**Tunable CaproGlu adhesives for enhanced tissue compatibility**

Ivan Šolić, Ivan Djordjevic, Manisha Singh, Terry W.J. Steele
School of Materials Science and Engineering, Nanyang Technological University, Singapore

**Statement of Purpose:** CaproGlu polymers are a novel class of biocompatible adhesives that allow fast bonding of tissues on-demand via UVA activation.[1] CaproGlu is diazirine-grafted polycaprolactone polyol (triol or tetrol; PCLT) display excellent stability and long shelf-life. Furthermore, they are fully biodegradable and non-toxic, which makes them a suitable alternative to traditional tissue fixation techniques, such as surgical sutures or staples. Many new tissue adhesives neglect the need to closely match the mechanical properties of the glue with those of the tissue in question. This can result in premature failure of the adhesive or damage to the tissue.[3] In this work, we address this problem, by tuning the mechanical properties of CaproGlu. We present CaproGlu formulations with tunable mechanical properties by simple variation of PCLT molecular weight and structure. By altering PCLT precursors, and the amount of grafted diazirine, we demonstrate the range of dynamic moduli that can increase by as much as an order of magnitude compared to standard CaproGlu.

**Methods:** CaproGlu adhesive formulation: CaproGlu 1000 (used as reference material[1,2]), CaproGlu-300 (CG-300), CaproGlu-540 (CG-540), CaproGlu-900 (CG-900), and CaproGlu-2000 (CG-2000), are prepared according to standard synthetic protocols developed within our laboratory.[2] The numbers in nomenclature represents different PCLT molecular weights and structures: 1000 Da (tetrol) and triols: 300, 540, 900 and 2000 Da respectively. In brief, 4-[3-(Trifluoromethyl)-3H-diazirin-3-YL] benzoic acid (Dz-COOH) is grafted onto hydroxyl (OH) groups of PCLT by esterification process with the aid of 1,1-carbonyldiimidazole (CDI), and dichloromethane (DCM) is used as a solvent, The control over Dz-COOH grafting concentration is accomplished by pre-determined OH/COOH ratio. The final product is purified in multi-step ether/water extraction. Grafting percentage of the prepared adhesives is determined by NMR (JEOL ECA 400) and $CDCl_3$ is used as a solvent.[2] Anton Paar Physica MCR 102 rheometer equipped with the custom-made photocuring system is used for the rheological analysis. UVA activation of adhesives is done by 365 nm UV light for 100 seconds at an intensity of 100 $mW \cdot cm^{-2}$ (10J UV dose). A PP10 parallel plate is used, with 1% shear and a frequency of 10 Hz. Scanning electron micrograph images are recorded after UVA activation.

**Results:** A series of CaproGlu formulation are synthesized and characterized with the summary of results in Fig. 1. **Figure 1A** shows photorheological profiles of prepared adhesives by monitoring the storage moduli (G') as a function of UVA irradiation time. An increase of G' values indicates successful crosslinking after UVA activation. Higher G' values in the case of CG-300, CG-540, CG-900, and CG-2000 are due to higher concentrations of diazirine moiety in these polymers (60-80%), while the grafting percentage in CG-1000 (reference) is 50%. The white paste shown in **Fig. 1B is** CG-2000 formulation before UVA curing, which becomes a yellow rubber after UVA curing (**Fig. 1C**). In **Fig. 1D**, CaproGlu 1000 is used as an *ex vivo* porcine muscle tissue adhesive. A thin layer of CaproGlu 1000 is applied on two pieces followed by activation with 365 nm UVA light. **Figure 1E** shows the SEM image of pure CaproGlu 1000 after UVA activation. The porous structure is a result of nitrogen gas generation upon UVA activation.

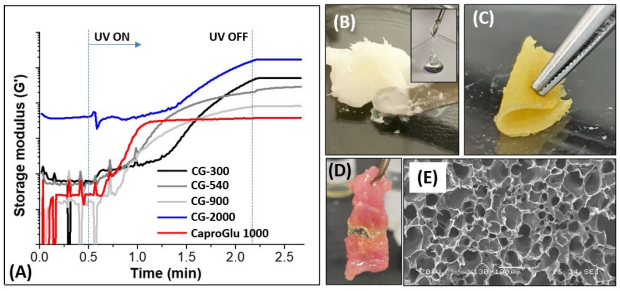


**Figure 1**. **(A)** Rheological data (G') of novel PCLT-based adhesives; **(B)** CG-2000 adhesive before UVA activation; insert shows liquid CaproGlu-1000 formulation before UVA activation. **(C)** CG-2000 adhesive after UVA (365 nm) activation; **(D)** CaproGlu used as a tissue adhesive after curing with 365 nm UVA light; **(E)** SEM image of pure CaproGlu.

**Conclusion:** A series of biocompatible, diazirine-functionalized, polycaprolactone-based adhesives are developed and characterised. By altering the molecular weight of starting material, a small library of adhesives with different mechanical properties was prepared. This allows us to expand and finely tune the application of prepared adhesives for different tissue types. In future work, detailed *in vivo* and *ex vivo* studies will be performed with the prepared CaproGlu adhesives as well as their toxicological analysis.

**References:**

[1.] Djordjevic I, *Biomaterials*. **2020**, 260; 120215. [2.] Djordjevic I, *Macromol. Rapid Commun*. **2020**, 2000235. [3.] Taboada, G. M., *Nature Reviews Materials* **2020,** *5* (4), 310-329.