Alginate/Polyacrylamide Hydrogels for Hemostatic Sealing

Joshua Pillai

[1]joshpillai949@gmail.com

***Abstract*— Conventional tissue sealing agents, such as sutures or tissue adhesives, have been widely utilized in clinical settings to promote early formation and stability of blood clots. While these traditional techniques offer some advantages in clinical settings, their limitations have now been resolved by current bioadhesive technology. However, current bioadhesives have not been fully utilized and are often limited by weak bonding, poor mechanical interface compatibility, and burdensome application. In this study, I explored the potential of using interpenetrating alginate/polyacrylamide (PAAm) hydrogels as a smart material for bioadhesive patches in superficial wound healing. After mechanical testing, the PAAm material matched the biomechanical properties of human skin, and had comparable toughness to commercial bioadhesives. Furthermore, the PAAm dressing showed adequate release of hydration through an *in vitro* dehydration test. These findings suggest that PAAm-based therapies may be viable alternatives to conventional tissue sealing agents by providing efficient delivery of therapeutics and resolving challenges in interfacing and application on devices.**

***Keywords*— bandages, tissue sealing agents, hydrogels, wound healing, and novel adhesives**

I. Introduction

As a method for closing subcutaneous or superficial wounds, suturing is the primary technique employed for over thousands of years. Within sutures, the materials used often depend on the wound type and cosmetic results. Specifically, absorbable sutures are typically used for deeper, two-layered wounds, while non-absorbable sutures are used for superficial wounds [1]. Although these variations help seal the majority of wound types, they often are limited because of their ability to retain their original shape and often resist manipulation during wound closure. This often leads to cavities in deeper wounds and undesired cosmetic results, such as scars.

In comparison, fibrin tissue adhesives have also been commonly used in clinical settings, such as the Food and Drug Administration (FDA)-approved dermabond tissue adhesive. These tissue adhesives mimic the process of coagulation cascade, where fibrinogen promotes the polymerization of long fibrin strands, and eventually promotes hemostasis [2]. However, these methods have not been utilized widely because of burdensome application on tissue: majority of these adhesives come in the form of a viscous solution, and require diffusion-based interpenetration or solidification of solution through outside stimuli, such as ultraviolet light.

From the shortcoming of sutures and tissue adhesives, novel bioadhesives have been fabricated to achieve perfect healing incision and line up of wounds to minimize scarring. These patches are relatively painless and cause far less inflammation than sutures and tissue adhesives [3]. Although bioadhesives resolve the majority of limitations faced by commercial technology, they have not been optimized for challenging clinical applications, such as gastrointestinal defects, or wounds that require delivery of therapeutics, such as psoriasis [4].

In this study, I introduce the use of the biopolymer alginate/polyacrylamide (PAAm) hydrogel as a potential drug carrier and as a material that matches the biomechanical properties of skin. First, I utilized the tunability of the PAAm hydrogel to fabricate a composite dressing with similar mechanical properties to human skin while maintaining nominal mechanical toughness and high coverage on skin [5]. I then conducted benchtop mechanical tests consisting of a uniaxial tensile test. To evaluate delivery time of therapeutics, an *in vitro* dehydration test was completed on porcine skin. With mechanical and

drug delivery evaluations, the PAAm hydrogel may be a promising biomaterial for improving bioadhesive patches in clinical settings.

II. METHODS

A. Materials

All reagents were procured from Sigma-Aldrich (Saint Louis, Missouri, USA) and used without further purification. The PAAm was composed of acrylamide (A8887) and alginic acid sodium salt (180947) monomers. Methylenebis(acrylamide) (MBAA) (146072), Ammonium Persulfate (APS) (A3678), and Tetramethylethylenediamine (TEMED) (T22500) were used as a covalent cross-linker, initiator, and accelerator, respectively.

For mechanical and hydration testing, porcine belly skin was retrieved from a commercial vendor (Fine Section Deli, Costa Mesa, California, USA). For mechanical testing, a force acceleration sensor (PASCO®, PS-3202, Hudson, Ohio, USA) was used to measure applied stress, and a 3M Tegaderm patch (3M®, Saint Paul, Minnesota, USA) was used as a control. For the *in vitro* dehydration test, a precision balance (Fisher Scientifics, Massachusetts, USA) was used to measure mass of the hydrogel.

B. PAAm Hydrogel Synthesis

Synthesis of the PAAm hydrogel followed a modified procedure of Yang et al., [6] and Sun et al., [7]. First, 2.47 g of alginic acid sodium salt was dissolved in 100 mL distilled water for 48 hours under ambient conditions. 14.32 g of acrylamide monomers were then dissolved into the alginate aqueous solution. MBAA (0.015 M), APS (0.046 M), and 201.22 µL of TEMED were then added to the monomer solution, respectively. The gel was then vector cut into predesigned moulds in preparation for mechanical or hydration evaluation. After the gel was cut, it was cured under ultraviolet light (365 nm, 5 watts) for 1 hour. After immediate synthesis, the hydrogels were conducted in the mechanical testing.

C. Mechanical Testing

Uniaxial tensile testing followed a modified procedure of Pan et al., [8], where a force sensor was used to precisely measure stress (kPa) while a video recorded displacement between the sample and sensor. A benchtop vise held one side of the gel, while a paper clamp, connected to the sensor, held the other side and was extended uniformly. To prevent slippage of the sample from the clamp, cyanoacrylate was applied between the sample and the clamp. As an independent control, a 3M Tegaderm commercial bioadhesive patch was tested. The ultimate tensile strength was then measured from the maximum applied stress (n = 5).

To compare the mechanical toughness of the PAAm hydrogel, the elastic modulus (E) was calculated as the standard comparison to that of human skin (n = 5).

$$E = \frac{\sigma}{\epsilon} \quad (1)$$

To calculate the elastic modulus of viscoelastic materials such as the hydrogel, the tensile test data was plotted at 2% engineering strain. The elastic modulus of the hydrogel was calculated by the given strain:

$$E = \frac{F/A}{\triangle L/L} \quad (2)$$

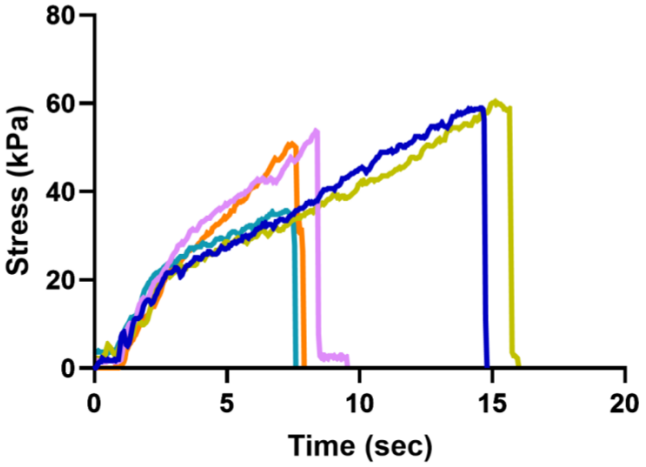

Fig. 1: Stress (kPa) vs. Time (sec) curves of the 3M Tegaderm uniaxial tensile test (n = 5).

For tensile testing data, the data is plotted in Fig. 1 and Fig. 2 for the 3M Tegaderm patch and PAAm hydrogel, respectively.

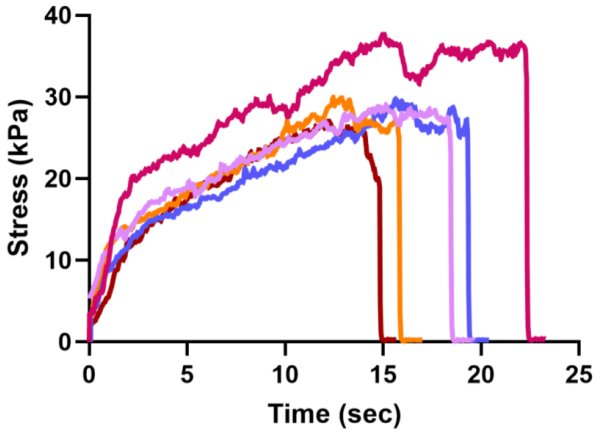

Fig. 2: Stress (kPa) vs. Time (sec) curves of the PAAm Hydrogel uniaxial tensile test ($n = 5$).

D. In vitro Dehydration Test

For drug loading of the hydrogel, the material was left to completely dehydrate for 8 hours under ambient conditions and to rehydrate in distilled water for 12 hours. The completely hydrated patch was then used for the hydration test. To mimic *in vivo* conditions, shallow abrasion wounds were pre-cut on the porcine skin. Before application of the patch on skin, the mass of the device was measured on a precision balance to measure the initial mass. After placement on skin, the samples were taken off periodically (4 hours) and measured on a precision balance to measure cumulative loss of hydration ($n = 5$). This was then repeated for 48 hours.

E. Statistical Analysis

Statistical analysis of all data was completed using the embedded algorithms of GraphPad Prism (version 9.2.0). For all tests, a two tailed student's t-test was conducted to evaluate statistical significance. The mean $\pm$ standard deviation, and sample sizes, n, are listed within the paper. The significance thresholds are labeled ***$P \leq 0.001$ and ****$P \leq 0.0001$. Additionally, all graphs were plotted on GraphPad Prism.

III. RESULTS AND DISCUSSION

A. PAAm Mechanical Results

For the results of uniaxial tensile testing, it was found that the PAAm hydrogel had an ultimate tensile strength of 28.01 $\pm$ 1.41 kPa in 15 seconds. For the 3M Tegaderm control patch, the ultimate tensile strength was 51.91 $\pm$ 9.87 kPa in 25 seconds. This is shown in Fig. 3.

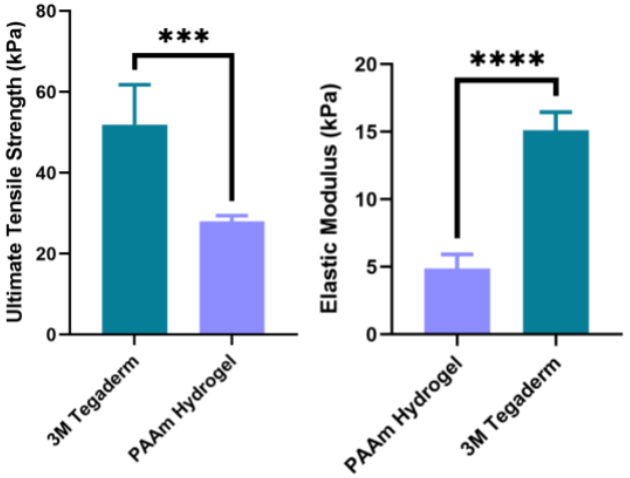

Fig. 3: Ultimate tensile strength ($n = 5$) and elastic modulus ($n = 5$) of the PAAm hydrogel and 3M Tegaderm bioadhesives.

Additionally, the elastic modulus of the PAAm hydrogel and 3M Tegaderm patch was 4.87 $\pm$ 1.05 kPa and 15.12 $\pm$ 1.32, respectively. This data is shown in Fig. 3.

Based on mechanical evaluation, the PAAm hydrogel, which had a modulus of less than 10 kPa, matched that of skin moduli (85 kPa) [9]. The hydrogel also had a similar moduli to the Tegaderm patch (****$P \leq 0.0001$).

For the ultimate tensile strength, the hydrogel matched the mechanical toughness of the Tegaderm patch ($P = 0.0007$, ***$P \leq 0.001$). This finding proves that the PAAm hydrogel is a pliable material that matches the properties of human skin while maintaining the toughness of conventional tissue adhesives.

B. In vitro Dehydration Test Results

After evaluation of the dehydration test, the PAAm hydrogel had a mass ratio (w/w) of 0.654 $\pm$ 0.036 % and 0.258 $\pm$ 0.039 % after 4 and 48 hours of adhesion on skin, respectively.

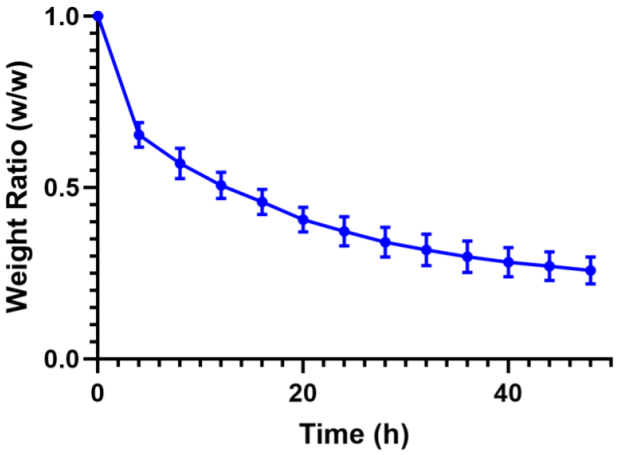

Fig. 4: Weight Ratio (w/w) vs. Time (h) curve for the Dehydration test results (n = 5).

Based on these results, the hydrogel remained hydrated for more than 48 hours. This is valuable not only for wound healing but also chronic wounds that essentially require consistent hydration, such as psoriasis or diabetic ulcers.

II. Conclusions

After mechanical and drug delivery testing, the PAAm had similar biomechanical properties to skin, allowing for ease of application on skin and practical bodily motion. The hydrogel not only contains an interface resembling the properties of skin but also of current tissue adhesives.

For the results of the dehydration test, it was found that the hydrogel maintained retention of therapeutics (distilled water) for more than 48 hours. These findings suggest that the hydrogel can not only be an effective alternative to tissue sealings but also a vehicle for chronic wound disorders. Furthermore, in previous studies it was found that the PAAm hydrogel was capable of delivering both hydrophobic and hydrophilic therapeutics [10]. This physical property of PAAm opens a wide array of potential drug administrations and applications in clinical settings.

Overall, the PAAm hydrogel is a suitable biomaterial that can be utilized for not only wound healing but also for drug delivery. These findings suggest that the PAAm hydrogel may be an effective alternative to tissue sealing for acute wounds and chronic wounds.

References

[1] M. Byrne and A. Aly, "The surgical suture," *Aesthetic Surgery Journal*, vol. 39, no. Supplement_2, 2019.

[2] L. Tacconi, R. Spinelli, and F. Signorelli, "Skin glue for wound closures in brain surgery: Our updated experience," *World Neurosurgery*, vol. 121, 2019.

[3] J. C. Wheat and J. S. Wolf, "Advances in bioadhesives, tissue sealants, and hemostatic agents," *Urologic Clinics of North America*, vol. 36, no. 2, pp. 265–275, 2009.

[4] J. Wu, H. Yuk, T. L. Sarrafian, C. F. Guo, L. G. Griffiths, C. S. Nabzdyk, and X. Zhao, "An off-the-shelf bioadhesive patch for sutureless repair of gastrointestinal defects," *Science Translational Medicine*, vol. 14, no. 630, 2022.

[5] Y. Liu, S. Cheong NG, J. Yu, and W.-B. Tsai, "Modification and crosslinking of gelatin-based biomaterials as tissue adhesives," *Colloids and Surfaces B: Biointerfaces*, vol. 174, pp. 316–323, 2019.

[6] C. H. Yang, M. X. Wang, H. Haider, J. H. Yang, J.-Y. Sun, Y. M. Chen, J. Zhou, and Z. Suo, "Strengthening alginate/polyacrylamide hydrogels using various multivalent cations," *ACS Applied Materials & Interfaces*, vol. 5, no. 21, pp. 10418–10422, 2013.

[7] J.-Y. Sun, X. Zhao, W. R. Illeperuma, O. Chaudhuri, K. H. Oh, D. J. Mooney, J. J. Vlassak, and Z. Suo, "Highly stretchable and tough hydrogels," *Nature*, vol. 489, no. 7414, pp. 133–136, 2012.

[8] W. Pan, B. Matsuda, and H. Yuk, "Biocompatible Hydrogel Ostomy adhesive," *MEDICAL DEVICES & SENSORS*, vol. 3, no. 6, 2020.

[9] C. T. McKee, J. A. Last, P. Russell, and C. J. Murphy, "Indentation versus tensile measurements of Young's modulus for soft biological tissues," *Tissue Engineering Part B: Reviews*, vol. 17, no. 3, pp. 155–164, 2011.

[10] F. Abasalizadeh, S. V. Moghaddam, E. Alizadeh, E. akbari, E. Kashani, S. M. Fazljou, M. Torbati, and A. Akbarzadeh, "Alginate-based hydrogels as drug delivery vehicles in cancer treatment and their applications in wound dressing and 3D bioprinting," *Journal of Biological Engineering*, vol. 14, no. 1, 2020.