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Is Hydrogel an Appropriate Bioadhesive Material for Sutureless Oral Wound Closure?

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ABSTRACT

Background and Aims: An effective surgical adhesive must possess strength, biodegradability, flexibility, non-toxicity, and the ability to accommodate to tissue movement. However, existing adhesives in the market lack some of these crucial properties. Both synthetic cyanoacrylate and natural fibrin glue have been explored for sutureless oral surgery, but they come with specific limitations. This perspective review aims to explore the novel potential of hydrogels as bioadhesives for wound closure in the oral cavity.

Methods: This review thoroughly examines the properties, applications, and limitations of hydrogels as bioadhesive materials for wound closure within the human body.

Results: We first provide a comprehensive description of materials used for sutureless oral surgery. Next, drawing on our expertise in the field of oral surgery, we propose novel potential applications for hydrogels in oral wound closure. We showed that Hydrogels represent promising bioadhesives in medical field and are undergoing continuous enhancement to expand their applications in wound closure.

Conclusion: Although hydrogels have been utilized in various dental conditions, their potential for closing wounds in the oral cavity remains unexplored.

1 | Introduction

Instead of conventional suturing for oral surgical and traumatic wounds, a minimally invasive technology utilizing biodegradable adhesive materials can be employed. These materials can retain flap edges in their original position, protect the wound from oral microbes during the healing process, and enhance healing outcomes. This approach reduces operation time and eliminates the need for suture removal, thereby overcoming several disadvantages associated with conventional sutures. These include secondary trauma to tissue caused by needle insertion as well as risk of inflammation, infection, and delay healing. Moreover, it eliminates the risk of needle puncture accidents [1].

Bioadhesion, the phenomenon in which substances, whether natural or synthetic, adhere to biological surfaces. According to their applications, they are grouped into three categories: (A) wound closure, (B) sealing leakage including blood leakage, and (C) immobilization such as wound dressing and drug delivery materials [2]. The requirements of bioadhesives for wound closure differ from those for sealing leakage and so on. Bioadhesive materials for wound closure in the oral cavity should be biocompatible, bioadhesive in wet environment, biodegradable, mechanically strong, easy to apply, and capable of incorporating drugs, cells, and biological factors into the tissue [3]. Till now, only two bioadhesives (cyanoacrylate and fibrin glue) have been evaluated in oral wound closure as an alternative to sutures.

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In recent years, hydrogels have gained great interest in the biomedical field due to their outstanding biocompatibility, biodegradability, and high-water content. Hydrogels are three-dimensional networks of crosslinked polymers that mimic the natural extracellular matrix (ECM) [4]. Our article provides a comprehensive overview of the current challenges in surgical bioadhesives, focusing on their application in surgical or traumatic wound closure, and proposes hydrogels as a promising solution.

2 | Bioadhesives Utilized in Oral Wound Closure

2.1 | Traditional Adhesive: Cyanoacrylate

Cyanoacrylate, a synthetic adhesive, has been evaluated for wound closure in dentistry. Approved by the U.S. Food and Drug Administration in August 1998, cyanoacrylate adhesives polymerize rapidly in the presence of nucleophiles such as anions (e.g., hydroxide, alcoholate and iodide) or weak bases (e.g. alcohol and amine), releasing a slight exothermic effect [5–7].

Cyanoacrylates are present in various forms depending on their chain length and complexity; these include methyl, ethyl, isoamyl, *n*-butyl, isohexyl, and octyl cyanoacrylates [8]. However, it has been observed that the harmful effect decrease as the alkyl chain length increases. Consequently, cyanoacrylate (CA) monomers with short alkoxy carbonyl side chains, such as methyl 2-cyanoacrylate and ethyl 2-cyanoacrylate, are no longer used. In contrast, *n*-butyl-2-cyanoacrylate (NBCA) and octyl-2-cyanoacrylate (OCA) have gained widespread utilization in clinical practice [9]. There are comprehensive literature reviews on the applications of cyanoacrylates in dentistry [1, 10]. A systematic review and meta-analysis of six studies involving a total of 250 patients has been published, examining the utilization of cyanoacrylate-based adhesive and comparing it to silk sutures in third molar surgery. Three studies are split-mouth design controlled clinical trials, and three are randomized controlled trials (RCTs). They concluded that the utilization of cyanoacrylate adhesive may offer benefits in terms of post-operative pain and swelling reduction [11]. Another systematic review and meta-analysis, involving eight studies with a total of 440 patients, evaluated the use of cyanoacrylate in third molar surgery and concluded that it promoted better results in pain reduction on the first postoperative day compared to the use of conventional suture [12]. Yet, cyanoacrylate is not used in clinical settings due to its reduced tensile strength (it should not be used in high-tension areas) [13]. Moreover, cyanoacrylate has disadvantages, including slight heat release, dry surface work, and degradation to produce harmful substances during polymerization [9]. They undergo degradation in the presence of water to produce formaldehyde and cyanoacetate as end products [6].

2.2 | Fibrin Glue

Fibrin glue (TISSEEL) is a naturally derived adhesive that functions similarly to natural glue, that adhering tissues

together. It is an absorbable blood-derived adhesive, mimicking the final stages of the coagulation cascade, forming a robust clot that seals wound edges. After 2 weeks of application, it physiologically degrades into granulation tissue [14]. A recent systematic review on the utilization of fibrin glue in periodontal surgery included four RCT [15] with a total of 101 patients. This systematic review indicates a low level of evidence for the use of fibrin sealant as an alternative to sutures in periodontal practice. In another study, authors compared fibrin sealant with suturing using 3–0 black silk in third molar extraction surgery through conventional Ward's incision, concluding that fibrin sealant is an effective means of mechanical and biological closure of intraoral wounds [16]. The main limitations of this material are allergic anaphylactic reactions and its inability to address massive bleeding [17]. Additionally, its insufficient adhesion or cohesion strength limits its application, and making it useful only as an adjunct to traditional wound closure [18].

3 | Hydrogel: A Promising Alternative?

Hydrogels are three-dimensional polymers of natural or synthetic origin with high water absorbing capacity, resulting in their gel-like form. Synthesized hydrogels exhibit significant properties such as biocompatibility, mechanical strength, biodegradability, swellability, and stimuli sensitivity [19]. They find a wide range of applications in tissue engineering and regenerative medicine [20]. Natural hydrogels composed of natural polymers such as polysaccharides (chitosan, cellulose, alginate), collagen-based hydrogels [21] and others. Synthetic hydrogels comprise of synthetic polymers such as polycaprolactone (PCL), poly (ethylene glycol) (PEG), poly (vinyl alcohol) (PVA), and poly (lactic acid) (PLA), or mixtures are also used [19].

Hydrogels can be presented in a solid form or as a liquid that forms gels through various mechanisms, among them cooling or heating. Moreover, they can be manufactured as sheets, matrices, films, and microspheres depending on the method of polymerization [22]. The hydrogel state is achieved through chemical crosslinking via covalent bonds, physical crosslinking through molecular entanglement, hydrogen bonding, hydrophobic interactions, and complexation involving polyelectrolyte interactions [19].

They can be classified depending on the origin, method of preparation, ionic charges, and physical structure [23]. A detailed discussion of their classifications is illustrated in Table 1.

3.1 | Applications of Hydrogels in Dentistry

- Dental caries and pulp tissue engineering

Hydrogel scaffolds incorporated with stem cells and growth factors have shown promise in pulp-tissue engineering for regenerating the dentin-pulp complex [28]. Gelatin methacryloyl (GelMA) has been extensively studied for tissue engineering applications, thanks to its beneficial properties, including hydrophilicity, integrin-binding motifs, and matrix metalloproteinase degradation [29]. Ribeiro et al.

TABLE 1 | Overview of hydrogel classifications.

Hydrogels classification				
Based on origin [24]	Based on method of preparation [25]	Based on cross-linking (structure) [24, 26]	Based on their reaction with the environment [22, 24]	Based on their degradability [27]
Natural hydrogels	Copolymeric (two or more different types of monomers)	chemical hydrogels (cross-linked by covalent bonds, which are stable and nonreversible)	pH-responsive	Biodegradable Hydrogels
Synthetic hydrogels	Homopolymeric (a single type of monomer)	Physical hydrogels (held together by noncovalent interactions which can be reversible)	Temperature-Responsive	Nonbiodegradable hydrogels
Hybrid hydrogels	Interpenetrating network (IPN) (two or more polymer networks)	Physical-chemical hydrogels (hybrid)	Magnetic and electric field responsive	Degradable under Specific environmental conditions
			Pressure responsive	
			Photo-responsive	
			Antigen responsive	
				Based on physical properties [25]
				Smart hydrogels
				Based on ionic charge [24]
				Non-ionic or neutral hydrogels (do not have a net electrical charge)
				Cationic (contain positively charged groups)
				Anionic (contain negatively charged groups)

developed GelMA hydrogel loaded with chlorhexidine (CHX) for intraoral delivery of CHX, offering an effective approach to treat dental infections. Moreover, GelMA can serve as a scaffold for delivering therapeutic agents into the root canal, allowing gradual release after application [30]. Numerous studies have demonstrated that hydrogels with appropriate ingredients can enhance the antibacterial activity and promote remineralization of the tooth, indicating strong potential for dental caries treatment [31].

- Periodontal diseases

In dentistry, hydrogels have been explored for drug delivery in periodontal diseases [32], and as scaffolds in periodontal tissue engineering [33]. They are used to deliver drugs to achieve antibacterial effects and to enhance the regeneration of both soft and hard tissues in periodontal pockets. Injectable and temperature-responsive hydrogels are more commonly used in various studies because their physico-chemical characteristics are better suited to the micro-environment of periodontal pocket. Chang et al. integrated naringin into a pH-sensitive hydrogel with thermogelling properties. This hydrogel composed of carboxymethyl hexanoyl chitosan and β -GP effectively reduced periodontal bone loss. Furthermore, a lower pH can influence drug delivery by altering the drug carrier structure [34].

- Peri implant diseases

Hydrogels have been used as coatings on implant surfaces to prevent peri-implantitis [35]. Hyaluronic acid hydrogel has been widely used to deliver and release bone morphogenetic protein (BMP-2) to enhance peri-implant osteogenesis [36].

- Oral cancer and oral mucosal diseases

Hydrogels have been utilized to deliver drugs to oral cancer and oral mucosal diseases [37]. In the application of hydrogel to deliver drugs to oral cancer drug delivery, hydrogels with adhesive or injectable properties are usually used to deliver chemotherapeutic drugs. For example, Shtenberg et al. combined alginate and liposomes in varying proportions to create a hybrid hydrogel with adhesive qualities, aiming to use this system for prolong release of the anticancer drug doxorubicin (DOX) over an extended period of time [38]. Similarly, Tan et al. integrated a metal-organic framework mixed with thermo-sensitive hydrogel PLGA-PEG-PLGA to develop an injectable system to load anticancer drugs (DOX and celecoxib) for localized of oral cancer treatment [39].

Hydrogels have been used in other oral conditions, such as alveolar Osteitis (dry Socket), osteonecrosis of the Jaw, and in repairing craniomaxillofacial defects [23, 40]. Some applications of hydrogels in dentistry are shown in Figure 1. However, their potential for wound closure in the oral cavity remains unexplored due to various obstacles.

3.2 | Challenges in Designing Hydrogels for Oral Wound Closure

Wound healing is a physiological process that begins directly after injury. The process of wound healing, progresses through

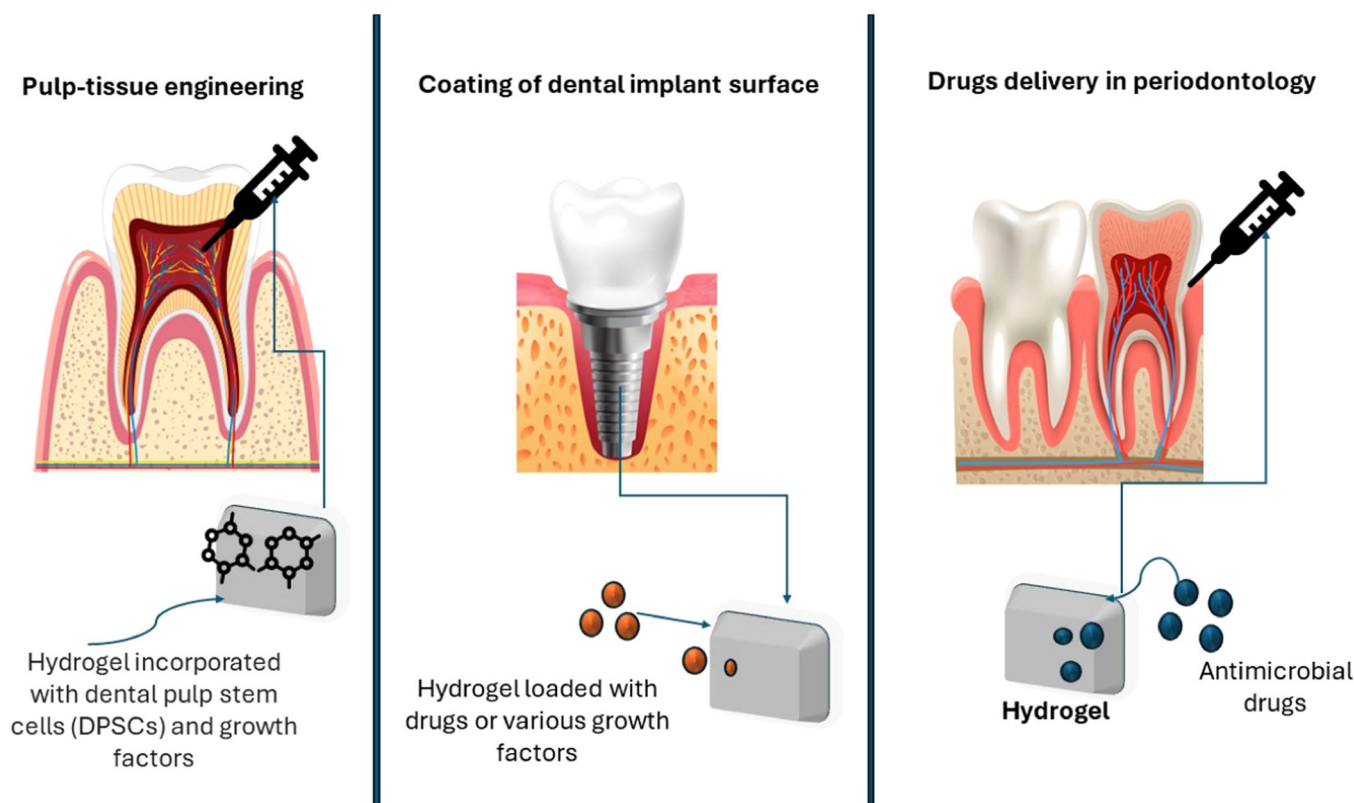


FIGURE 1 | Some hydrogel applications in dentistry; Pictures are under free licence and designed by Freepik then combined by power point. Some components drawn by the authors.

four overlapping stages including, hemostasis, inflammation, proliferation, and remodelling [41]. During the healing process, the bioadhesive should have the ability to form strong interfacial bonds, the ability to have strong cohesive properties, and the ability to remain biocompatible throughout the lifespan of the bioadhesive [42].

Requirements and challenges of using hydrogels as sutures in the oral cavity are outlined in the points below:

- **Adhesiveness:** Hydrogels should maintain strong interfacial bonds with wet oral tissue surfaces. Most bioadhesive utilize more than one type of interaction to maintain these bonds, including chemical crosslinking, diffusion, van der Waals forces, electrostatic interaction, physical interlocking, and micromechanical interactions [42]. However, hydrogel bioadhesives may lose their adhesion in wet environments like in the presence of blood or tissue fluids, hindering interactions between biological surfaces and hydrogels. To overcome this limitation, researchers have adopted the design of new generative hydrogels inspired by mussels, which adhere to wet substances via excreted proteins containing dihydroxyl phenylalanine [18, 43]. Different techniques are employed to boost hydrogel wet adhesion, including incorporating physical or chemical anchoring components into the hydrogel structure, removing interfacial fluids by utilizing hydrophobic residues and dry hydrophilic scaffolds, and deploying multiple adhesive mechanisms concurrently [3]. Researchers have created Mussel-inspired hydrogel (HA-catechol/4-arm-PEG-SH), which is made of a catechol-modified polymer using 4-arm-PEG-SH as a cross-linker, and it exhibits

excellent adhesion in wet environments [44]. Wu et al. utilized a resilient bioadhesive hydrogel for sutureless repair of dural tissues in rodent and porcine system in a wet environment and under supraphysiological pressure. This dural tough adhesive (DTA) consists of two polymer networks: a polyacrylamide network with permanent cross-linking, offering high elasticity, and an alginate polymer network with reversible crosslinking, capable of redistributing mechanical force energy in underlying tissues. Additionally, a highly adhesive layer of chitosan is incorporated into this tough gel. The authors confirmed its biocompatibility over a 4-week period in a rat craniotomy model [45].

- **Mechanical strength:** Hydrogel must have a good cohesive strength and remain stable after it applied to the tissue. While hydrogels are biocompatible and biodegradable polymers, they have limitations in mechanical strength, (stiffness around 10 kPa and toughness less than 10 J m^{-2}), which severely restrict their application in continuous load-bearing applications such as tissue engineering, where tissues usually exhibit high toughness (1000 J m^{-2}), high tensile strength (30 MPa), and high stiffness (1 MPa) [46]. Researchers are investigating various mechanisms for fabricating tough hydrogels, which can be categorized into three main groups: (1) homogenous tough hydrogels including tetra-polyethylene glycol (Tetra-PEG) hydrogels, click chemistry hydrogels, radiation crosslinked hydrogels, and slide ring hydrogels, (2) energy dissipating hydrogels such as interpenetrating polymer hydrogels (IPNs), double network hydrogels,

and fiber-reinforced hydrogels, and (3) tough hydrogels with multifunctional crosslinker [47]. A stronger hydrogel could be developed by increasing the level of cross-linking. However, as cross-linking increases, the hydrogel's ability to stretch decreases, resulting in a more brittle hydrogel. As a result, achieving an optimal level of cross-linking is crucial to produce a hydrogel that balances both strength and elasticity [48]. Researchers succeeded in creating mechanically tough hydrogels in the last 20 years [49, 50]. Biomimetic hydrogels, designed to mimic the properties, structure, or function of natural biological tissues, often utilize tannic acid (TA) and interpenetrating polymer network (IPN) hydrogels with both covalent and physical crosslinking. This combination provides enhanced cohesion and adhesion [51, 52]. A good hydrogel adhesive should exhibit strong adhesion and mechanical strength when placed on moving tissue, as in the case of oral tissue. This has been shown to be possible, as demonstrated by the utilization of adhesive hydrogel patch (The THMA/PEGDA/SA hydrogel), driven by hydrogen bonds instead of sutures, in a moving area such as joint wound closure [53].

- **Biocompatibility:** A bioadhesive should maintain biocompatibility, allowing for wound closure without causing local or systemic reactions in the host and without toxic effects. Many synthetic polymers are biocompatible and nontoxic to the human cells. In one study, the cytotoxicity of hydrogels such as poly (prop acrylic acid), poly glutamic acid, poly (methacrylic acid), poly (acrylic acid), and poly (methacrylic acid) hydrogels were tested on HeLa cells, and these hydrogels demonstrated 90% cell survival [54]. Most polysaccharides are biocompatible, while although many synthetic hydrogels are nontoxic, their cytocompatibility is inferior to that of natural polysaccharides [54].
- **Biodegradability:** Another aspect to consider is biodegradability; the hydrogel should have the ability to degrade over time as the tissue heals. Nevertheless, the adhesive needs to maintain its mechanical strength for a period of time (approximately 1 to 2 weeks) to prevent premature rupture of the repaired oral mucosa wound. Moreover, the degradation end products must be non-cytotoxic and should allow for rapid cellular ingrowth to regenerate functional tissue [42]. Hydrogels degrade through various mechanisms, depending on their chemical composition and environmental conditions (pH and temperature) of oral cavity. Hydrogels may undergo degradation and subsequent elimination from the body through bio-erosion and bio-absorption. Biodegradable polymers include hydrophilic, natural, and synthetic polymers [54].

The application of hydrogels in oral cavity wounds closure presents challenges due to the continuous movement of oral muscular tissue and the wet environment resulting from the presence of saliva. These challenges necessitate new scientific investigations and innovative engineering designs of hydrogels. Scientists should specifically design hydrogels for oral wound closure, emphasizing their wet adhesion properties. Moreover, other factors such as the specific wound pH environment and

tissue movement can affect the adhesion of such materials. Based on insight from the literature [3], advancements in hydrogel engineering enable their utilization in gastrointestinal wounds with a high pH environment and tissue movement, indicating promising clinical translation in sutureless oral wound closure [3].

4 | Perspectives and Conclusions

Our study proposes the potential of using hydrogels as an innovative approach for suturing oral wounds. This exploration is motivated by the unique properties of hydrogels, including moisture-retaining properties, flexibility, adaptability and biocompatibility. Stimuli-responsive hydrogels, also known as smart hydrogels, are hydrogels that experience significant changes in their swelling behaviour in response to in environmental stimuli such as temperature, pH, and so on [55]. The swelling properties of hydrogels can be beneficial in oral wound closure. Hydrogels can absorb and retain large amounts of water, which helps to maintain a moist environment at the wound site. This is crucial for promoting faster healing and reducing tissue dehydration. Moreover, as hydrogels swell, they can create a cushioning protecting layer over the wound which protects the wound from mechanical stress or irritation. Moreover, the swelling behaviour of hydrogels allows them to act as a carrier for medications. The adoption of hydrogels in oral wound management could transform clinical practices by offering a less invasive, and more comfortable alternative to traditional suturing.

Some hydrogels present promising potential for use as sutures in wet environments. For instance, mussel-inspired hydrogel such as catechol-modified hydrogels, which are based on polymers like polyethylene glycol (PEG) or polysaccharides modified with catechol groups, are noteworthy due to their excellent wet adhesion and flexibility properties. On the same instance, a chitosan-based hydrogel composed of chitosan, a known natural polysaccharide derived from chitin, which is recognized for its biocompatibility, biodegradability, and intrinsic antibacterial properties. Combining these materials with agents such as Catechol-functionalized chitosan and dibenzaldehyde-terminated polyethylene glycol (DB-PEG2000) has created a formulation that has shown potential for sutureless dural closure in preclinical studies [56]. With further advancements and modifications, this approach could be a promising candidate for use in the oral cavity. In a summary, this study provides initial insights into the application of hydrogels for oral suturing, it encourages further research and development in this emerging field. The probability of their adoption depends on various factors, including clinical efficacy, safety profile, cost-effectiveness, and surgeon preferences.

Author Contributions

Huda Moutaz Asmael Al-Azzawi: conceptualization, formal analysis, methodology, resources, Validation, visualization, writing—original draft, writing—review and editing. **Rita Paolini:** conceptualization, supervision, visualization, writing—original draft, writing—review and editing. **Antonio Celentano:** conceptualization, methodology, project administration, resources, supervision, validation, visualization,

writing—original draft, writing—review and editing. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors confirm that no original data were collected for this perspective study. All relevant literature and materials used for this review are referenced within the article. Antonio Celentano had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency Statement

The lead author Antonio Celentano affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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