective and comfortable treatment options.

6 Polymer-Based Gel Formulations

6.1 Comparison of Hydrogel Formulations

Advancements in polymer-based gel formulations for oral ulcer treatment focus on comparing hydrogels with varied compositions, mechanical properties, and clinical efficacies. Traditional hydrogels, often single-polymer networks, provide basic support and drug delivery but lack the necessary mechanical robustness for the oral environment. In contrast, advanced formulations using multi-polymer networks or reinforcing agents like polyethylene ultra-thin films offer enhanced mechanical strength and durability, essential for prolonged mucosal contact [6]. Hydrogels incorporating hypromellose, gelatin, and gellan gum exhibit improved mucoadhesion and controlled drug release, enhancing

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their effectiveness for oral applications [3]. The synergistic effects of multiple polymers improve swelling behavior and bioadhesion, facilitating sustained therapeutic release at injury sites. Bioactive components such as chlorhexidine further enhance therapeutic potential through antimicrobial activity and tissue healing.

Comparative studies show that reinforced hydrogels outperform non-reinforced ones in clinical efficacy, offering superior pain relief and faster healing for oral ulcers [2]. Incorporating degradable tough adhesive materials improves mechanical toughness and biocompatibility, addressing traditional hydrogel limitations and providing a more reliable therapeutic option [1]. Recent advancements highlight the importance of material selection and design in optimizing clinical outcomes, especially in drug delivery applications where tailored properties—such as biocompatibility, controlled release mechanisms, and responsiveness to triggers (e.g., pH, temperature, enzymes)—are crucial for maximizing efficacy and minimizing toxicity. The development of injectable and nano hydrogels supports personalized medicine strategies, enabling targeted drug delivery and enhanced treatment effectiveness while addressing cost-effective healthcare needs [6, 5]. By exploiting the unique properties of multi-polymer networks and reinforcing agents, these formulations offer promising solutions for managing oral ulcers and other mucosal conditions, ultimately improving patient comfort and treatment efficacy.

6.2 Polymer Combinations and Swelling Behavior

The swelling behavior of polymer-based hydrogels is crucial for their performance in oral treatment applications, influenced by specific polymer combinations. Variations in these combinations affect the gel's ability to absorb water and biological fluids, impacting mechanical properties, adhesion, and drug release profiles [6]. Selecting appropriate polymers and their ratios within the hydrogel matrix is essential for optimizing these characteristics, ensuring effective conformance and contact within the oral cavity's dynamic environment.

Hydrogels with interpenetrating polymer networks (IPNs) exhibit enhanced swelling due to synergistic interactions, facilitating increased water absorption vital for structural integrity and adhesive properties in wet conditions [6]. For example, incorporating polyethylene glycol (PEG) and polyvinyl alcohol (PVA) improves swelling capacity, enhancing mucoadhesion and prolonging drug release [6]. Crosslinking density within the polymer matrix also influences swelling behavior. Higher crosslinking density reduces swelling but enhances mechanical strength, suitable for robust adhesion and prolonged mucosal contact [6]. Conversely, lower crosslinking density increases swelling capacity and flexibility, advantageous for high fluid absorption and rapid drug release.

Incorporating bioactive polymers like chitosan and alginate imparts antimicrobial activity and enhanced biocompatibility while influencing swelling behavior [6]. These polymers can form ionic crosslinks with other gel components, modulating swelling properties and contributing to overall hydrogel performance in oral applications.

6.3 Effectiveness in Targeted Drug Delivery

Polymer-based hydrogels excel in targeted drug delivery due to their capacity for localized and controlled release of therapeutic agents, enhancing treatment efficacy and reducing systemic side effects. These hydrogels adhere to specific sites within the oral cavity, ensuring direct drug delivery to ulcerated tissues, where therapeutic effects are maximized [6]. Their bioadhesive properties promote strong, prolonged adhesion to mucosal surfaces, facilitated by polymers interacting with biological tissues through hydrogen bonding, van der Waals forces, and mechanical interlocking [8]. Sustained contact with the target site is crucial for optimal drug release, allowing a continuous supply of therapeutic agents at effective concentrations.

Swelling behavior significantly modulates drug release rates. As hydrogels absorb moisture, they undergo phase transitions that facilitate drug diffusion, allowing precise control over drug delivery timing and dosage, optimizing therapeutic outcomes while minimizing adverse effects [6]. Customizing polymer compositions within the hydrogel matrix enables fine-tuning of release profiles to meet specific clinical needs. By adjusting the ratios of hydrophilic and hydrophobic components and crosslinking density, hydrogels can be designed with tailored release kinetics that align with pharmacokinetic requirements [6]. This control is beneficial for treating oral ulcers, where the dynamic environment necessitates precise drug delivery strategies.

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The effectiveness of polymer-based hydrogels in targeted drug delivery is highlighted by their ability to provide localized, sustained, and controlled release of therapeutic agents. Innovative mucoadhesive-thermosensitive gel formulations for oral mucositis treatment with metronidazole represent a significant advancement in oral treatment modalities. These formulations gel rapidly at buccal mucosa temperatures and demonstrate controlled drug release over an eight-hour period, enhancing drug delivery precision and efficacy, ultimately leading to improved patient outcomes and satisfaction in healthcare management [4, 5].

7 Challenges and Future Directions

7.1 Current Challenges in Adhesive Hydrogel Development

The development of adhesive hydrogels for oral therapy is hindered by several challenges that impact their clinical adoption. Key issues include the complexity of hydrogel formulations, which demand precise polymer synthesis to attain desired clinical properties [6]. Variability in these formulations can lead to inconsistent gelling properties, affecting their therapeutic reliability [4]. Furthermore, the cytotoxicity of certain materials necessitates rigorous safety assessments to ensure biocompatibility [6].

Understanding adhesive interactions at the molecular level is critical, especially within the dynamic oral environment. Achieving sufficient adhesion strength remains challenging due to the potential cytotoxicity of some bioadhesive components, which limits their clinical utility [7]. Stability issues of hydrogel films and variability in drug release profiles further complicate therapeutic effectiveness [3].

Challenges also include bonding to dentin and potential bond degradation over time, which are often overlooked in current research [11]. Addressing these requires innovations in adhesive technology to ensure durable and reliable bonding solutions. Economic constraints demand cost-effective production methods that maintain performance and safety standards [5]. The paucity of extensive clinical trials complicates validation of hydrogel effectiveness, as seen with limited studies on products like Gelenzyme® [10].

A comprehensive strategy involving advancements in material science, investigations into bioadhesion mechanisms, and thorough clinical evaluations is essential. These efforts are crucial to developing safe, effective, and reliable adhesive hydrogels for medical applications, such as tissue adhesion, wound closure, and drug delivery, ultimately enhancing healthcare outcomes [1, 8, 11, 5].

7.2 Sterilization, Biodegradability, and Transition to Clinical Use

Transitioning adhesive hydrogels from research to clinical use requires addressing sterilization, biodegradability, and clinical efficacy. Ensuring sterility is paramount, as microbial contamination poses significant risks. Common sterilization methods, such as gamma irradiation and ethylene oxide treatment, can alter the polymer matrix's properties, affecting performance [9].

Biodegradability is critical for hydrogels to safely degrade into non-toxic byproducts post-therapy. The GelMA–dHAP method shows promising biocompatibility and bioactivity, yet its biodegradation pathways need further exploration [9]. Rigorous testing is necessary to confirm hydrogels' efficacy and safety in clinical settings, involving clinical trials to evaluate therapeutic benefits and potential adverse effects across diverse patient groups. These trials focus on biocompatibility, controlled drug release, and personalized treatment capabilities, enhancing disease management and minimizing systemic toxicity [1, 8, 6, 5, 10]. Overcoming these challenges and demonstrating clear advantages over existing treatments are essential for successful clinical integration of hydrogels. Continuous research and development are vital to refine these materials and establish standardized protocols for their sterilization, biodegradability, and clinical application.

7.3 Future Directions in Research and Development

Future advancements in adhesive hydrogel technology for oral therapy will be driven by research aimed at enhancing functionality and expanding applications. Optimizing crosslinker types and molecular weights is crucial to improve degradation rates and mechanical properties, ensuring

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hydrogels are effective and biodegradable in clinical settings [1]. This optimization is vital for developing hydrogels that degrade safely post-therapy, reducing the need for removal procedures.

There is growing interest in innovative bioadhesive formulations tailored for specific medical applications [8]. This includes developing multifunctional bioadhesives that integrate with technologies like bioelectronics and smart drug delivery systems, broadening their utility beyond traditional therapies [7]. These advancements could facilitate personalized medicine, where hydrogels are customized to meet individual patient needs [6].

The potential presence of SARS-CoV-2 in oral lesions highlights the need for research into the immunological responses of affected patients, informing targeted treatments for viral-induced oral conditions [12]. Understanding these responses is crucial for designing hydrogels that effectively address viral infections and related complications.

Optimizing the GelMA–dHAP scaffold for clinical use is a promising research avenue, focusing on improving sterilization processes and assessing long-term performance in human applications [9]. This research could yield hydrogels with enhanced bioactivity and biocompatibility suitable for various clinical scenarios.

Exploring self-adhesive restorative materials and enhancing chemical bonding potentials in adhesives are emerging trends that promise to improve hydrogel formulations' performance [11]. By focusing on these areas, future research can contribute to creating more effective and reliable adhesive hydrogels, ultimately enhancing patient outcomes in oral therapy and beyond.

8 Conclusion

The survey underscores the pivotal role of adhesive hydrogels in revolutionizing oral ulcer therapy, demonstrating their ability to substantially improve therapeutic outcomes and patient experiences. The integration of bioadhesive biomaterials into medical practice signifies a major advancement, offering new avenues for enhancing patient satisfaction and health results. These materials are notable for their robust adhesion to moist mucosal surfaces and their capacity for prolonged therapeutic agent release, establishing them as a promising advancement in the management of oral ulcers.

Furthermore, the survey highlights the innovative potential of bioadhesives in surgical settings, providing safer and less invasive options for wound care and device stabilization. This innovation is especially crucial in oral therapy, where effective adhesion and precise drug delivery are essential for successful treatment results.

Additionally, the findings suggest that oral lesions may act as early indicators of COVID-19, appearing before respiratory symptoms, which calls for further exploration. This revelation highlights the necessity for ongoing research into the use of bioadhesive technology in addressing viral-induced oral conditions.

Adhesive hydrogels thus hold considerable potential for advancing the treatment of oral ulcers and other mucosal disorders, offering a novel strategy for enhancing patient care and therapeutic efficacy. As research and development in this field continue to evolve, these materials are poised to become integral to contemporary healthcare, reshaping patient treatment and care practices.

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References

[1] Benjamin R Freedman, Oktay Uzun, Nadja M Maldonado Luna, Anna Rock, Charles Clifford, Emily Stoler, Gabrielle Östlund-Sholars, Christopher Johnson, and David J Mooney. Degradable and removable tough adhesive hydrogels. *Advanced Materials*, 33(17):2008553, 2021.

[2] Liza Meutia Sari, Zaki Mubarak, and Dina Keumala Sari. Evaluation of clinical, histology, tnf-α, and collagen expressions on oral ulcer in rats after treatment with areca nut and chrysanthemum oral gel. *F1000Research*, 10:623, 2023.

[3] Monika Wojtyłko, Anna Froelich, and Barbara Jadach. Hypromellose-, gelatin-and gellan gum-based gel films with chlorhexidine for potential application in oral inflammatory diseases. *Gels*, 10(4):265, 2024.

[4] Melike Ongun, Emre Tunçel, Esra Kodan, Fatma Nur Tuğcu Demiröz, and Fahriye Figen Tırnaksız. Development and characterization of mucoadhesive-thermosensitive buccal gel containing metronidazole for the treatment of oral mucositis. *Journal of Faculty of Pharmacy of Ankara University*, 44(3):517–539, 2020.

[5] Nibedita Saha, Nabanita Saha, Tomas Sáha, Ebru Toksoy Öner, Urška Vrabič Brodnjak, Heinz Redl, Janek von Byern, and Petr Sáha. Polymer based bioadhesive biomaterials for medical application—a perspective of redefining healthcare system management. *Polymers*, 12(12):3015, 2020.

[6] Nguyen Hoc Thang, Truong Bach Chien, and Dang Xuan Cuong. Polymer-based hydrogels applied in drug delivery: An overview. *Gels*, 9(7):523, 2023.

[7] K Uma. Bioadhesives for clinical applications–a mini review. *Materials Advances*, 4(9):2062–2069, 2023.

[8] Wanglin Duan, Xiangbing Bian, and Yazhong Bu. Applications of bioadhesives: a mini review. *Frontiers in Bioengineering and Biotechnology*, 9:716035, 2021.

[9] Qiang Zhang, Chunyu Qian, Wanshu Xiao, Huajun Zhu, Jun Guo, Zili Ge, and Wenguo Cui. Development of a visible light, cross-linked gelma hydrogel containing decellularized human amniotic particles as a soft tissue replacement for oral mucosa repair. *RSC advances*, 9(32):18344–18352, 2019.

[10] Martina Salvatorina Murgia, M Meuli, and Casu C MannuC. New enzymatic gel as adjuvant treatment for wound healing processes in oral surgery, a mini-review and a case report. *Sch J Med Case Rep*, 1:55–60, 2021.

[11] Bart Van Meerbeek, Kumiko Yoshihara, Kirsten Van Landuyt, Yasuhiro Yoshida, and Marleen Peumans. From buonocore's pioneering acid-etch technique to self-adhering restoratives. a status perspective of rapidly advancing dental adhesive technology. *Journal of Adhesive Dentistry*, 22(1):7–34, 2020.

[12] Thais Bianca Brandao, Luiz Alcino Gueiros, Thayanara Silva Melo, Ana Carolina Prado-Ribeiro, Ana Cristina Froelich Alo Nesrallah, Gladys Villas Boas Prado, Alan Roger Santos-Silva, and Cesar Augusto Migliorati. Oral lesions in patients with sars-cov-2 infection: could the oral cavity be a target organ? *Oral surgery, oral medicine, oral pathology and oral radiology*, 131(2):e45–e51, 2021.

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