



A highly adhesive and naturally derived sealant



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ABSTRACT

Conventional surgical techniques to seal and repair defects in highly stressed elastic tissues are insufficient. Therefore, this study aimed to engineer an inexpensive, highly adhesive, biocompatible, and biodegradable sealant based on a modified and naturally derived biopolymer, gelatin methacryloyl (GelMA). We tuned the degree of gelatin modification, prepolymer concentration, photoinitiator concentration, and crosslinking conditions to optimize the physical properties and adhesion of the photo-crosslinked GelMA sealants. Following ASTM standard tests that target wound closure strength, shear resistance, and burst pressure, GelMA sealant was shown to exhibit adhesive properties that were superior to clinically used fibrin- and poly(ethylene glycol)-based glues. Chronic *in vivo* experiments in small as well as translational large animal models proved GelMA to effectively seal large lung leakages without the need for sutures or staples, presenting improved performance as compared to fibrin glue, poly(ethylene glycol) glue and sutures only. Furthermore, high biocompatibility of GelMA sealant was observed, as evidenced by a low inflammatory host response and fast *in vivo* degradation while allowing for adequate wound healing at the same time. Combining these results with the low costs, ease of synthesis and application of the material, GelMA sealant is envisioned to be commercialized not only as a sealant to stop air leakages, but also as a biocompatible and biodegradable hydrogel to support lung tissue regeneration.

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1. Introduction

While traditional surgical closure and treatment of tissue defects is achieved by sutures, staples, or wires, the application of adhesives for different types of lesions is essential. The repair of parenchymatous defects, such as in the lungs, liver, or kidney, is particularly challenging since the consistency of these tissues does

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not facilitate strong fastening of sutures or staples. Within the lungs, repetitive and quickly varying stress exerted by respiration poses additional risks for failure of the repaired tissue, which is further complicated by the non-sterile environment in the pulmonary airways, creating the possibility of wound infection [1]. Even in tissues that can be sutured, the usage of adhesives may be necessary to allow for better sealing, such as in the closure of small stitching channels in a sutured artery wall [2]. Furthermore, limited access to defect sites can make conventional suturing nearly impossible since there is often not enough space to place sutures. This issue may be solved by applying adhesive prepolymers that polymerize on site, since these materials can be delivered to the area of interest through thin applicators [3,4].

For maximum clinical efficacy, tissue adhesives must demonstrate strong adhesiveness to the tissue, not only to initially close the defect, but to also allow for subsequent wound healing. During this process, controlled degradation of the applied adhesive is desirable [5]. The adhesive should also be biocompatible to avoid an excessive host inflammatory response [6]. Furthermore, most clinical applications require an adhesive with the ability to function under wet conditions. Economic aspects to be considered include application and curing within a reasonable period of time as well as cheap and safe production of the material [7]. Besides these requirements, further features may be desirable depending on the target tissues. For example, defects in highly vascularized tissues require adhesives with hemostatic properties, air or liquid leakages necessitate effective sealants that withstand high pressures, and lesions in flexible tissues should be treated with elastic adhesives to preserve their functionality. Thus, it is crucial to optimize the adhesion and physical properties of tissue adhesives based on the desired applications.

Various types of surgical adhesives and sealants that are comprised of natural, synthetic, and semi-synthetic substances have previously been developed [8,9]. The most common naturally derived tissue adhesives are fibrin- and collagen-based adhesives. While these adhesives are biocompatible, their major drawbacks are their low mechanical characteristics and adhesion strength as well as high production costs and risk of infectious contamination, resulting from the biological source of the materials [10,11]. On the other hand, synthetic-based adhesives, especially clinically used cyanoacrylates, exhibit improved adhesion strength as compared to naturally derived sealants. However, they also provide low biocompatibility and biodegradability, and evoke a foreign body response or even necrosis due to toxic degradation products. Moreover, due to their high stiffness, cyanoacrylate-based adhesives impede physiological movement of elastic and soft tissues such as in the lungs, heart, and blood vessels. Due to these limitations, their usage is predominantly limited to external applications such as the closure of skin wounds [10,11].

The adherence of most tissue adhesives is restricted to dry tissue surfaces. Polymeric hydrogel-based sealants/adhesives can cross-link even under wet conditions and can serve as fluid barriers [12]. Predominantly, poly(ethylene glycol) (PEG)-based formulations such as Coseal™, DuraSeal™ and FocalSeal® have been tested as adhesives both *in vitro* and *in vivo* [13–18]. Unmodified PEG is non-immunogenic, which favors its *in vivo* applications, whereas its inert properties also avoid ingrowth of cells and do not allow tissue healing and repair [16]. Furthermore, due to low mechanical and adhesive characteristics of commercially available hydrogel-based sealants, their clinical indications are predominantly focused on the additional sealing of sutures, and not on the use in suture-free surgical procedures [18,19].

Highly elastic hydrogel-based sealants have been developed for the sealing and closure of elastic tissues such as the lungs. However, most of these sealants lack the appropriate mechanical

properties, adhesion strength, and burst pressure performance required for sealing of lung tissue leakages [4]. Adequate lung leakage repair requires sealants with high elasticity that feature strong mechanical and adhesive characteristics even under repetitive and extensive tension. After lung surgery, a prolonged air leak is one of the most common complications, leading to extended chest tube drainage time, which is associated with pain and immobilization for the patient. This in turn increases the risk of infections and broncho-pleural fistulae and, subsequently, leads to a longer hospital stay with associated higher healthcare costs [20–23]. In order to prevent these complications, a variety of natural and synthetic materials have been examined for use, including fibrin sealants, collagen-based sealants, and synthetic glues [24]. For example, a photopolymerizable gelatin-based lung sealant has been developed by covalently crosslinking di-tyrosine in gelation in the presence of ruthenium and sodium persulphate (SPS) [25]. The engineered sealants exhibited a lap adhesion strength higher than commercially available adhesives, like fibrin-based products, and induced minor inflammation at the sealed site in the lungs after 2 weeks. Although the optimized sealant formulation was highly elastic with an extensibility of up to 650%, its low elastic modulus (14 kPa) may not provide suitable cohesive properties for lung sealing. In addition, the high concentrations of SPS (20 mM) and porcine gelatin (17.5%) used to obtain this highly elastic gelatin hydrogel induced toxicity in the *in vitro* studies. Progel™ (Neomend, Irvine, CA, USA), based on human albumin and a PEG crosslinker, has been commercialized as the flagship sealant product to stop air leakage in lung procedures and has shown good burst pressure results [26,27]. However, the high cost of isolating human albumin and the potential for disease transmission causes concerns, as it does for other blood-derived products. Another limitation of Progel™ is that, as a product based on albumin and PEG, it lacks the function of hemostasis, which may be required for sealing when there is blood emanating from the wound. In summary, due to the above-mentioned limitations of lung adhesives/sealants, the introduction of a new biocompatible, highly adhesive, and elastic sealant with strong mechanical properties is warranted.

Photopolymerization of gelatin methacryloyl (GelMA) is an inexpensive and technically simple approach to fabricate hydrogels for biomedical applications [28–33]. The cytocompatibility of GelMA hydrogel has been previously proven *in vitro* and *in vivo*, implying its potential to be used as a suitable biomaterial for various tissue engineering applications [34–36]. While the engineered formulation of GelMA hydrogel was suitable for 3D cell spreading and engineering vascularized tissues, this particular composition did not provide adequate adhesion to wet surfaces to allow for usage as a flexible and highly adhesive sealant.

The present study is aimed at engineering an optimized formulation of GelMA hydrogels to act as tissue adhesives and sealants for the closure of defects in highly stressed elastic tissues such as the lungs. To obtain a GelMA sealant with high adhesion strength, the degree of gelatin modification, the prepolymer concentration, the photoinitiator concentration, and the cross-linking conditions of GelMA prepolymers were optimized. Different ASTM (American Society for Testing and Materials) standard tests were followed to characterize and optimize the adhesive properties of the GelMA sealant, which were compared to several clinically available fibrin- and PEG-based glues/sealants. Furthermore, the biocompatibility of the engineered GelMA sealant was tested using a rat subcutaneous implantation model. The *in vivo* performance of the engineered material for sealing lung leakages was also evaluated using chronic rat and porcine lung incision models.

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