

Versatile Solid-State Medical Superglue Precursors of α -Lipoic Acid

Published as part of Journal of the American Chemical Society *special issue* "Nano-Biomaterials for Tissue Interactions and Therapeutics".

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Cite This: *J. Am. Chem. Soc.* 2025, 147, 13377–13384



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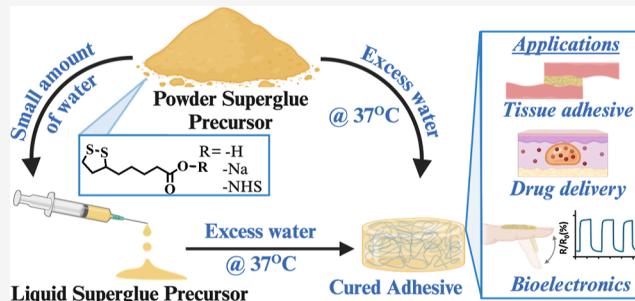
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ABSTRACT: α -Lipoic acid (α LA) is an attractive building block for medical adhesives. However, due to poor water solubility of α LA and high hydrophobicity of poly(α LA), elevated temperatures, organic solvents, or complex preparations are typically required to obtain and deliver α LA-based adhesives to biological tissue. Here, we report α LA-based powder and low-viscosity liquid superglues that polymerize and bond rapidly upon contact with wet tissue. A monomeric mixture of α LA, sodium lipoate, and an activated ester of lipoic acid was used to formulate the versatile adhesives. Stress-strain measurements of the wet adhesives confirmed the high flexibility of the adhesive. Moreover, a small molecule regenerative drug was successfully incorporated into and released from the adhesive without altering the physical and adhesive properties. In vitro and in vivo studies of the developed adhesives confirmed their cell and tissue compatibility, biodegradability, and potential for sustained drug delivery. Moreover, due to the inherent ionic nature of the adhesives, they demonstrated high electric conductivity and sensitivity to deformation, allowing for the development of a tissue-adherent strain sensor.



INTRODUCTION

Strong, fast-acting medical adhesives that adhere well to wet tissues and have features like high biocompatibility, degradability, and tissue-like flexibility are challenging traits to achieve in synthetic adhesives.^{1–4} Additionally, different surgical procedures and tissue topologies often demand adhesives in varying form factors to ensure optimal performance.^{5,6} Moreover, biodegradable tissue adhesives that can load and release active pharmaceutical agents in a controlled manner are particularly valuable for chronic wound management and regenerative medicine.^{7–10} Medical-grade cyanoacrylate superglues offer high-strength and rapid-curing as a result of polymerization initiated by the moisture and other nucleophilic functional groups present in tissues. However, their application is mainly limited to external wound closure due to their cytotoxicity, rigidity, and inability to degrade.^{11–13} Solid form factors of superglues (e.g., powders or films) would be attractive for on-contact mechanical bonding or sealing of tissues; however, solid-state medical superglues have not been reported.

Recently, polymers of α -lipoic acid (α LA, Figure 1A) have attracted significant attention as potential medical adhesives due to their high biocompatibility, biodegradability, adhesiveness, and flexibility.^{14–17} The R-isomer of α LA is an essential cofactor for aerobic metabolism in animals; however, a racemic mixture of α LA is considered safe and has been widely used as

a nutritional supplement. Practical utilization of poly(α LA) was obstructed over decades due to spontaneous depolymerization.^{18–21} Consequently, significant efforts have been devoted to stabilizing poly(α LA) either through copolymerization or chain end quenching additives.^{22–28} Additives like polyphenols, biopolymers, metal ions, and salts were also exploited to obtain α LA-based polymers/gels for topical wound care.^{29–33} However, weak adhesive strength, slow curing time, rapid degradation, and complex preparations represent barriers to adoption in clinical settings.

Recently, we developed a versatile polymerization method for α LA that inhibits depolymerization through chain end stabilization with activated esters of α LA or other carbonyl electrophiles.³⁴ Moreover, we have shown that ethanolic or DMSO solutions of α LA and S1/S2 (Figure 1A) undergo rapid polymerization when they come in contact with water and form robust bonds when applied to wet tissue. However, prepolymerized poly(α LA) in solution or thin film form

Received: December 23, 2024

Revised: March 30, 2025

Accepted: April 1, 2025

Published: April 10, 2025



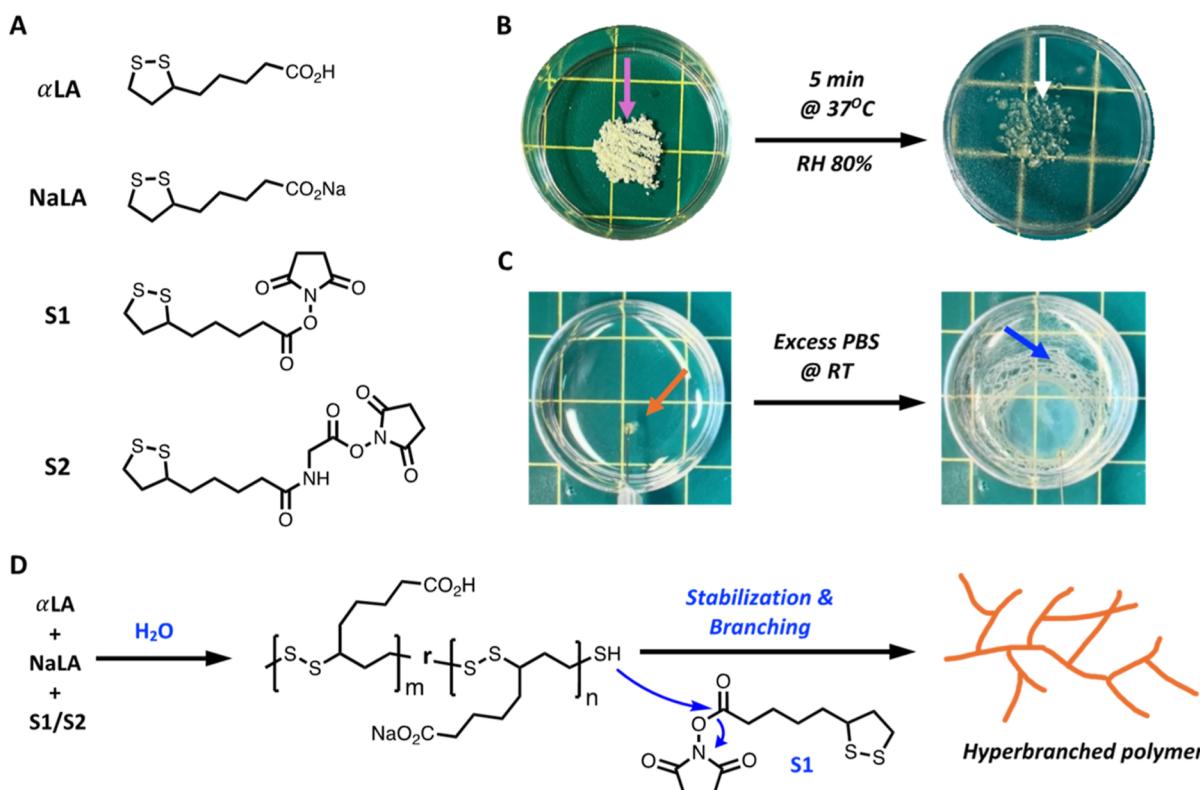


Figure 1. Monomer structures and general polymerization scheme. (A) Chemical structure of monomer and stabilizers. (B) Photographs of ***αLA-PS1*** before (left, purple arrow) and after (right, white arrow) exposure to 37 °C (RH90%) for 5 min. (C) Frame grabs of video ([Movie S2](#)) showing ***αLA-LS1*** before (left, orange arrow) and after (right, blue arrow) exposure to excess isotonic saline at room temperature. (D) General scheme of copolymerization and chain end stabilization.

showed significantly lowered adhesive strength against wet tissue,³⁴ which we surmised to be a result of higher hydrophobicity of poly(α LA) compared to monomeric/oligomeric α LA, thus reducing surface wettability and lowering adhesion strength. Therefore, we believe that the key to strong adhesion of poly(α LA) to tissue is to perform *in situ* polymerization of α LA. However, the poor water solubility of α LA requires the use of organic solvents to prepare monomer precursor solutions, limiting their application *in vivo*.

Here, we report bulk copolymerization of α LA and its derivatives under physiological conditions. The method enables the development of α LA-based powder (α LA-PS) and aqueous liquid superglue (α LA-LS) precursors, which polymerize in contact with wet surfaces at physiological conditions to form a robust adhesion with wet tissue. The method also allowed for the incorporation and sustained release of a small molecule regenerative drug without any significant change in physical and adhesive properties. Moreover, due to the inherent ionic nature of the monomeric composition, the adhesives show high conductivity suitable for use in sensing applications.

■ RESULTS AND DISCUSSION

Whereas solid α LA exhibits a melting temperature (T_m) of ~ 65 °C, Cui et al. reported an innovative deep eutectic system of α LA and the sodium salt of α -lipoic acid (NaLA, Figure 1A), which melts and polymerizes rapidly at temperatures < 50 °C for mixtures with a 2-fold or greater mass excess of α LA over NaLA.³⁵ Although the reduced thermal polymerization

temperature and wet adhesion afforded by eutectic mixtures is potentially attractive for topical wound closure, the obtained copolymers exhibited modest adhesive strength to tissue and degraded rapidly underwater,³⁵ possibly excluding their use when mechanical force transmission is required beyond a few days.

Inspired by this work, we anticipated that combining the eutectic property of the α LA and NaLA mixture with recently developed NHS-ester-modified α LA monomers would afford a powder superglue with higher strength, greater control over degradation rate and rapid water-induced isothermal polymerization.

Development of Powder Superglue (α LA-PS) Precursors. Differential scanning calorimetry (DSC) analysis of pure α LA and NaLA confirmed the expected T_m values of \sim 65 °C (Figure 2A) and >270 °C (T_m/T_d , Figure S1), respectively. To investigate the possibility of developing a bulk powder superglue-like adhesive, a variety of combinations of α LA, NaLA, and S1/S2 were prepared as intimate powder mixtures of the individual solids (α LA-PS1 and α LA-PS2, Table 1). Although the DSC analysis of the α LA-PS1 powder mixture shows that the melting point of the mixture drops to 45 °C, no significant macroscopic changes were observed initially (Figures 2A and S1).³⁵ However, when the powder was stored in the open air at room temperature (22 °C), it was noted to be hygroscopic, turning into a sticky gel after several hours. Moreover, when the powder mixture was stored at 37 °C in the open air, the powder-to-gel-like transition was observed within 30 min (Figure S2). Encouraged by this observation, we hypothesized that the transition from powder to gel can be

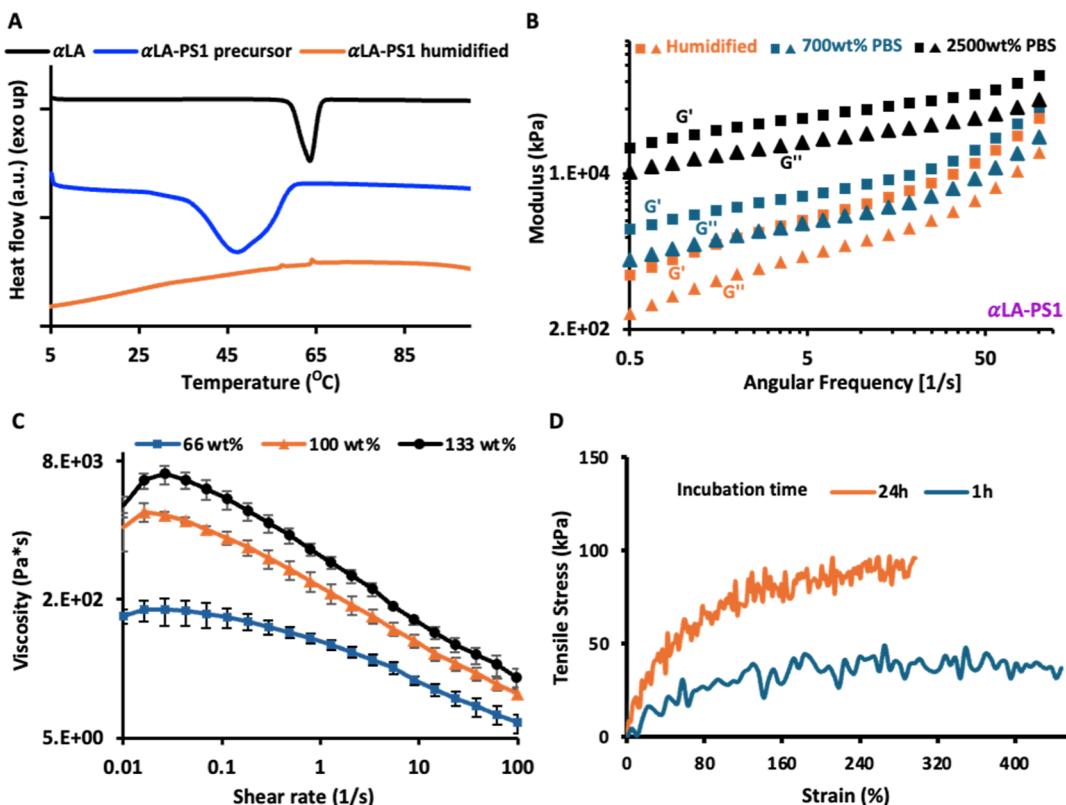


Figure 2. Thermal and mechanical properties of α LA-PS and α LA-LS. (A) DSC traces (first heating cycle) of α LA, α LA-PS1 precursor, and α LA-PS1 after exposure to 37 °C (RH 90%) for 5 min. (B) Rheological analysis of α LA-PS1 immediately after humidification and polymerization for 10 min at 37 °C with 700 and 2500 wt % isotonic PBS in a frequency sweep rheological experiment at a constant strain of 0.4% and 37 °C. (C) Water-dependent viscosity of α LA-LS1 at rt. All viscosity measurements were performed within 3 days after α LA-LS preparation. (D) Stress–strain curves of α LA-LS1 1 h and 24 h after incubation in excess isotonic saline at 37 °C.

Table 1. α LA Adhesive Systems^a

adhesive	form*	composition (Mol %)			
		α LA	NaLA	S1	S2
α LA-PS1	P	67	27		6
α LA-PS2	P	49	45		6
α LA-LS1	L	66	27	7	
α LA-LS2 [#]	L	66	27	7	

* P = powder; L = liquid; # contain 2 wt % NaDPCA with respect to the solid.

accelerated at higher humidity and physiological temperatures. To test our hypothesis, the α LA-PS1 mixture was heated at 37 °C and 90% relative humidity for 5 min (Figure 1B). Interestingly, a complete powder-to-gel transition was observed, and a DSC investigation also confirmed the complete disappearance of the monomeric crystalline phase (Figures 2A and S3). A similar powder-to-gel transition was also observed at a lower α LA/NaLA ratio (α LA-PS2, Table 1 and Figure S3) and in the powder mixtures without S2, at 37 °C and 90% relative humidity. Rheological analysis of the gel obtained from powder α LA-PS1 revealed higher storage modulus than loss modulus, indicating elastic solid-like nature of the gel (Figure 2B). To our surprise, when excess aqueous saline was added to the gel, an instant transition to a yellow elastic solid was observed, with a significantly higher modulus than the corresponding gel, indicating a rapid water-induced extension of polymerization (Figures 2B, S4 and Movie S1). Another set of rheological analyses confirmed a direct

correlation between the modulus and the amount of saline solution added to the gel, highlighting the dependence of the degree of polymerization on water content (Figure S18). We believe that due to the conjugate acid–base nature of α LA + NaLA, the hydroscopic monomeric powder mixture absorbs water, which induces self-assembly, where the local concentration of the cyclic backbone increases and accelerates self-catalyzed polymerization (Figure 1D).³⁴ With increasing water content, the packing density in assemblies rises, consequently increasing chain extension, as reflected in modulus. We surmise that water-induced polymerization of the powder monomer mixture is aided by the suppressed melting temperature of the mixture (eutectic); thus, we refer to this as a ‘hydroeutectic’ polymerization effect.

Development of Aqueous Liquid Superglue (α LA-LS). Evidence of shear-thinning properties of the gel (Figure S5) suggested the possibility of a flowable shear-thinning liquid superglue (α LA-LS) that would polymerize with further addition of water. To test this hypothesis, a mixture of α LA, NaLA, and S1 at a mol ratio of 66:27:7 (α LA-LS1, Table 1) was dissolved in ethanol containing different amounts of water. S1 was used due to its lower electrophilicity and higher stability than S2. Interestingly, upon evaporation of ethanol, a low-viscosity injectable liquid was obtained, retaining water and only 24 wt % ethanol, and no apparent change in viscosity was observed over several months of storage in the freezer (Figure S19–S22). However, α LA-LS1 underwent rapid solidification when exposed to excess water (Figure 1C and Movie S2). The rheological analyses of the prepared α LA-LS1

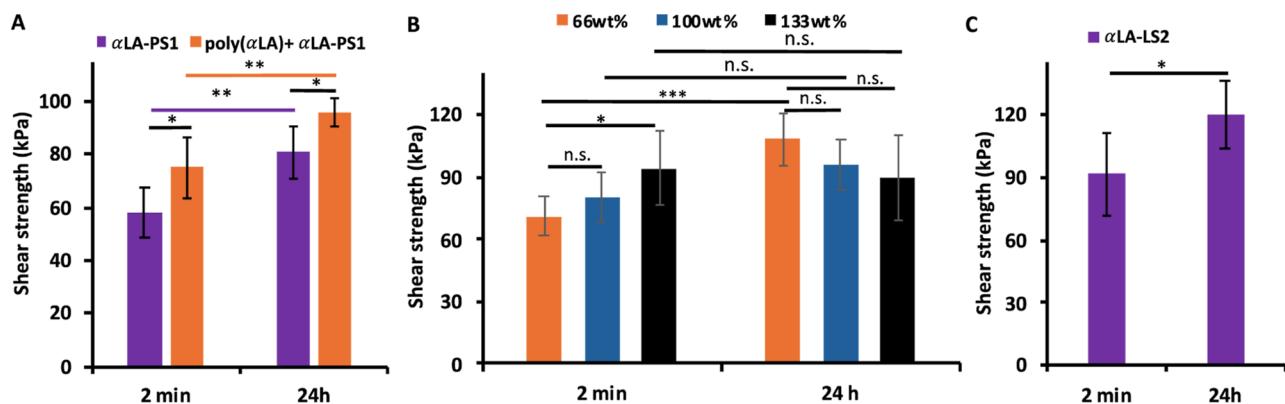


Figure 3. Lap Shear strength of α LA polymers against wet bovine pericardium fixed onto polycarbonate plate. (A) Lap shear strength comparison of α LA-PS1 and α LA-PS1-coated poly(α LA) thin film 2 min and 24h after incubation in 1x PBS at 37 °C. (B) Lap shear strength comparison of α LA-LS1 containing different amounts of water after 2 min and 24h incubation in 1x PBS at 37 °C. (C) Lap shear strength of α LA-LS2 containing 2 wt % NaDPCA and 100 wt % water after 2 min and 24h incubation in 1x PBS at 37 °C. N = 5. p-Value was calculated with Student's t-test in Microsoft Excel (2 array, 2 tails, 2 type). n.s., $p > 0.05$; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$.

confirmed the shear thinning behavior, with increasing viscosity as the water-to-monomer ratio increased (Figure 2C). We believe higher water concentration in the α LA-LS1 increases the degree of polymerization, leading to higher viscosity (Figure S18). The frequency sweep analysis of the liquid precursor further confirmed the polymeric nature of the mixture, where the modulus increases significantly after exposure to excess water (Figure S6). Stress-strain measurements of thin films prepared by in situ aqueous polymerization of α LA-LS1 confirmed the high flexibility of the adhesive even after 24h incubation in isotonic saline solution at 37 °C (Figures 2D and S7). Moreover, increased tensile strength and reduction in strain at break with longer exposure to the isotonic saline solution indicates continuous maturation of the polymer network over time (Figure 2D).

Investigation of Adhesive Strength. To investigate the adhesive properties of the developed α LA-PS and α LA-LS, lap shear measurements were performed against wet bovine pericardium. The powder or liquid precursor was applied to the wet bovine pericardium, and lap joints were formed with another piece of tissue followed by incubated in an isotonic saline solution at 37 °C. The lap shear strength of α LA-PS1 was 58 ± 9 kPa and 80 ± 9 kPa, 2 min and 24 h after incubation, respectively (Figure 3A). The increase in adhesion strength after 24 h incubation is consistent with stress-strain measurements that showed maturation of the polymer network at a longer incubation times. Analyses of failure mode visually with the aid of *N*-bromosuccinimide to stain the adhesive, indicated a cohesive mode of failure in both cases (Figure S8). Another set of lap shear measurements of α LA-PS2 showed a shear strength of 41 ± 11 kPa after 2 min and 71 ± 17 kPa after 24 h incubation (Figure S9). The lower shear strength of α LA-PS2 than α LA-PS1 is consistent with previous observations^{34,35} and is attributed to the reduced number of noncovalent interactions with the tissue surface with increasing amount of NaLA in the adhesive.

A thin film of poly(α LA) prepared from α LA and S1 (mol ratio 93:7) shows poor adhesive strength against wet tissue due to high hydrophobicity and poor surface wettability (33 ± 8 kPa, after 2 min incubation, Figure S9). We anticipated that decorating the surface of poly(α LA) thin film with α LA-PS1 powder precursor could offer a promising off-the-shelf adhesive patch that would adhere the patch to a wet tissue through the

hydroeutectic polymerization mechanism described above. To test this hypothesis, one face of a thin poly(α LA) film was coated with a thin layer of α LA-PS1 powder (15 mg/cm²; see Supporting Information). Interestingly, lap shear measurements of the α LA-PS1-coated poly(α LA) thin film against wet bovine pericardium 2 min after incubation was 74 ± 11 kPa and increased to 96 ± 5 kPa after 24h incubation (Figure 3A), confirming the viability of the developed strategy and further expanding the versatility of the poly(α LA) adhesive system.

Next, the adhesive strength of α LA-LS1 prepared with varying water content was investigated. A roughly linear trend between lap shear strength and water content was observed after 2 min incubation in PBS at 37 °C (Figures 3B and S10, 66 wt %: 71 ± 10 kPa; 100 wt %: 80 ± 12 kPa; 133 wt %: 94 ± 18 kPa). Interestingly, after 24h incubation, an inverse trend between lap shear strength and water content was observed (66 wt %: 108 ± 13 kPa; 100 wt %: 96 ± 12 kPa; 133 wt %: 89 ± 20 kPa). We believe at a shorter incubation time, the lap shear strength of α LA-LS1 is limited by the cohesive strength of the polymer network due to a lower degree of polymerization. In contrast, at longer incubation times when the polymer network matures, the interfacial adhesion strength of α LA-LS1 determines the overall lap shear strength. As the degree of polymerization and cohesive strength in the α LA-LS1 precursor increases with the increasing water content, the lap shear strength of α LA-LS1 shows a linear trend with water content at a short incubation time. However, at a longer incubation time, when the cohesive strength of the adhesives reaches an equilibrium, the opposite trend in lap shear strength reflects the lower surface wettability of the α LA-LS1 precursor with the increasing water content due to increasing hydrophobicity.

The presence of stabilizer S1 or S2 in these systems is essential for optimal adhesive performance. For example, lap shear measurements of S2-free α LA-PS1 and α LA-PS2 showed significantly lower adhesion to tissue (α LA-PS1 30 ± 8 kPa; α LA-PS2 22 ± 8 kPa) after 24 h incubation (Figure S9). Furthermore, removing S1 from the α LA-LS1 formulation resulted in significant reduction of shear strength (43 ± 15 kPa) after 24h of incubation (Figure S10). Together, these observations demonstrate the importance of the chain end stabilizer in obtaining stable adhesive.

In Vitro and In Vivo Characterization of the Adhesives. We assessed the biological performance of α LA-PS1 and α LA-LS with a preliminary set of in vitro and in vivo experiments. Poly(α LA) is known to undergo GSH-mediated biodegradation; therefore, in vitro degradation of polymerized α LA-LS1 was investigated in an isotonic saline solution containing 0.1 mM GSH (see Supporting Information).^{36,37} As expected, gradual degradation of the polymer was observed over the course of 15 days (Figure 4A). Moreover, in vitro

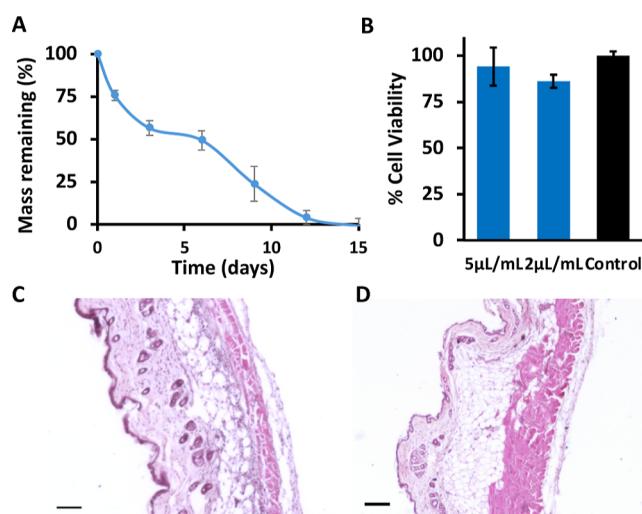


Figure 4. In vitro and in vivo biological performance of α LA-PS and α LA-LS. (A) In vitro degradation profile of α LA-LS1. (B) Viability of murine fibroblasts (NIH 3T3) after 24h exposure to α LA-LS1. (C,D) Representative hematoxylin and eosin (H&E)—stained histological images of the implantation site (C) and healthy control (D) (skin). No signs of acute inflammation or structural anomalies were observed at the implantation site. Scale bars 100 μ m.

coculture of NIH 3T3 mouse fibroblast cells in the presence of in situ-polymerized α LA-PS1/ α LA-LS1 for 24h showed cell viability similar to the control of growth media (Figures 4B and S11).

The in vivo biocompatibility of the developed adhesives was also investigated through subcutaneous implantation of α LA-LS1 at the back of mice ($n = 4$). No visual signs of behavioral changes or inflammation at the injected site were observed during the course of the study. Moreover, histological analyses of the skin at the application site and other organs 3 days after implantation showed no sign of acute inflammation or adverse reactions from the adhesive, thereby establishing the favorable biocompatibility of the developed adhesives (Figures 4C,D, S12 and S23).

Drug Delivery Potential of the Adhesives. The α LA superglue can be potentially used as a drug delivery system by entrapment of small molecule drugs capable of enhancing tissue regeneration.³⁸ We investigated this using the α LA-LS2 formulation combined with the 4-prolylhydroxylase inhibitor 1,4-dihydrophenanthrolin-4-one-3-carboxylate (DPCA), chosen for its effect on enhancing tissue regeneration.^{39–41} Interestingly, when a α LA-LS2 liquid precursor was prepared with the sodium salt of DPCA (NaDPCA), a translucent viscous liquid was obtained (Figure S13), indicating the presence of particles in the mixture. In a control experiment performed by adding NaDPCA to a diluted aqueous ethanolic solution of α LA and NaLA, DLS analysis indicated the

formation of nanoparticles (Z_{avg} 137 \pm 8 nm; Pdi 0.240 \pm 0.017, Figure S14). We believe due to the higher pK_a of the aromatic carboxylic acid compared to aliphatic carboxylic acid, NaDPCA becomes water-insoluble as a result of protonation by α -lipoic acid, leading to in situ nanoprecipitation of DPCA. Rheological analyses of α LA-LS2 confirmed the shear thinning property and only a slight difference in viscosities from the corresponding α LA-LS1 (Figure S15). Moreover, a rapid solidification was also observed when α LA-LS2 was added to excess water. The lap shear measurement of α LA-LS2 showed a lap shear strength of 91 \pm 19 and 119 \pm 12 kPa after 2 min and 24 h incubation, respectively, confirming the excellent compatibility of α LA-LS2 to incorporate drugs while being an effective tissue adhesive (Figure 3C). The drug release profile was also investigated from in situ-polymerized α LA-LS2. A steady release of the drug was observed over time, reaching 50% release in 100 h (Figure S16). Moreover, in vitro coculture of mouse embryonic fibroblast cells and α LA-LS2 shows 4-prolyl hydroxylase inhibition and successful HIF-1 α stabilization with an appreciable increase in intensity between 8 and 24 h, confirming the sustained release of bioactive NaDPCA from the adhesive (Figure S24).

Conductive Properties of the Adhesives. There is a growing unmet need for biodegradable, flexible, conductive tissue adhesives for implantable, wearable devices, and bioelectronics for health monitoring.^{42,43} The most commonly used conductive materials for wearable devices are often obtained by mixing the polymer matrix or hydrogel with toxic conductive fillers or salts, which restricts their in vivo applications.⁴⁴ Based on the inherent conjugate acid–base nature of the monomer composition, we anticipated that the developed adhesive would be conductive in nature. A conductive biomaterial with robust tissue adhesion and high stretchability can reduce interfacial resistance and delamination critical to the reliable performance of bioelectronic and wearable devices.^{42,45} Therefore, we investigated the electrical conductivity of an in situ-polymerized α LA-LS1 by measuring the current (I)–voltage (V) characteristics of a circuit that included the adhesive, a 9 V battery, and a light-emitting diode (LED) (Figure 5). Interestingly, conductivities of 1.74 \pm 0.16 and 1.65 \pm 0.08 mS/cm were observed after incubation in isotonic saline solution for 30 min and 4 h, respectively (Figure 5A). The nonlinear nature of the I – V curve indicates that the conductivity is ionic in nature. The electrical conductivity of our α LA superglue adhesive was strong enough to power an LED when connected to a standard 9 V commercial battery (Figure 5B and Movie S3), demonstrating its potential to be integrated into standard electronic devices. Additionally, relative changes in resistance during repeated stretch and relaxation cycles (Figure 5C, Movies S4 and S5) indicate that the developed adhesive can be used as a strain sensor.

To demonstrate the capabilities of the developed adhesives for practical use in human–machine interfaces, we conformably attached the adhesive-based device to the surface of a gloved index finger (as shown in the insets of Figure 5D). Upon repeated bending of the finger, a synchronous change in relative resistance was clearly observed (Figure 5D). The electromechanical response of the adhesive device permitted the discrimination of different angles of finger bending (such as 60° and 90°), paving the way for its potential use in bioelectronic, wearable, and soft robotic applications.

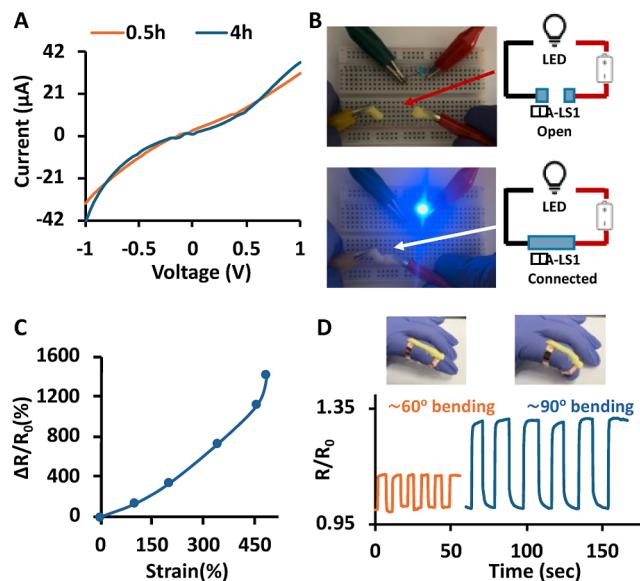


Figure 5. Conductive properties of α -LA-LS1. (A) Current–voltage characteristics of α -LA-LS1 measured after incubation periods of 0.5 and 4 h without any applied strain. (B) Electrical conductivity demonstration by powering an LED: the upper panel shows the circuit without the material being in contact, while the lower panel depicts glowing LEDs upon touching the adhesive. (C) Relative change of resistances under stretching strains ranging from 0% to 48%. (D) Time-dependent relative resistance change of the adhesive during device bending, conformably attached to finger gloves, at bending angles of 60° and 90°.

CONCLUSIONS

In summary, we have developed α -lipoic acid-based powder and shear-thinning liquid superglue precursors that cure instantly upon exposure to excess water or wet tissue. Rapid curing was suggested to be a result of a so-called “hydro-eutectic” effect, whereby the hygroscopic and eutectic nature of the powder monomer mixture combined to drive rapid hydration and polymerization when exposed to water. Lap shear measurement of the developed adhesives against wet bovine pericardium showed high shear strength, whereas *in vitro* and *in vivo* experiments demonstrated the adhesives to be biodegradable and biocompatible. Incorporation of a small molecule regenerative drug into the adhesive was easily accomplished as an additive in the monomer mixture and did not produce significant changes in adhesive physical properties and performance. Finally, the developed adhesives are inherently conductive and deformation-sensitive, suggesting potential use as a wearable or implantable strain sensor.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.4c18448>.

Rapid solidification of the gel (**MP4**)

Instant polymerization at the air–water interface (**MP4**)

Powering a light-emitting diode with a 9V commercial battery when the circuit is completed with two pieces of α -LA-LS1 adhesive 30 min after incubation in 1x PBS at rt (**MP4**)

Dependence of the intensity of a light-emitting diode on the strain% of α -LA-LS1 adhesive (30 min after

incubation in 1x PBS at rt) connected in a circuit with a 9V commercial battery (**MP4**)

Changes in resistance in a multimeter when α -LA-LS1 (30 min after incubation in 1x PBS at rt) was stretched (**MP4**)

Rapid polymerization of α -LA-LS2 upon exposure to excess isotonic saline at room temperature (**MP4**)

Experimental procedures, properties, characterization of developed materials, and description of movies (**PDF**)

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Funding

We thank the National Institutes of Health (grant RO1DE021104) and the Life Sciences Entrepreneurship Center at UC Berkeley for partial support of this work. S.P. thanks the Swiss National Science Foundation (SNSF) postdoc mobility fellowship PS00PN_202898 for providing support. S.K.G would like to acknowledge the Fulbright-Nehru Postdoctoral Research Fellowship (Grant Number: 2969/FNPDR/2023).

Notes

The authors declare the following competing financial interest(s): S.P., and P.B.M. have a financial interest in AsparaGlue Inc., a company that is commercializing technology reported in this paper.

ACKNOWLEDGMENTS

We thank J. Shin for reviewing histological images. We also thank K. Prakash, a member of the Healy laboratory at the University of California, Berkeley, for assisting with the rheometer. We acknowledge the NMR facility at the College of Chemistry NMR facility at the University of California, Berkeley.

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