

Introduction

Healthy skin maintains a slightly acidic environment (pH ~4.5–6), which supports barrier integrity and antimicrobial defense. When the skin is disrupted through abrasions, lesions, or surgical incisions, this barrier is compromised, exposing underlying tissue and interstitial fluids with a more neutral pH (~7.4). As healing becomes impaired, inflammation, enzymatic activity, and bacterial colonization can further elevate the local pH into a more alkaline range (approximately 7.2–8.9), which is strongly associated with infection, delayed healing, and tissue degradation [1]. Because of this, wound pH has emerged as an important non-invasive biomarker for monitoring healing progression and identifying wound stress. However, most conventional wound dressings remain passive and do not provide real-time feedback on the wound microenvironment.

Recent advances in hydrogel systems have demonstrated that dynamic covalent bonding can be used to create materials with self-healing, injectable, and stimuli-responsive properties, making them highly suitable for biomedical applications [2]. In particular, boronic acid–diol interactions enable reversible crosslinking that is sensitive to environmental conditions such as pH. To address current limitations, we developed a pH-responsive hydrogel using alginate functionalized with 4-aminophenylboronic acid (4-APBA) and combined with polyvinyl alcohol (PVA). This system leverages dynamic boronate ester bonding to form a reversible network while incorporating phenol red for visible pH indication. By integrating environmental responsiveness with structural adaptability, this hydrogel functions as both a protective wound material and a real-time indicator of wound stress.

Materials and Methods

Alg-PBA SYNTHESIS

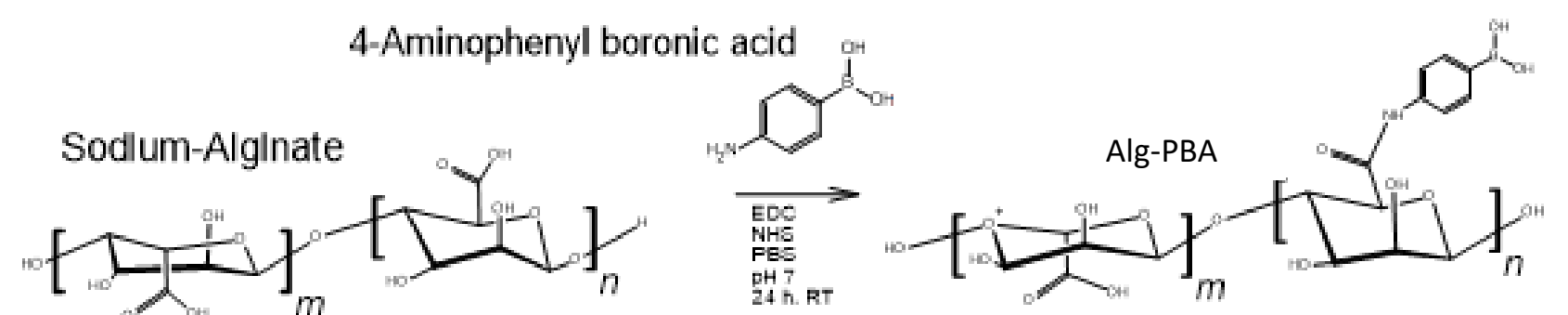


Figure 1. Synthesis of Alg-PBA via EDC/NHS coupling. Sodium alginate was functionalized with 4-aminophenylboronic acid (4-APBA) using EDC/NHS chemistry to form amide bonds between alginate carboxyl groups and amine groups of 4-APBA, resulting in boronic acid–modified alginate (Alg-PBA), consistent with previously reported methods [2].

Alg-PBA/PVA HYDROGEL FABRICATION

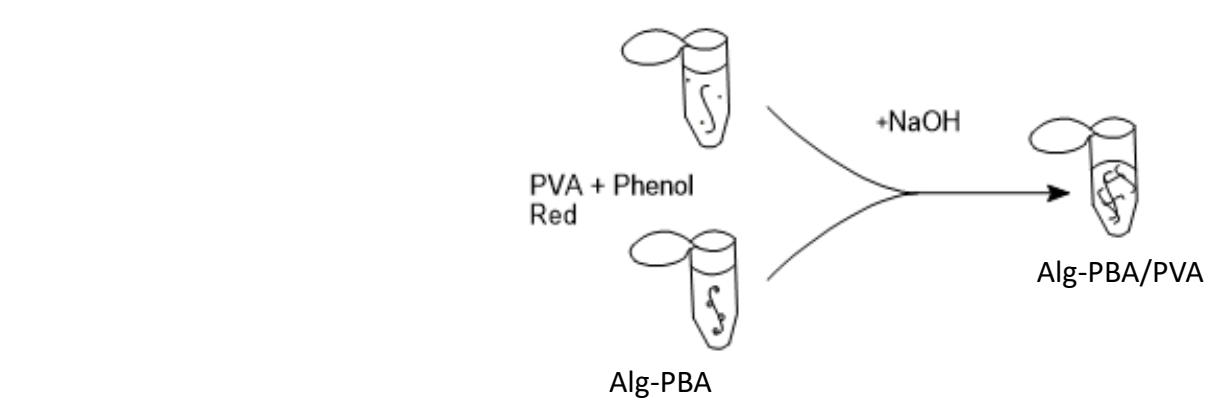


Figure 2. Illustration of Alg-PBA/PVA hydrogel preparation. A 20% (w/v) PVA stock solution containing phenol red and a 8% (w/v) Alg-PBA stock solution were prepared. The two stock solutions were mixed at different ratios to form precursor solutions. Subsequently, 1% NaOH was added dropwise to increase the pH for promoting the formation of boronate ester bonds between PVA and Alg-PBA and leading to hydrogel formation.

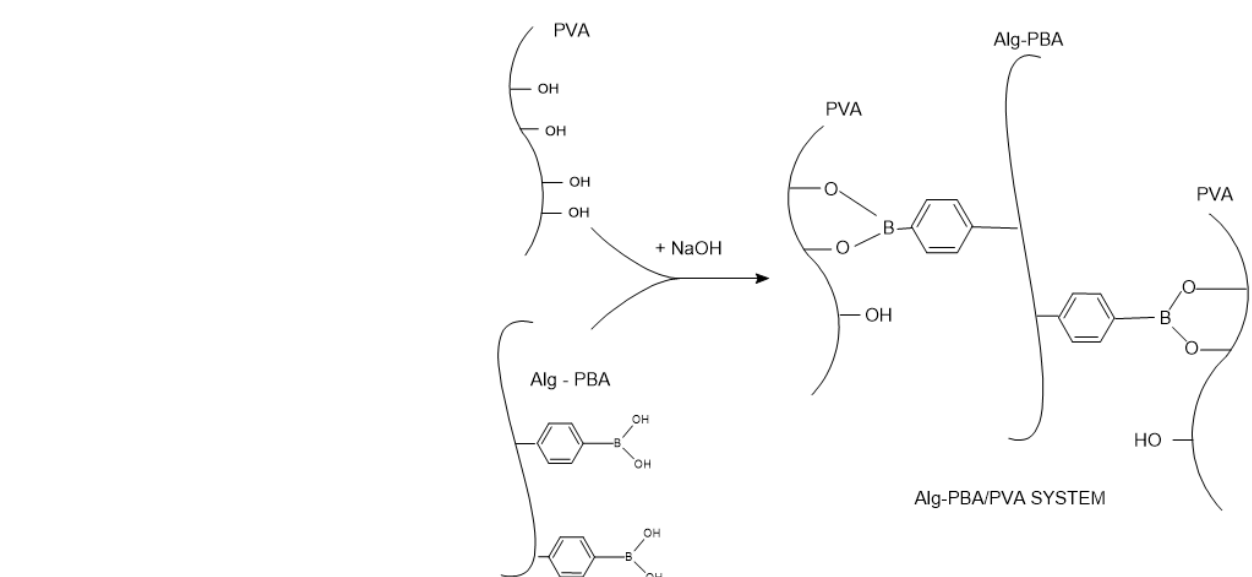


Figure 3. Crosslinking mechanism of Alg-PBA/PVA hydrogel via boronate ester formation. Under basic conditions, boronic acid groups of Alg-PBA react with hydroxyl groups of PVA to form reversible boronate ester bonds.

Experimental Results

FTIR AND UV-VIS CONFIRMATION OF CONJUGATION

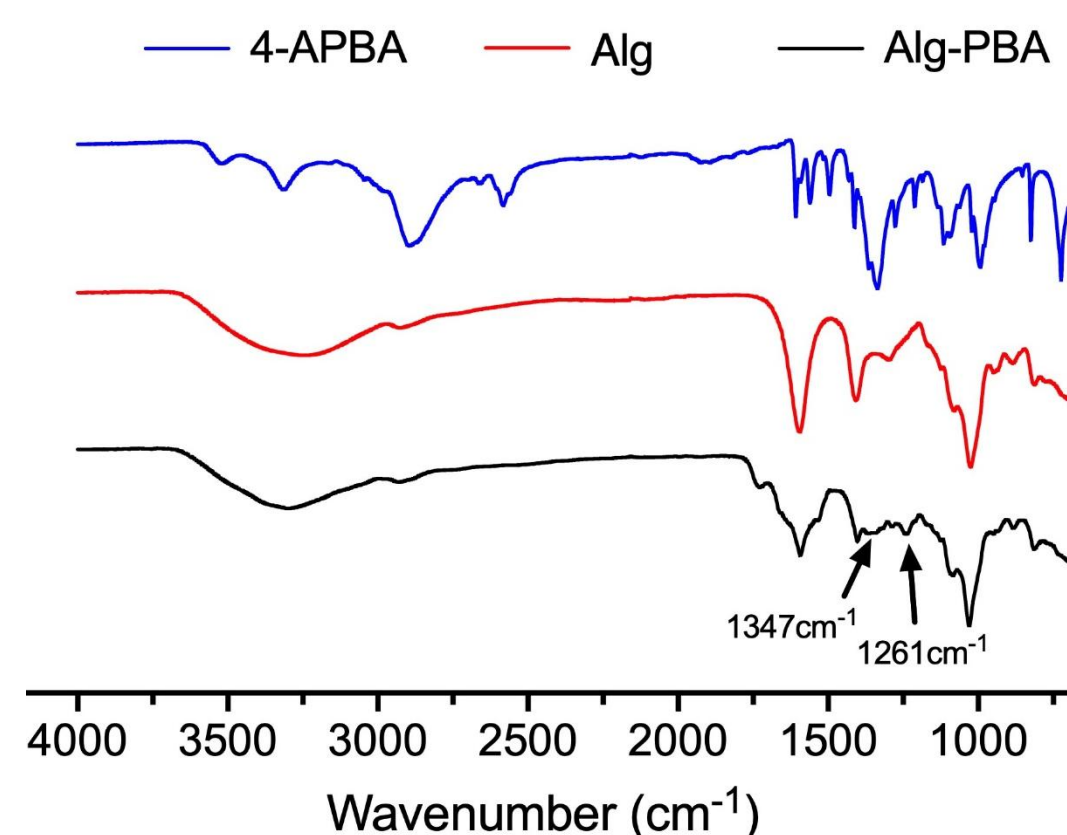


Figure 4. FTIR spectra of alginate (Alg), 4-APBA, and Alg-PBA. The appearance of characteristic peaks at 1347 cm^{-1} (B–O) and 1261 cm^{-1} (B–C) in the Alg-PBA spectrum confirms conjugation of PBA group onto the alginate backbone. UV-Vis spectroscopy further quantified the conjugation degree at **24.67%**..

FTIR analysis confirmed conjugation of 4-APBA to alginate through EDC/NHS coupling. The Alg-PBA spectrum shows characteristic boronic acid peaks at 1347 cm^{-1} (B–O) and 1261 cm^{-1} (B–C), as indicated in Fig. 4, demonstrating successful incorporation of boronic acid groups. UV-Vis spectroscopy further supported this result, showing a conjugation degree of 24.67%. This functionalization is critical for enabling boronate ester crosslinking with PVA, which drives hydrogel formation, self-healing behavior, and pH responsiveness.

pH-Responsive Color Change test:

Hydrogel samples (as seen in Fig. 1) containing phenol red were exposed to pH 6–12 PBS solutions. The gel shifted from yellow (pH 6–7) to orange/red (pH 9–12). Using known wound-pH ranges, this test supports the hydrogel's ability to indicate wound healing status when placed on skin.

- Yellow → healing/healthy
- Orange/Red → alkaline, chronic, or infected

INJECTABILITY

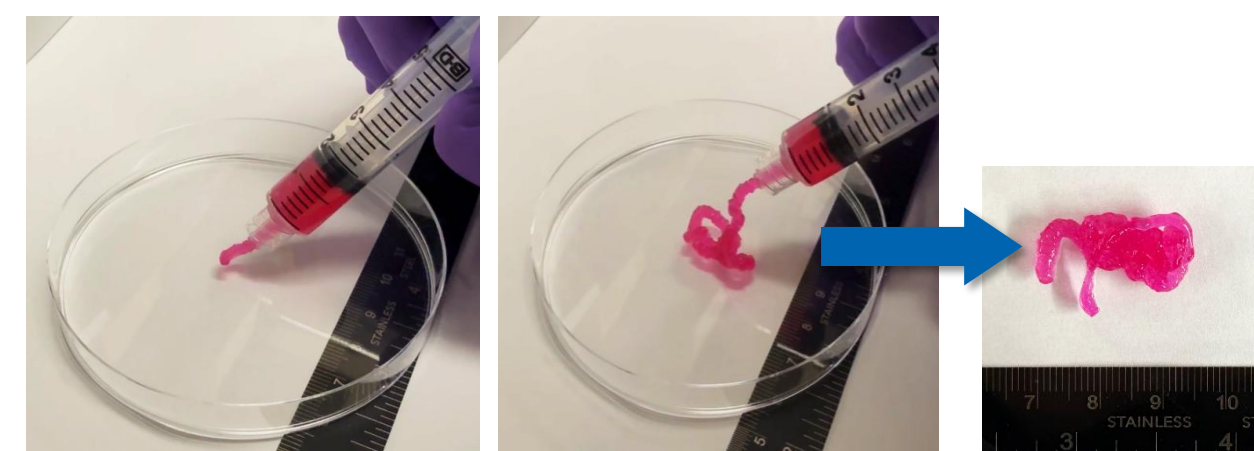


Figure 4. Injectability test The hydrogel was smoothly extruded through a standard syringe setup with no clogging, confirming clinically feasible injectability. The images display the hydrogel at the initial, midpoint, and final form via injection.

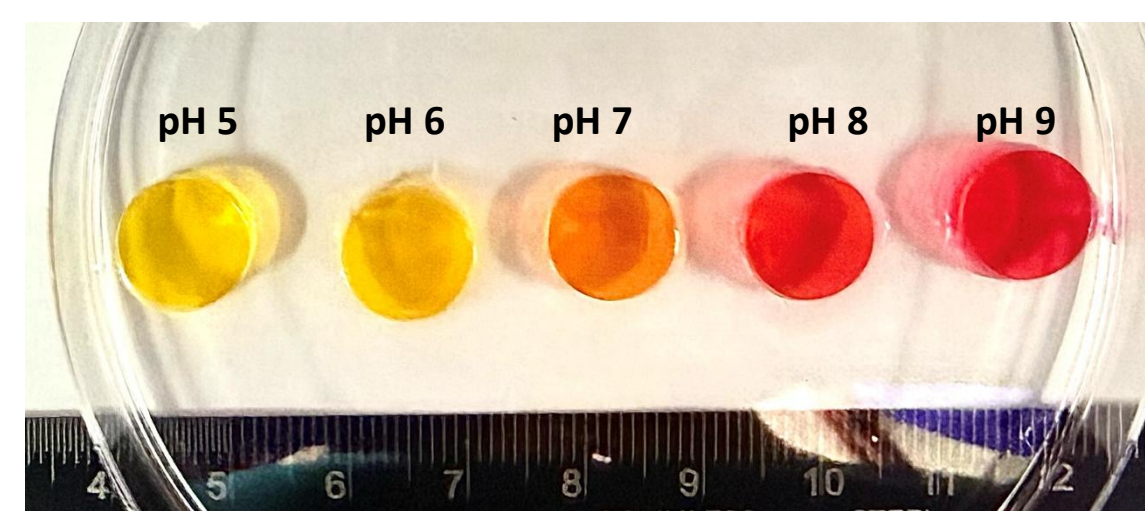


Figure 5. pH Color Change The image shows the pH-responsive color change of the hydrogel containing phenol red. The pH ranges from 5, 6, 7, 8 and 9 going left to right.

SELF HEALING TESTS

The hydrogel was cut and rejoined to assess dynamic recovery. Segments re-adhered, and the healed sample tolerated gentle stretching and compression, confirming restoration of network integrity and a dynamic, reversible hydrogel.

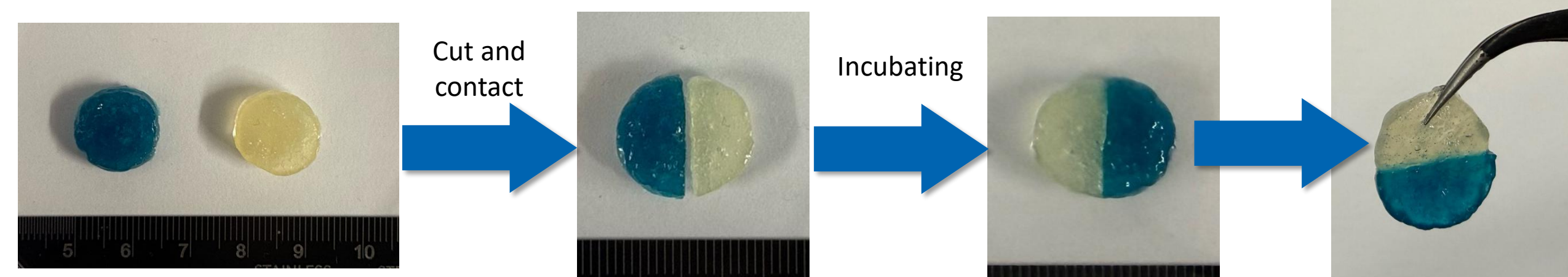


Figure 6. Self-Healing Behavior of the Hydrogel The self-healing behavior was evaluated using food dye as a visual indicator. After being cut and reassembled, the hydrogel was allowed to heal overnight. Successful hydrogel recovery was confirmed by the restored structural integrity, along with the diffusion of dye across the interface.

COMPRESSION TEST

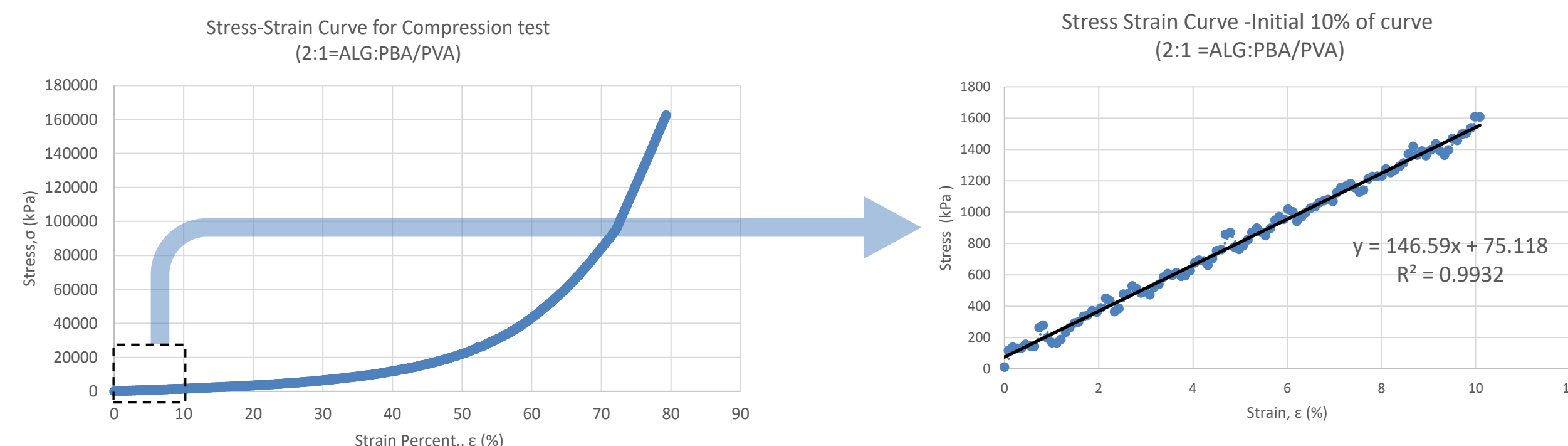


Figure 7 Stress–strain curves obtained from compression tests. The full curves are shown on the left, and the initial 10% strain region used for Young's modulus calculation is shown on the right. The average Young's modulus (E) of the 2:1 PBS ALG:PBA/PVA samples was 107.9 kPa (n = 2).

A mechanical testing machine was used to compress the hydrogel, and analyzed via the Stress-Strain curves (as seen in Fig. 7), yielding an average Young's modulus of 107.9785 kPa. The gel (as seen in Fig. 8) did not fracture and only slightly shrank and compressed, indicating a viscous, durable network. Because no maximum tensile strength was reached, rheology testing is needed to further characterize viscoelastic behavior. Additionally, the samples did not reach a failure point during testing, suggesting that the hydrogel can withstand increasing strain without breaking.

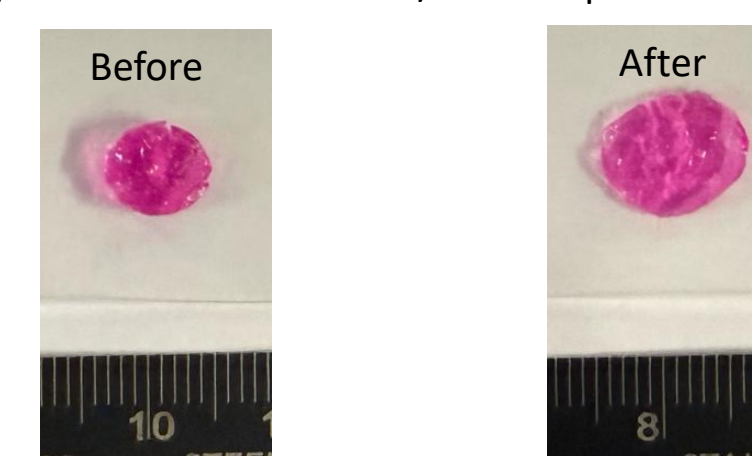


Figure 8 Compressed Hydrogel The image showed the self-healing hydrogel before (left) and after (right) compression test. This hydrogel was incubated for gelation at 37° for 1-hour prior to the test. Following the compression test of 90% deformation of the hydrogel, the final hydrogel was flattened.

Discussion

- Successful functionalization of alginate with 4-APBA was confirmed through FTIR and UV-Vis, enabling formation of a dynamic crosslinked network
- Boronate ester interactions with PVA allowed for **reversible and self-healing hydrogel behavior**
- Hydrogel maintained structural integrity during **injectability testing**, supporting use in irregular wound geometries
- Clear and reversible **pH-dependent color change** (phenol red) was observed within physiologically relevant ranges
- Swelling behavior indicated a **porous network**, supporting fluid absorption and potential drug loading
- Mechanical testing showed an average **Young's modulus of ~107.9 kPa**, soft and compliant material, easily deformable under low strength and able to conform to irregular surfaces
- Lack of fracture during testing supports **dynamic bonding and self-healing capability**, the hydrogel is soft and is malleable

Conclusions

- ✓ Developed a **pH-responsive, injectable, and self-healing hydrogel** using Alg-PBA, PVA, and phenol red dye.
- ✓ Dynamic boronate ester bonds enabled **reversible crosslinking and structural adaptability**
- ✓ Demonstrated strong **mechanical performance, injectability, and environmental responsiveness**
- ✓ Phenol red provided **real-time visual indication of wound pH and healing state**
- ✓ System shows strong potential as both a **protective dressing and diagnostic wound monitoring tool**

Future Works

Future work will focus on improving the hydrogel's mechanical performance while maintaining its injectability and responsiveness.

- 1.) Incorporation of **Ca²⁺ ions** will be explored to enhance gelation, in which calcium ions bridge between guluronic acid regions of alginate chains to form ionic crosslinks. This introduces an additional network that may improve structural stability and tunability.
- 2.) Further investigation into **tissue adhesion mechanisms** will be conducted to better understand and enhance the hydrogel's ability to interact with biological surfaces.
- 3.) **Swelling studies** will be performed to better quantify fluid uptake and drug loading potential under physiological conditions.
- 4.) **Rheological testing** will also be implemented to characterize viscoelastic behavior, self-healing kinetics.

Ultimately, these improvements will support the development of a more robust hydrogel system for applications in wound healing, surgical monitoring, and injectable therapeutic delivery.

References and Acknowledgements

- [1] Ding X, Li G, Zhang P, Jin E, Xiao C, Chen X. Injectable self-healing hydrogel wound dressing with cysteine-specific on-demand dissolution property based on tandem dynamic covalent bonds. *Advanced Functional Materials*. 2021;31(9):2011230.
- [2] Rembe JD, Witte M, Ertas N, Dissemmond J, Garabet W, Hovhannisyan M, Beckamp K, Schelzig H, Wagenhäuser MU, Stuermer EK. pH profiling reveals progressive wound acidification during healing and higher pH in chronic non-healing wounds: a prospective, multicenter cohort study. *Scientific Reports*. 2026;16:10522.

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