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2021

Singh, M., Solic, I. & Steele, T. W. J. (2021). Hydrophobic bioadhesive composites for human motion detection. ACS Macro Letters, 10(11), 1353-1358. https://dx.doi.org/10.1021/acsmacrolett.1c00559

https://hdl.handle.net/10356/158570

https://doi.org/10.1021/acsmacrolett.1c00559

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Hydrophobic bioadhesive composites for human motion detection

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Abstract

Conductive hydrogels are rapidly rising as sensing materials for bioelectronics applications but lack mechanical and adhesion strength due to their excess water content. We propose a diazirine-grafted polycaprolactone adhesive (aka CaproGlu)/carbon nanotubes (CNTs) composite that can provide wet adhesion and strong mechanical properties at the tissue-machine interface. The introduced CNTs not only reinforced the CaproGlu but also formed electrically conducting pathways. The CaproGlu composites exhibited conductivity of 0.1 S m^{-1} and charge storage capacity of 5 µC cm^{-2}. The resulting composites are biocompatible and can be used as strain sensors to detect mechanical deformations.

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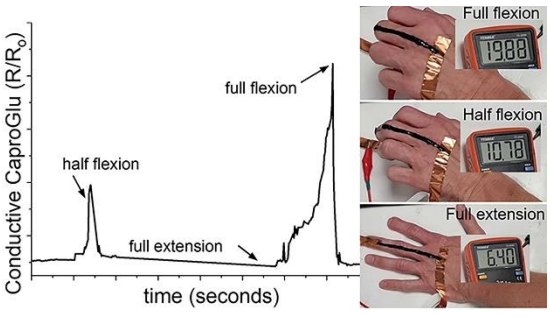

Introduction

Conductive hydrogels provide impressive biocompatibility and conformability for various biomedical applications such as biosensing, implant interfacing, and wearable electronics[1-2]. These applications require the interfacing biomaterials to be stretchable and easy to adhere to highly complex and curvilinear tissues (e.g., skin, heart, etc.)[3]. Fragile and week mechanical/ adhesion properties of hydrogels constitute an obstacle to their long-term applicability. Moreover, because of their hydrophilic nature, hydrogels can potentially swell excessively, and the increased water content can further compromise their mechanical properties[1, 4]. Recent attempts of toughening the hydrogels involved the incorporation of conductive fillers (e.g., silver, or gold nanowires)[4]. These fillers improved their mechanical and electrical properties but showed negligible improvement in their adhesive characteristics. As a result, hydrogels are unable to form stable interconnect patterns in hydrated conditions and require complicated fixation methods, such as perfluoropolyether (PFPE), for their fabrication into electrodes[5]. The development of interface materials that can adhere to soft tissues, mimic tissue mechanical properties, has electrical conductivity, and cyclic flexibility to accommodate repetitive body movements are needed for bioelectronic and sensing applications.

CaproGlu is a novel synthetic bioadhesive that transitions from liquid to a viscoelastic bio rubber upon application of ultraviolet (UV) light dose[6]. In CaproGlu, a photocurable crosslinker (aryl-diazirine) is grafted onto the surface of polycaprolactone (PCLT) polymer. Diazirine is an initiator-free covalent crosslinker that is relatively stable under ambient conditions but can be activated via voltage, heat, or UV[7-13]. In a more recent study, diazirine-based materials have also been shown to crosslink under visible light (445 nm)[14]. However, activation at 445 nm only occurs in presence of a catalyst and is reported to be stable in absence of one. Diazirine grafted PCLT (aka CaproGlu) allows fine-tuning of mechanical and

adhesion properties via carbene insertion chemistry. CaproGlu is hydrophobic, exhibits strong wet adhesion, withstands gamma irradiation sterilization, and is biocompatible[6, 15]. However, endowing the CaproGlu with good conductivity while maintaining mechanical and adhesion strength is still challenging. Herein, carbon nanotubes (CNTs) are introduced into CaproGlu at varying weight percentages following the percolation theory, forming CaproGlu composites. The CNTs are hypothesized to provide a three-dimensional electron transfer network throughout the non-conductive CaproGlu matrix. CNTs are chosen because of their high electrical conductivity, high charge injection ability, and low mass density[16]. Diazirines have been reported in the literature to functionalize CNTs for sensing and coating applications[17-18]. Owing to the hydrophobic interactions between CaproGlu and CNTs, these CaproGlu composites are anticipated to provide better dispersion of CNTs than those in water. This work presents preliminary data on the influence of CNT additives on the mechanical, adhesion, and electrical properties of CaproGlu. The CaproGlu composites are also tested for strain sensing capabilities and successfully exhibited the potential for human motion detection.

Experimental Section

Preparation of CaproGlu composites

CaproGlu bioadhesives with ~50% diazirine conjugation were synthesized as per the method published previously[6] and detailed synthesis steps are reported in the supplementary information. The NC7000™ multi-walled carbon nanotubes (CNT) were purchased from NANOCYL® (Belgium) in powder form. The technical details of the CNTs, as provided by the supplier, are also available in the supplementary information. Different weight percentages of 0.1-3% of multi-walled carbon nanotubes (CNT) additives were physically mixed into the CaproGlu. The resulting composites with mixed CNTs and CaproGlu are

referred to as 'CaproGlu composites' throughout this manuscript. The composites were UV-cured with an intensity of 250 mW cm^{-2} for 60 seconds to obtain the viscoelastic films.

Measurement of conductivity

A two-point probe setup was used for the measurement of the resistance of the CaproGlu composites. A concentric ring geometry was used, and a constant voltage of 1 V was supplied using the Keithley 2450 Sourcemeter and the current was recorded. A voltage of 1V is chosen to avoid the electrochemical activation (~1.5V) of diazirine[19]. The recorded current was then used to calculate the resistance as per Ohm's law. The relationship between surface resistivity (ρ) and the surface resistance (R) for a concentric ring probe geometry was calculated by ASTM D257-14 method, $\rho = R \times \frac{2\pi}{\ln\left(\frac{R2}{R1}\right)}$ where, R1 is the outer radius (1.5 mm) of the center electrode, and R2 is the inner radius (2 mm) of the outer ring electrode. Since the composite films are thin (~0.5 mm), then the volume resistivity is assumed equal to the surface resistivity multiplied by the thickness.

Characterization of mechanical properties

A rheometer MCR 102 (Anton Paar) was used to measure the real-time oscillatory rheological properties and tack adhesion. UV curing @ 365 nm was performed at an intensity of 250 mW cm^{-2}. The following rheological parameters were used — frequency: 1 Hz, Shear strain: 1%, gap: 0.2 mm, Probe PP10 (stainless steel). For the tack adhesion test, the samples were pre-sheared for 1 s at a shear rate of 1 1/s, and then the probe was moved up at a velocity of 50 μm/s.

Electrochemical characterization

Electrochemical characterizations were performed with a three-electrode configuration using a Potentiostat (Metrohm Autolab, The Netherlands) with a built-in frequency-response

analyzer. For impedance measurements, a voltage of 10 mV (RMS) was used, and the complex impedance was measured using a sinusoidal input voltage over a range of frequencies from 10^5 to 0.1 Hz. For cyclic voltammetry (CV), CaproGlu composites were coated on the working electrode of area 0.071 cm^2. CV measurements were conducted at a scan rate of 100 mV s^{-1} in a potential window of -0.6 to 0.8 V vs. Ag/AgCl reference electrode in phosphate-buffered saline (PBS) solution.

Results and Discussion

Scope and study design

CaproGlu has previously been reported to adhere to wet tissues with on-demand covalent crosslinking[6]. The hydrophobic nature and tissue-mimicking properties of CaproGlu make it a strong candidate for human-machine interfacing and sensing applications, but CaproGlu lacks electrical conductivity. Herein, carbon nanotubes are physically mixed into CaproGlu bioadhesives at varying weight percentages of 0.1-3% as per the percolation theory (**Figure 1**). High dynamic viscosity (~7 Pa.s) of CaproGlu and hydrophobic interactions within the composite may also allow for fair dispersion of CNTs in the CaproGlu (**Figure S1** and **Figure S2**). Liquid CaproGlu composites turn into thin viscoelastic films by UV-curing via carbene-mediated insertion chemistry (**Figure 1B-1E**). We evaluate the mechanical, adhesive, and electrical structure-activity relationships at varying CNT concentrations via real-time UV rheology, tack test, and two-point probe method, respectively. The sensitivity of the CaproGlu composites against the detection of various mechanical deformations is also studied.

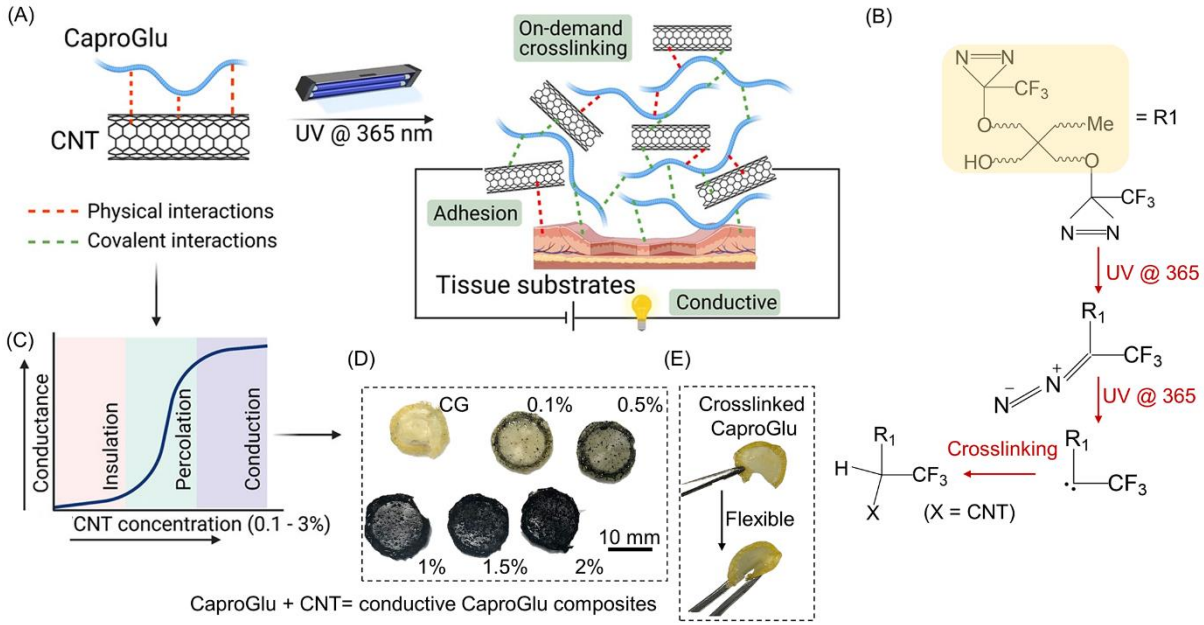

Figure 1: Overall Scheme and study design. A) Multi-walled carbon nanotubes (CNT) are physically mixed into CaproGlu (CG). CaproGlu can undergo a transition from liquid to viscoelastic solid (bio rubber) upon exposure to UV light. B) The crosslinking mechanism of CaproGlu under UV stimulation. A carbene intermediate performs as the active crosslinker and crosslinks with primary amines, sulfhydryls, carboxylic acid, and carboxyls groups available on the soft tissues. C) CaproGlu composites are prepared at a varying concentration of CNTs (0.1-3 wt %) as per the percolation theory. D) Thin viscoelastic films of the composites are obtained upon UV-mediated crosslinking. E) Crosslinked films are compliant and flexible.

Mechanical and adhesion properties are optimized at ~1.5% CNT

Real-time rheology assesses the viscoelastic properties of the CaproGlu composites upon UV exposure. The storage (G') and loss (G") moduli are recorded against time for control CG samples (i.e., pristine CaproGlu). Before UV application, G"> G' shows that CaproGlu is a viscous fluid (**Figure 2A**). Upon UV activation, G' starts to rise rapidly, demonstrating a transition to viscoelastic solid. The rheological parameters were recorded for all the

formulations of the composites, and storage modulus (G') was seen to be rapidly increasing with UV light activation (**Figure 2B**, **Figure S3**). Before UV onset, the storage modulus of the composites is higher than the control CG, which could suggest a uniform dispersion of CNTs in the matrix. Storage modulus (G') after 5 minutes of UV dose increased to 225 kPa for 1.5% CNT concentration, which is ~2.3-folds to that of the control CG (**Figure 2C**). The G' lies in the range of 100-250 kPa, which is similar to the mechanical modulus of various soft tissues (e.g., arteries, skin, heart, etc.)[20]. Once the UV is turned off, the mechanical properties (G') of the cured CaproGlu composites stabilize within 20-30 seconds (**Figure S4**). The G' was seen to be decreasing as the amount of CNTs was increased to 2 wt % or higher. This could be attributed to the absorption of UV light by CNTs, leaving insufficient energy for diazirine activation. For CNT additives of 2 wt % or higher, thermal curing (~105 ^{o}C) can be opted to avoid partial curing via UV (**Figure S5**). The viscosity of the composites lies in the range of 10-7000 Pa.s, similar to that needed for extrusion printing of biomaterials[21-22]. This confirms the direct printability of the CaproGlu composites for the fabrication of various conductive circuits.

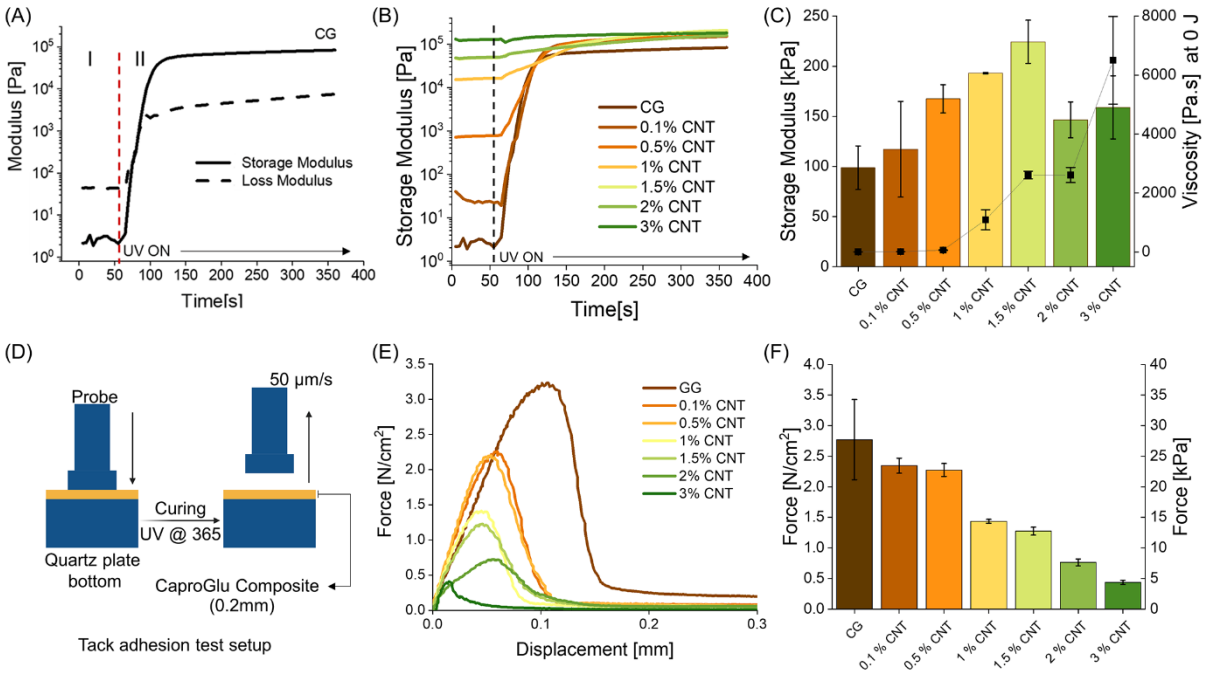

Figure 2: Evaluation of mechanical properties. A) Real-time rheological parameters (G', G") for CaproGlu (CG) control. B) Comparison of real-time stimuli-based oscillatory rheology (G') for CaproGlu composites. C) Storage modulus after 5 minutes of UV-mediated curing (bar plots); dynamic viscosity of the CaproGlu composites before curing (scatter plots). D) Set up of tack test. E) Representative force vs. displacement plots as a function of varying CNT concentration (thickness 0.2 mm). F) Comparison of maximum tack adhesion strength.

Tack test measures the adhesion strength of the composites — mimicking the tensile forces acting in the human body (**Figure 2D**). The representative load vs. displacement curves demonstrate elastic behavior with reducing yield strength as the amount of CNTs is increased from 0.1% to 3% (**Figure 2E)**. For 1.5 % CNTs, the composites reached a maximum strain of around 300% (thickness 0.2 mm). Compared with control CG, the maximum adhesion strength of 1.5% CNT is reduced to half (**Figure 2F**). This is ascribed to the reduction of diazirine (covalent crosslinker) in the composites as the amount of CNTs increases. Depending on the concentration of CNT, the adhesion strength obtained is in the range of 5-30 kPa. The adhesion strength could also be tuned by varying its covalent crosslinker conjugation. Higher conjugation corresponds to higher adhesion strength[6].

Electrical properties and strain sensing

As measured by the two-point probe method, the conductivity of the CaproGlu composites can be tuned between 6 nS m^{-1} to 0.1 S m^{-1}. This is comparable to the electrical conductivity of the soft tissues (0.1-1.6 S m^{-1})[23], suggesting that the CaproGlu composites can potentially be employed as electrical adhesives at the human-machine bioelectronic interfaces. Percolation is achieved at a CNT concentration of 1% (**Figure 3A**). The resistance of UV-cured composites is lower as compared to uncured counterparts for CNT concentration

beyond 1% (**Figure 3A**). The transition of composites from liquid to viscoelastic solid could result in an increasing percolation probability because of the tunneling through the diazirine/diazoalkanes[19]. The desired conductivity and optimum concentration of the conductive additives are cautiously considered based on the percolation transition. As a result, there is a tradeoff between the electrical and mechanical properties of the composites. Comparing the rheological, adhesion, and electrical data (**Figure 2**), the concentration of CNTs is best optimized at 1.5%. The conductivity of 1.5% CNTs reached about 22 x 10^5 folds higher than that of CG control exhibiting an insulator-to-conductor transition. An illustration of the conductivity of the CaproGlu composites is shown in **Figure 3B**, where a straight electric circuit was hand-painted over a flexible collagen substrate to power a LED (**Video S1**). To test conductivity under the isotonic physiological conditions, the composites were soaked in PBS for 6 hours. A two-point probe measures the resistance and shows that the conductivity of the soaked CaproGlu composites increases by ~33 % (**Figure 3C**). This may be attributed to the permeation of the H^+, OH^- ions into the porous composites. We also anticipate that the hydrophobic nature of the composites would provide longer stability under hydrated conditions than that of hydrogels, hence potentially improving the lifespan of the implants/sensors.

The applicability of the composites for bioelectronic applications requires that the circuits maintain their electrical conductivity under physiologically relevant strains (e.g., bending, tension, shearing, etc.). To test this, the electric patterns of composites were hand-painted over flexible collagen substrates and connected in a circuit with LED (**Figure 3D**). The circuits when twisted and bent – both inward and outward, preserved the continuity as indicated by the bright LED. The LED remained on and maintained the brightness despite being deformed multiple times. To test the quantitative changes in the electrical conductivity, the resistances were recorded under conditions of shear, tensile, and bending

strains (**Figure 3E- 3G**). CaproGlu's resistance (R) is measured under physiological strains and normalized with respect to initial resistance (R_o). We observed an increase in the resistance (~55 %) as the shear strain was increased to 100% (**Figure 3E**). To measure the applicability of the CaproGlu composites for strain sensing and human motion detection, we performed cyclic mechanical deformations and recorded the resistance. For strain sensing, a thin electric circuit was hand-painted over the balloon of an Edwards transfemoral balloon catheter (**Figure 3F**). The balloon was inflated and deflated repeatedly exhibiting a strain of ~ 36 %. The CaproGlu composites-based strain sensors were also hand-painted over the forefinger and crosslinked using UV light @ 365 nm (**Figure 3G**). After the applied mechanical deformations in both the balloon and forefinger, the strain sensors reacted to the motions rapidly. The change in resistance during balloon (inflation/deflation) or finger (bent/relaxed) motions indicated a similar behavior where every peak corresponds to a cycling of the balloon/finger motion. The variation in the resistance observed was up to ~ 65 % and ~ 54 % for deformations in the balloon and finger, respectively. We observed no signs of breakage indicating an electrical discontinuity in the circuits. The increase in the resistance during the mechanical deformations is attributed to the stretching of the conductive networks of CNTs in the CaproGlu composites.

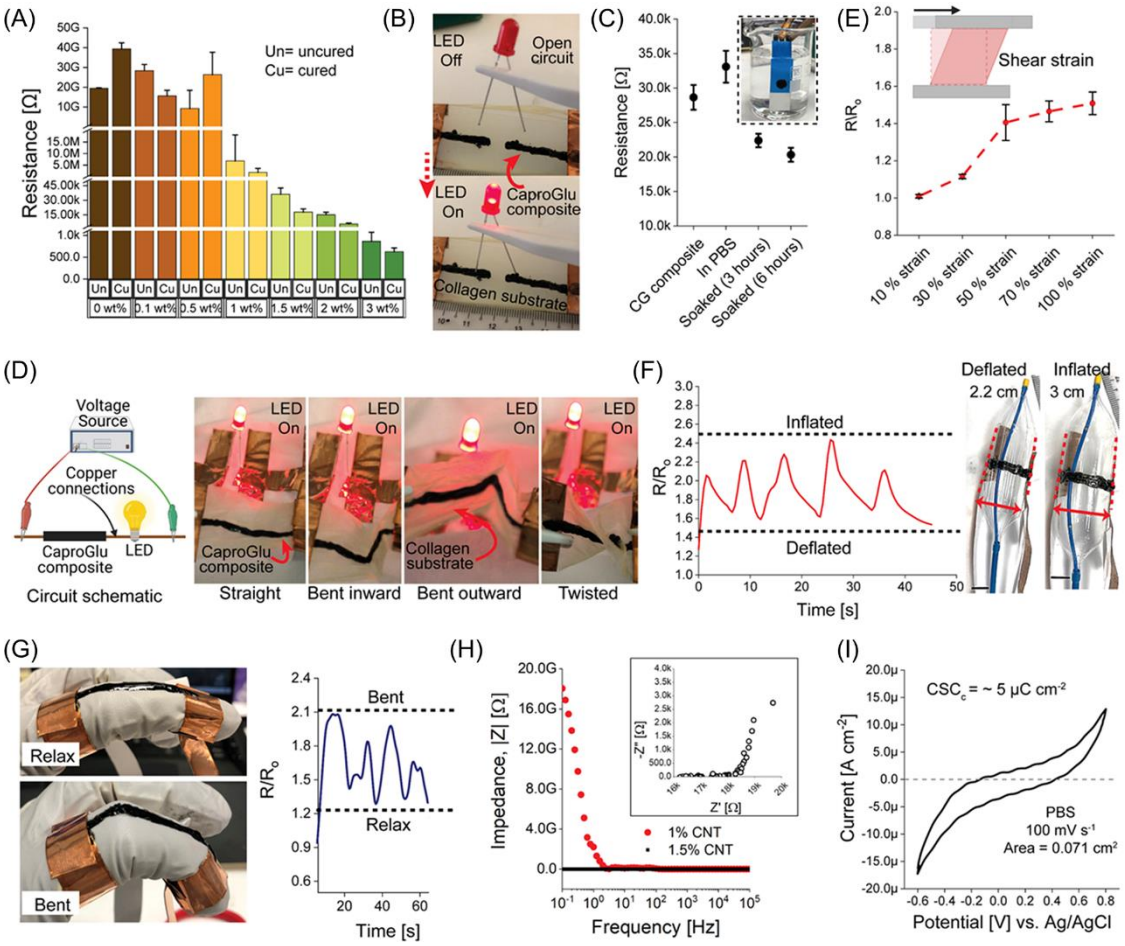

Figure 3: Electrical and electrochemical characterizations. A) Comparison of resistance measured by the two-point probe method. B) LED connected in a circuit made up of CaproGlu composites illustrating electrical conductivity. C) Influence on the electrical conductivity upon incubation in phosphate-buffered saline (physiologically relevant isotonic conditions) for up to 6 hours. D) Illustration of electrical continuity in the electric circuits hand-painted using CaproGlu composites during multiple cycles of bending or twisting. E) Influence on conductivity under shear strains. F) Influence on conductivity under tensile strains showing composites' ability to sense the mechanical deformations. G) Effect on conductivity during bending movements. H) Impedance spectroscopy of composites vs. control CG. I) Electrochemical characterization of composites via cyclic voltammetry.

The applicability of the composites at the human-machine bioelectronic interface for stimulation and recording requires electrochemical characterization via electrical impedance spectroscopy (EIS) and cyclic voltammetry (CV). EIS investigations show that the impedance reduction at low frequencies is significant in the case of 1.5% composites than that of 1% CNT (**Figure 3H**). The almost vertical tail in Nyquist plots of 1.5% CNTs at low frequencies shows the capacitive behavior of the CaproGlu composites (**Figure 3H, inset**). The composites also exhibit 25 % lower impedance in the physiologically relevant frequency range of 10^2-10^5 Hz. CV evaluates the charge transfer capacity (CSC) of the CaproGlu composites at the interface. CSC estimates the number of charges that can be injected during a tissue stimulation and is calculated by taking the integral of the cathodic current. The assessed CSC is 5 µC cm^{-2}, which is comparable to that of metallic electrodes (1-50 µC cm^{-2})[24-25].

In conclusion, we have demonstrated a liquid, conductive polymer composite that can be rapidly transitioned into a conductive bio-rubber, and still be bioadhesive. We are not aware of any other biocompatible, shelf-stable, conductive liquid polymers that have this ability and can also withstand gamma irradiation sterilization. Untreated carbon allotropes, e.g., CNTs, can be directly dissolved in the liquid CaproGlu base which is a contrast to all hydrogel formulations that require surface-functionalized CNT. The carbene-chemistry involved in CaproGlu is one of the only known methods in literature to covalently react with carbon nanotube surfaces under ambient conditions. The prepared composites can successfully identify the small strains for human motion detection. The sensing capabilities demonstrated in this work can also be expanded to applications such as electronic skin, wearable electronics, and electrode coatings for tissue recording or stimulation. The preliminary data warrant future work on bioelectronic and electroceutical applications.

Acknowledgments

This work was supported by the Ministry of Education Tier 2 Grant (MOE2018-T2-2-114): CaproGlu, Double-sided wet-tissue adhesives, NTUitive POC (Gap) Fund NGF/2018/05: Aesthetic Applications of CaproGlu Bioadhesives, and A*Star IAF PP Grant (H19/01/a0/0II9): CathoGlu Bioadhesives-preventing catheter extravasation and skin infections. Figures, videos, and digital illustrations are created with Adobe Illustrator, Adobe Photoshop, BioRender, Adobe Premiere Pro, and Blender. The data is plotted and evaluated with OriginPro 2019 software.

Conflict of interest

The authors declare no conflict of interest.

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