Original Article

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Dentistry Section

Development and Evaluation of Novel Alginate-based Photocrosslinkable Tissue Adhesive: An In-vitro Study

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ABSTRACT

Introduction: In clinical practice, traditional methods like sutures and staples are employed to halt bleeding and expedite wound healing. However, these techniques, which involve piercing tissue, come with drawbacks including the risk of inflammation, infections, and the formation of scars. Surgical sealants and tissue adhesives offer a way to mitigate some of these disadvantages associated with conventional sutures and staples. Tissue adhesives have emerged as a newer alternative for non invasive wound closure.

Aim: To develop and analyse the properties of alginate-based photocrosslinkable tissue adhesive.

Materials and Methods: This in-vitro analysis was done at the Department of Periodontology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India from April 2022 to May 2022. The tissue adhesive was prepared by mixing Alginate, N-Hydroxysuccinamide (NHS) and 1-Ethyl, 3-Dimethylaminopropyl Carbodiimide (EDC) and methacrylate which was used as photo initiator. The preparation was followed by characterisation of the material, strength test and evaluation of biocompatibility.

Results: Surface characteristics test showed homogeneous slices in Scanning Electron Microscope (SEM) analysis. Mechanical test compressive strain was found to be 3% for both the specimens whereas tensile strain was 211.40% and 269.50% for specimen 1 and 2, respectively. Biocompatibility test of the newly developed adhesive showed that adhesive caused the L929 cells to multiply less than the fibrin glue.

Conclusion: All these results suggested that the developed material is a promising soft tissue adhesive for various applications in dentistry.

Keywords: Biomaterial, Innovative tissue adhesive, Natural polymers, Wound closure

INTRODUCTION

Tissue adhesives have emerged quickly during the past 30 years, becoming more and more essential components of contemporary medicine. They facilitate approximation of tissue-tissue or tissue-non tissue surfaces, and promotes natural wound healing processes, displaying some appealing qualities such as non invasive approximation, better patient acceptance, more convenient for operator, better aesthetics, and localised drug release [1,2]. Numerous distinct tissue adhesives have been developed to suit various clinical criteria after several decades of active research activity. Three categories of tissue adhesives that are now being used in clinics can be identified as natural tissue adhesives, synthetic and semi-synthetic tissue adhesives, and biomimetic tissue adhesives [3,4]. These tissue adhesives are widely used in a variety of tissues, including the dermal, breast, cardiac, gastrointestinal, head and neck, hepatic, neurological, orthopaedic, paediatric, thoracic, bone, dental, and microvascular surgery [5-7].

The tissue adhesives primarily rely on molecular bonding, mechanical coupling, and thermodynamic adhesion for adhesion [8]. The most commonly accepted is molecular bonding. In brief, hydrogen bonding, capillary forces, van der Waals forces, static electric force, and covalent bonds all contribute to the interatomic and/or intermolecular interactions that are formed between the tissue surface and adhesive molecules [9].

Tissue adhesives are increasingly being used in medical contexts. Tissue adhesives frequently help with tissue repair, reduce the risk of surgery, promote tissue mending between disconnected tissues, and hasten haemostasis. Commercial biomedical adhesives, such as cyanoacrylate and fibrin, can be separated into biological and synthetic adhesives. The material known as cyanoacrylate glue was made by mixing a cyanoacetate with formaldehyde and a catalyst [10]. It enabled rapid scar growth and repair. Massive bonding power and the capacity to stick to moist surfaces have increased the use in the medical field. However, cyanoacrylate induced severe inflammation and tissue necrosis when it was polymerised in close proximity to the cell culture [11]. Fibrin glue has been demonstrated to increase the amount of graft uptake, especially when used in conjunction with challenging sites to be grafted or locations with relatively greater mobility [12]. However, the results showed weaker bonding strength and it degraded quickly. Therefore, it had primarily been employed to achieve haemostasis in the organs like liver or spleen [13]. To address these issues (biocompatibility and bonding strength) with commercial tissue adhesives, biomimetic monomers such l-3,4-Dihydroxylphenylalanine (DOPA) and its derivatives, as well as natural adhesives including gelatin, collage, polysaccharides have been developed [14].

Alginate, a naturally occurring polysaccharide that is obtained from marine algae, was selected for the current study as the polymeric ingredient for the gelatin adhesive. Alginate is derived from the seaweeds and consists of high concentration of carboxylic groups, which are necessary for the crosslinking reaction of carbodiimides and also a natural viscosity modifier with a bioadhesive nature [15]. The o-iso-acylurea derivative, which is highly reactive, is created when the carbodiimide binds to a carboxylic group, which was original derived from the gelatin or alginate [16]. An initial amino group (originally from the gelatin) nucleophilically attacks this active structure to create an amide bond. A urea molecule (a derivative of the carbodiimide type) is produced as a consequence of the nucleophilic assault. This tissue adhesive has the property to be particularly alluring for tissue approximation because lacerated tissues have exposed amino and carboxylic groups that can participate in the crosslinking reaction [17]. This activated form undergoes a nucleophilic attack by a primary amino group (originally from the gelatin) and forms an amide bond. As a result, a urea

molecule which is derivative of the carbodiimide type is released as a byproduct [18]. The aim of the present study was to develop and evaluate the photocrosslinkable alginate-based tissue adhesive.

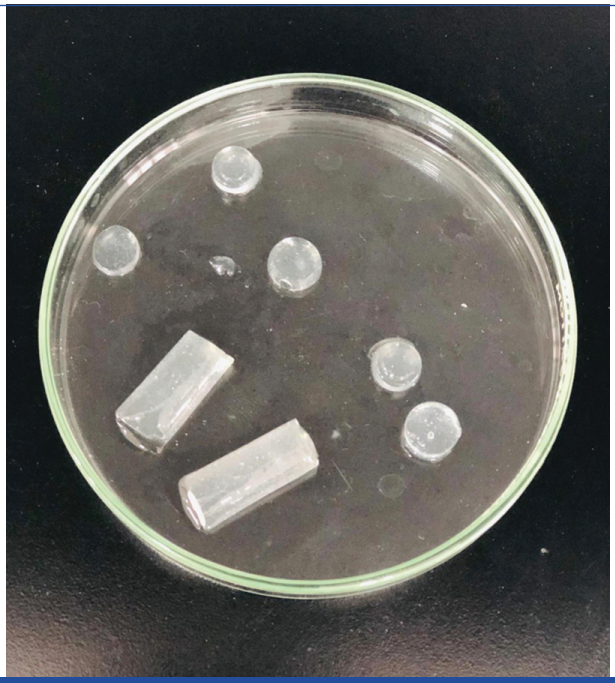
MATERIALS AND METHODS

This in-vitro analysis was done at the Department of Periodontology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India from April 2022 to May 2022. The study protocol was approved by the Scientific Review Board of the Institution with Institutional Human Ethics Committee (IHEC) number IHEC/SDC/PERIO-2101/22/233.

Study Procedure

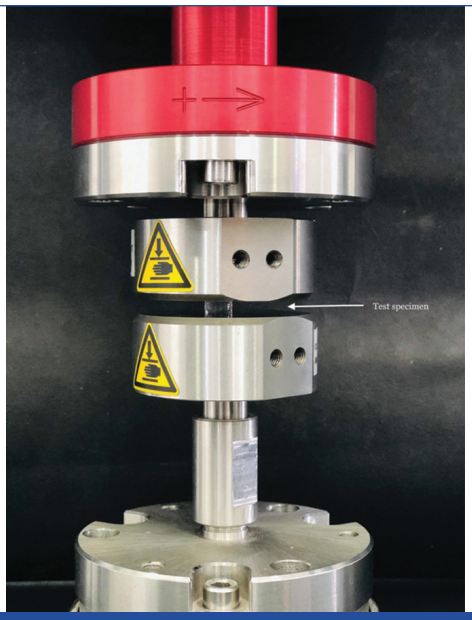
Preparation of adhesive: During the process of development of this tissue adhesive, first 10X Phosphate Saline buffer was prepared by mixing 10 mL of Phosphate Saline Buffer (PBS) with 90 mL distilled water. This prepared PBS was then mixed with alginate and stored separately. Thus, activated Alginate was ready. In another beaker, 115 mg of NHS was mixed with 50 mg 1- EDC along with 1 mL of diluted 10X Phosphate Saline Buffer. This second mixture was then mixed with previously prepared activated alginate. This final mixture was stored at -80 degrees until residue gets sedimented enough to be isolated separately. Then the residue was washed with ethanol for 4-5 times. The supernatant was discarded. Then the pellets that were formed were stored at -80 degrees. Then they were vacuum dried to remove the moisture. Then 1 gram of alginate was mixed with 100 mL of deionised water in a 250 mL beaker. In another beaker 10 g of sodium hydroxide was dissolved in 50 mL of deionised water. From this 2 mL of Sodium Hydroxide (NaOH) was transferred to a 100 mL beaker. To this 7.8 mL methacrylate was added which is a photo initiator [19].

Characterisation: Scanning Electron Microscope (SEM) analysis was performed to determine the structural morphology of the adhesive (JEOL, JSM- 6490LA, Japan). By using a razor blade to cut small parts (3 mm diameter), adhesive samples were made [Table/Fig-1]. Platinum was sputtered in vacuum onto the sections in order to improve the conductivity (JEOL, JFC-1600, Japan) and then SEM analysis was performed [20]. A Fourier Transform Infrared Spectroscopy (FTIR) spectrometer was used to characterise the FTIR spectra of glue (Perkin- Elmer RX1). In a 1:5 ratio, dried adhesive was crushed and completely combined with potassium bromide (Sample: KBr). The Infrared (IR) spectra between 500 and 3500 cm-1 were examined [21].



[Table/Fig-1]: Samples of tissue adhesive cut using a razor blade.

Strength test: Using the Universal Testing Machine, the tensile and compressive strengths were evaluated (Instron 6800 Series Servohydraulic Test Machines). Test specimens with the shape and size in accordance with American Society for Testing and Materials (ASTM) standard were created for the tensile and compressive strength tests. The specimen's end was held in the machine's upper cross-head by one end (fixed). The machine's loading unit slowly imparted load to the specimen while the other end of the specimen was held in the adjustable (movable) cross-head [Table/Fig-2]. Two specimens each were analysed for compressive and tensile strength. The force applied for compressive and tensile strength test for both the specimens were 0.83 N; 0.87 N and 0.21 N; 0.11 N, respectively [22].



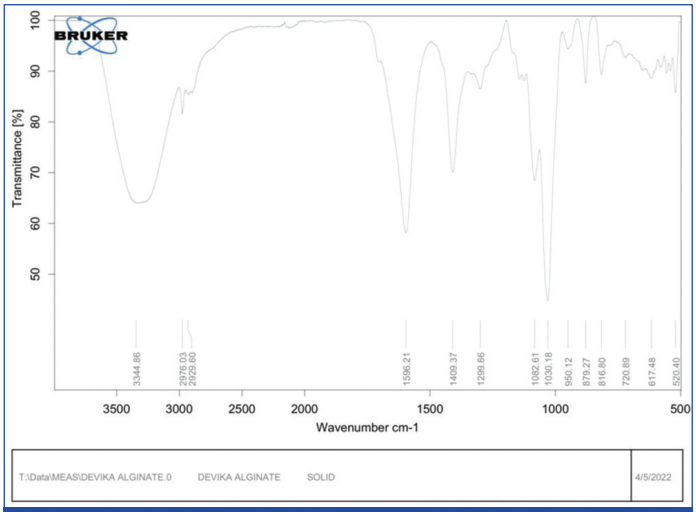
[Table/Fig-2]: Strength test of tissue adhesive test specimen using Instron Universal Testing Machine.

Cell viability: The Live/Dead® assay exhibits the polymer's biocompatibility towards cells in a qualitative manner. The biomaterial was used to cultivate the cells. The marker SYTO® 9 which is fluorescent in nature interacted with the living cells, giving healthy cells a green stain. Unviable cells, on the other hand, were stained red, indicating dead cells [23]. The alginate-based tissue adhesive was compared with fibrin glue. To qualify the viability test, a live/dead fluorescence assay kit (made by Molecular Probes) was employed. Living Dead® is used in a qualitative biocompatibility test. In a 96-well plate, the cells were seeded (3x106 cells/mL) and cultured in (Dulbecco's Modified Eagle Medium- low glucose) DMEM-LG with 10% Foetal Bovine Serum (FBS) for 24 hours at 37°C. This was followed by culturing the cells with the Poly-L-Lactic Acid (PLLA) scaffolds (2×5 mm) for 24 hours. To analyse the viability of the cells, a live/dead fluorescence test kit (made by Molecular Probes) was utilised. After 24 hours, the solution of calcein AM and ethidium homodimer-1 was applied on the cells in accordance with the instructions given by manufacturers after being washed with 200 microlitre of PBS. After 30 minutes of incubation at 37°C, the cells were washed and kept in PBS. Using the Nikon E800's inverted fluorescence microscopy programme, the cells were examined (Image Pro-Plus software).

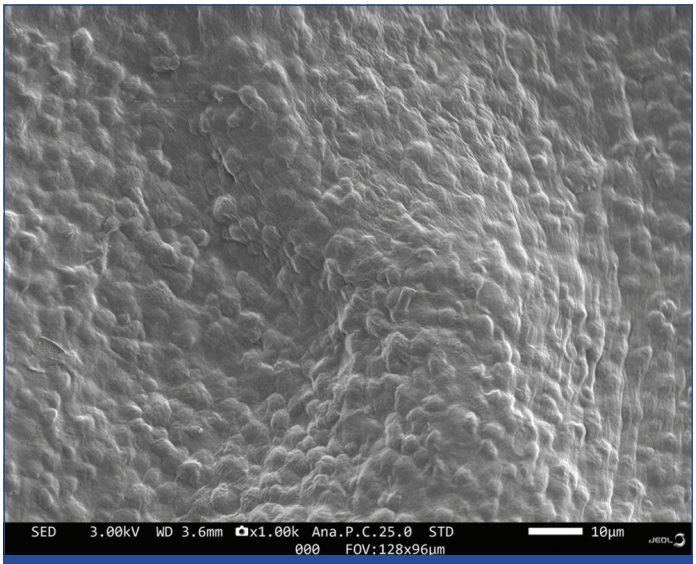
RESULTS

Characterisation of sodium alginate photocrosslinking: Photocrosslinking of alginate and photoinitiator was confirmed by using FTIR. The peak was observed at 1030.18 cm -1 indicating C-O-C structure [Table/Fig-3].

SEM analysis: Microstructures of the alginate-based photocrosslinkable tissue adhesive is shown in [Table/Fig-4]. The pore shapes of the tissue adhesive were small and regular with smooth walls.

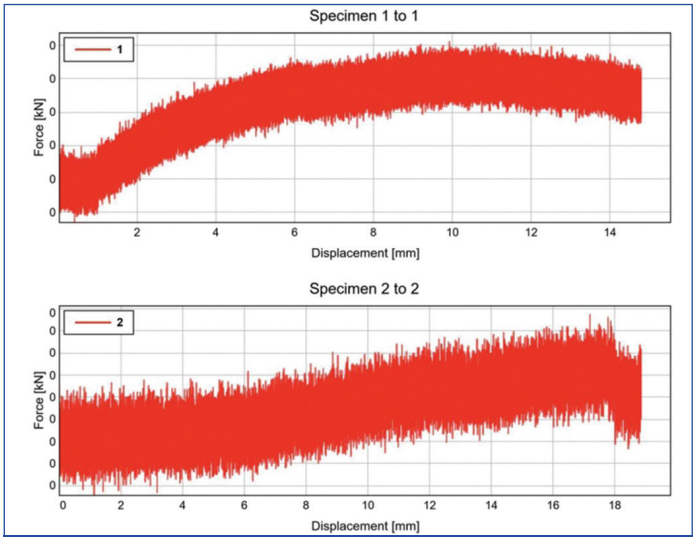


[Table/Fig-3]: FTIR of alginate-based tissue adhesive.



[Table/Fig-4]: SEM analysis of alginate-based photocrosslinkable tissue adhesive.

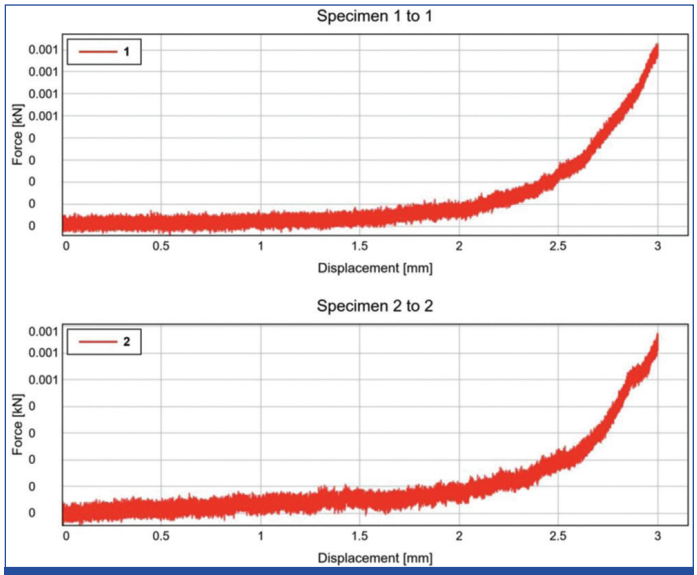
Strength test: Compressive and tensile strength of the specimen was tested by using Instron Universal Testing Machine. The displacement observed for specimen 1 was 14 mm at 0 kN whereas for specimen 2 was 18 mm as shown in [Table/Fig-5]. The compressive stress at maximum force 0.83 N was 0.07 MPa for specimen 1 whereas the compressive stress for specimen 2 was 0.05 MPa at maximum force 0.87 kN. Compressive strain was found to be 3% both for specimen 1 and 2 as shown in [Table/Fig-6]. Displacement of both specimen 1 and 2 is 3 mm at 0 kN shown in [Table/Fig-7]. Tensile strain at maximum force 0.21 N was 211.40% for specimen 1 and 269.50% for specimen 2 as shown in [Table/Fig-8].



[Table/Fig-5]: Graphs showing compressive strength of alginate-based tissue adhesive.

Maximum force (N)	Compressive stress at maximum force (MPa)	Specimen label
0.83	0.07	Tissue adhesive (Alginate)
0.87	0.05	Tissue adhesive (Alginate)
Compressive displacement at break (Standard) (mm)	**Compressive strain (displacement) at break (Standard) (%)**	**Compressive stress at break (Standard) (MPa)**
3.00	3.00	0.07
3.00	3.00	0.05

[Table/Fig-6]: Compressive strength of alginate-based tissue adhesive.

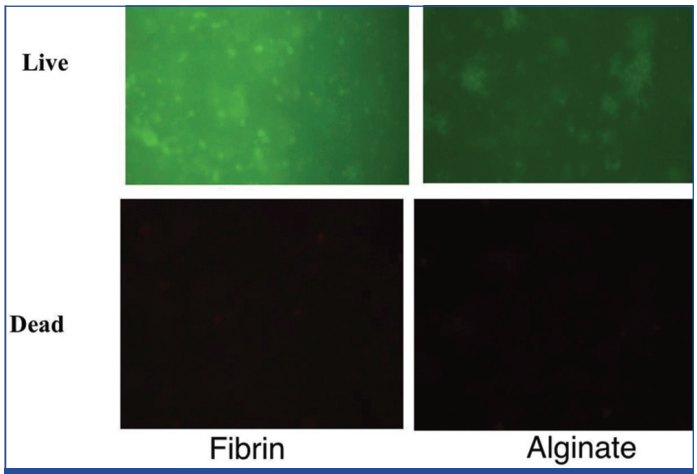


[Table/Fig-7]: Graphs showing tensile strength of alginate-based tissue adhesive.

Maximum force (N)	Tensile stress at tensile strength (MPa)	Tensile strain (displacement) at break (standard) (%)
0.21	0.00	211.40
0.11	0.00	269.50
Specimen label		**Tensile stress at Break (Standard) (MPa)**
Tissue adhesive (Alginate)		0.00
Tissue adhesive (Alginate)		0.00

[Table/Fig-8]: Tensile strength of alginate-based tissue adhesive.

Cell viability: [Table/Fig-9] displays the Live/Dead® approach through inverted fluorescence microscopy results. The results from the qualitative cytotoxicity test revealed that the alginate-based tissue adhesive caused the L929 cells to multiply lesser than the fibrin



[Table/Fig-9]: Images showing cell viability on live/dead® test.

glue did, whereas the fibrin glue caused less number of dead cells to be visible than the alginate-based tissue adhesive did. These were based on the intensity of fluorescence. There wasn't any major difference in the intensity of fluorescence which shows that our synthetic Alginate-based tissue glue is an effective and biocompatible material.

DISCUSSION

In the present study, an alginate-based photocrosslinked tissue adhesive was developed for tissue approximation. The support and regulation of cell adhesion, migration, proliferation, and differentiation by tissue adhesive is crucial for wound healing [24]. When these adhesives have served their purpose, they should break down into harmless byproducts [25]. Controlling the physical parameter such as compressive and tensile strength in adhesives may be very beneficial for their usage as tissue adhesives because the mechanical characteristics of materials can also have a significant impact on cell activity [26]. Strong tissue adhesives were created on the basis of reactions of cyanoacrylate with nucleophiles and albumin with dialdehydes. Comparing these products to fibrin-based sealants, they exhibit enhanced adhesion strength [27]. Nevertheless, because of its quick reaction time, the adhesive may result in tissue necrosis, misplacements, and emboli [28,29]. Although certain commercial tissue adhesives have a high adhesion strength, their delayed gelation times may not be sufficient to halt bleeding in the event of an unexpected blood loss [30,31]. Recent research and development have focused on the novelty of bio adhesives that combine gelatin with an alginate polymer which undergoes cross linking by carbodiimide [32].

Surface characterisation of the newly developed adhesive was tested using SEM and FTIR both the tests evaluated microstructure of the material. Surface Morphology described the surface of the Alginate-based adhesive, highlighting its topographical features, such as roughness, texture, and any observable structural patterns. It was found that the texture was porous and inhomogeneous in nature.

In a previous study done by Ono K et al., assessment of photocrosslinkable chitosan as an adhesive in surgical applications showed strong sealing ability of the tissues [33]. The surface characterisation of alginate-based tissue adhesive was also done by Rana M et al., using SEM analysis and the results showed smooth surface of the hydrogel with adhesive characteristics [34].

Mechanical strength i.e., compressive and tensile strength was determined via universal testing machine. Compressive and tensile strain was tested and displacement was observed at maximum force. The stress test was performed by applying the maximum force. This suggests the maximum compressive load the adhesive can withstand before failure. This is a very important property that relates to the adhesive's ability to hold tissues together under compressive forces, such as during wound healing or tissue bonding. Tensile Strength shows the maximum tensile force the adhesive can endure before breaking. This explains how this property is relevant to applications where tissues might experience stretching or pulling forces. The results obtained were in accordance with the previous study where copolymeric tissue adhesives demonstrated promising adhesion strength [35]. The adhesive strength of this biological adhesive is on par with that of the commercially accessible fibrin glue [36].

Various other tissue adhesive systems have been developed in the past. Dextran derivatives (Dex-U) and 2-Hydroxyehyl Methacrylate (HEMA) have been combined to create the photocrosslinkable copolymeric bioadhesive system known as the Dex-H system, but the material's biocompatibility was not sufficient [37]. A sealant for mending corneal perforations was developed using the algae-MA hydrogel network. Charron PN et al., recently investigated the adherence of Alg-MA to biological tissues via a similar gelation technique. Hydrogels made from algae-MA had weak adherence to moist tissues. The majority of photochemically activated tissue adhesives include the addition of photoactive chemical groups to naturally occurring polymers like proteins and polysaccharides. Wide ranges of polymer backbones, biocompatibility, and biosorption are all provided by naturally occurring polymers [38-40]. To summarise, the authors have focused on the design and development of tissue adhesives which are procured from natural sources like seaweeds which is polymeric in nature and is photocrosslinkable.

Biocompatibility is a critical aspect when considering the suitability of a tissue adhesive for medical applications. The present study assessed cell viability of the adhesive by live/dead® approach and demonstrated less survival of the L929 cells in presence of alginate-based adhesive when compared with fibrin glue. This suggested alteration in the concentration of the adhesive must be done in future preparation to ensure cytocompatibility of this biomaterial.

Limitation(s)

While the present in-vitro investigation yielded encouraging findings, there is still a need to explore the approach to solve the issue related to its biocompatibility and also the mechanical robustness necessitating further refinement before its practical application in clinical settings. Also, other properties such as bonding strength, gelation time, wettability and temperature stability were not assessed for its application in the oral environment.

CONCLUSION(S)

Alginate-derived tissue adhesives show great potential for numerous applications, particularly in the realm of soft tissue handling. Hence, the Alginate-based photocrosslinkable adhesive investigated in the present research has the potential to serve as a versatile biomaterial in a variety of medical applications. Alginate-based materials exhibit biocompatibility, high strength, and low production costs. Although these test results have yet to be validated in clinical settings, which may be the future focus of the study.

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