Characterization of a Thiol-Ene/Acrylate-Based Polymer for Neuroprosthetic Implants

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ABSTRACT: Thiol-ene/acrylate shape-memory polymers can be used as base substrates for neural electrodes to treat neurological dysfunction. Neural electrodes are implanted into the body to alter or record impulse conduction. This study characterizes thiol-ene/acrylate polymers to determine which synthesis methods constitute an ideal substrate for neural implants. To achieve a desired \( T_g \) between 50 and 56.5 °C, curing conditions, polymer thickness, monomer ratios, and water uptake were all examined and controlled for. Characterization with dynamic mechanical analysis and thermal gravimetric analysis reveals that thin, thiol-ene/acrylate polymers composed of at least 50 mol % acrylate content and cured for at least 1 h at 365 nm are promising as substrates for neural electrodes.

INTRODUCTION

Biotechnological advancements have created an emerging field for flexible implants that help reduce the burden of damaged body systems, such as neurological dysfunction. Although previous technologies provide promising solutions, they have their share of drawbacks, such as lack of long-term robustness and too much stiffness. ¹,² For example, silicone-based neural electrodes are soft in vivo but may lack the stiffness to pierce soft tissue and have led to glial scar formation that reduces long-term stability.³ One reason is due to a chronic response from the body owing to the mechanical mismatch between the foreign, stiff electrode implants, and the significantly softer body tissue.⁴−⁸ Fortunately, flexible shape-memory polymers (SMPs) can address this problem and reduce the abiotic–biotic mismatch by being stiff during insertion, yet soft in vivo.⁹−¹²

A shape-memory polymer (SMP) is a polymer that can change its shape when exposed to an external stimulus, such as temperature, solvent, pH, or electricity.¹³−²² The temperature at which the polymer changes its shape is defined as the transition temperature (\( T_{\text{trans}} \)). A shape change due to a change in environmental temperature is called a thermally induced shape-memory effect (SME). Meanwhile, a shape change due to the introduction of a solvent, typically water, is called a softening-induced shape-memory effect, which occurs due to the polymer’s molecular structure.²⁴−²⁶ When the polymer interacts with the solvent, a physical swelling effect or chemical plasticizing effect occurs between the solvent molecules and the polymer network. The solvent molecules become absorbed in the polymer and plasticize the polymer by reducing the interaction forces in the polymer network.²⁵ This force depression makes the polymer chains more flexible and lowers the \( T_{\text{trans}} \).²⁶ The thiol-ene/acrylate SMP system relies on both thermally induced and softening-induced shape-memory effects.

Although there has been extensive research on the SMP systems such as polyacrylate and polyurethane system, less is known about the thiol-ene/acrylate system. The thiol-ene/acrylate SMP system is a tunable system that allows for the creation of specific polymer formulas that are composed of different concentrations of monomers from thiol, alkene, and acrylate families.²⁷,²⁸ These monomers form a “click” reaction, meaning that the so-called mixed-mode reaction produces high-yield products with high reaction specificity and minimal byproducts while occurring in simple reaction conditions.²⁹ In comparison to the acrylate system, the thiol-ene/acrylate system forms stable uniform networks, a low cure stress product, and is not inhibited by oxygen.¹⁰,²⁸ Moreover, the thiol-ene/acrylate system benefits from strong interactions between the thiol groups and noble metals. This improved adhesion from the thiol-ene/acrylate polymer has proven to be successful in intracortical probes that used noble metals, such as gold, to record the neural activity while displaying long-term robustness.¹,³⁰ It has recently been demonstrated that thiolene/acrylate polymers are biocompatible¹² and capable of sterilization with ethylene oxide,³¹ which makes them ideal candidates for biomedical applications.

SMPs have been extensively studied for their potential in biomedical devices, such as acting as vascular stents, self-tightening sutures, and neuroprosthetics.²,³²−³⁵ By synthesizing and characterizing a thiol-ene/acrylate SMP system, this study...
strives to determine how differences in the polymer structure and synthesis process affect its potential as a neural electrode substrate. We implement various fabrication methods and composition ratios to understand how to tune the glass transition temperature ($T_g$) so that the softening-induced SME results in the polymer being stiff near normal body temperature but soft after plasticization in bodily fluids. Dynamic mechanical analysis (DMA) test results show $T_g$ shift based on different curing scenarios and varying monomer ratios. Meanwhile, the thermal gravimetric analysis (TGA) was performed to understand differences in the polymer structure and degradation process, and water uptake. Samples 3A and 3B were not tested against each other, but against themselves.

**RESULTS**

Table 1 provides an overview of the variations in the polymer synthesis for each part of the study. In each part, one variable was altered, whereas all of the other variables were held constant, so the results would be solely due to the variable in question.

| part I | part II | part III |
|--------|---------|----------|
| curing conditions | processing | polymer composition |
| samples 1A | samples 1B | samples 2A | samples 2B | samples 3A | samples 3B |
| 31 mol % TCMDA | 31 mol % TCMDA | 31 mol % TCMDA | 31 mol % TCMDA | 10, 20, 45, 50 mol % TCMDA | 10, 31, 50 mol % TCMDA |
| spin-coated | spin-coated | casted | spin-coated | casted |
| 365 nm | 254 nm | 365 nm | 365 nm | 365 nm |
| 30, 60, 120 min | 30, 60, 120 min | 120 min | 120 min | 60 min | 60 min |

“Part I of the study tested how differences in the curing wavelength, as well as exposure to UV light during the polymerization process, affected the $T_g$. Part II tested the differences in the polymer characteristics when casted compared with when spin-coated. Part III examined how monomer mole variations affect $T_g$, the degradation process, and water uptake. Samples 3A and 3B were not tested against each other, but against themselves.

**Figure 1.** The thiol-ene/acylate polymers cured under 365 or 254 nm UV bulbs and for various amounts of time, characterized by (a) dynamical mechanical analysis for $T_g$ and (b) thermal gravimetric analysis for degradation characteristics.
addition, the storage modulus in the rubbery regime for the 254 nm cured polymers increased with time and was greater than that in regime for the 365 nm cured polymers. Meanwhile, the samples cured at 365 nm showed no significant change in $T_g$ as the time of curing increased. Furthermore, the DMA measurements, shown in Figure 1b, reveal that aside from the 30 min 365 nm cured sample, there were no significant differences among the curing times or curing wavelengths. The 30 min 365 nm cured sample started to degrade at a lower temperature than its counterparts.

**Part II: Casting versus Spin-Coating.** Part II of the study tested the differences between the casting method and spin-coating method. Thicker, casted samples are commonly used in polymer characterization studies. However, future applications of SMPs will use much thinner polymers as substrates for neural electrodes. The determined optimal curing method from part I of the study was held constant for the part II samples, as were the mole percentages of the monomers and the time cured in the UV-curing chamber. The DMA was performed on both the casted and spin-coated samples to determine how the methods affected $T_g$. Meanwhile, the TGA was performed to reveal how the polymer structure may differ between the two methods.

The DMA measurements, as shown in Figure 2a, display the casted and spin-coated polymer with similar transition and modulus curve shapes but differing in $T_g$. The spin-coated sample displays a higher $T_g$ of 39.4 °C than the casted sample, which had a $T_g$ of 32.2 °C. As for the TGA measurements, shown in Figure 2b, the spin-coated sample starts degrading at a lower temperature than the casted sample.

**Part III: Altered TCMDA Content.** In part III of the study, we wanted to understand how the mole percentages of TCMDA, the acrylate component, affected the characteristics of the polymer. In the samples 3A, the mole percentages of TCMDA varied at 10, 20, 31, 40, and 50%, whereas the spin-coating process, curing wavelength, and curing time were all held constant. The DMA was performed to determine how the acrylate percentage alters the $T_g$. The TGA was performed to understand differences in the degradation temperature between the varied TCMDA mole percentages and the structural characteristic of the polymer.

The DMA performance in part III, as shown in Figure 3a, on the thiol-ene/acrylate polymers with varied ratios of TCMDA revealed an increase in $T_g$ and a spread in the transition curve with increase in the mole percentage of TCMDA. The $T_g$ varied from 28.0 °C for the 10% TCMDA polymer to 45.9 °C for the 50% TCMDA polymer. In addition, the TGA data on the polymers with varied TCMDA content, as shown in Figure 3b, reveal unique characteristics when taking the derivative of the degradation percentage curve. The 10 and 20% TCMDA degradation rate curves showed similar symmetrical curves that degraded uniformly, whereas the 40 and 50% TCMDA both had a front-shoulder that degraded before the rest of the polymer. The 31% TCMDA results displayed a mixture of the low-TCMDA percentage and high-TCMDA percentage curve characteristic.

Despite differences between the casted and spin-coated polymers, the samples for swelling tests were made with the casting method to create larger, thicker samples to decrease the amount of swelling. Each of the three polymers reached a water uptake percentage of TCMDA varied at 10, 20, 31, 40, and 50%, whereas the spin-coated polymer, when soaked in PBS, when compared with dry polymers. Because of the softening-induced shape-memory effect when soaking...
the polymer, ideal $T_g$ values should range between 50 and 56.5 °C. Every step of the synthesis process has the potential to alter the polymer’s $T_g$. Previous studies have cured the polymer under either 254 or 365 nm UV light for curing times ranging from 15 min to 2 h. Part I of the study was conducted to determine whether one UV wavelength was more optimal for curing, or if they had no effect. In part I, DMA data in Figure 1a reveal sharper tan δ curves for the 365 nm samples, when compared with the 254 nm samples, indicating a more homogeneous polymer that changes shape at approximately the same temperature. On the other hand, the 254 nm cured curves possess more spread, suggesting a less homogeneous polymer that slowly changes shape over a range of temperatures. Explanations for the nonhomogeneous-like characteristics may include the strength of the UV light. The 254 nm light exhibits a high energy that may have damaged the intramolecular and intermolecular bonds among the monomers, creating radicals that can react in unintended ways, such as with oxygen. As a result, the surface of the polymer has a different monomer structure than the deeper, less-exposed areas of the polymer. The minor bond-linkage differences between different regions of the polymer lead to a non-homogeneous sample. As the length of time of exposure to the high-energy 254 nm UV light increases, more damages occur on the bonds, thus creating more nonhomogeneity and a tan δ curve with a greater spread.

Additionally, in Figure 1a, the higher storage modulus in the 254 nm cured polymers indicates more cross-linking among the monomers than that in the 365 nm cured polymers, which may create more mesh-like structures leading to less bond rotation. In addition, oxidized sulfur—oxygen double bonds may result between trimethylolpropanetri(3-mercaptopropionate) (TMTMP) and other monomers, creating less rotational freedom between the bonds. As a result of the two explanations, the more exposure to the UV light the polymer has, the less internal freedom there is in the polymer to change shape, and more energy is needed to rotate the bonds. Therefore, the $T_g$ increases as the curing time increases.

In the TGA measurements in part I of the study, shown in Figure 1b, the 30 min 365 nm cured sample degraded at a lower temperature than the other samples because the lower-energy 365 nm UV light did not have enough time to fully polymerize the monomers. This created weaker bonds compared with those in the samples that had either more time to polymerize or were polymerized with more energy. Polymers cured at 365 nm for at least 1 h are more suitable candidates for neuroprosthetic implants compared with 254 nm cured samples because their $T_g$ was independent of the curing time and the samples displayed greater structural homogeneity. For the 365 nm samples, there were no significant differences in the polymer characteristics when cured for 1 h than when cured for 2 h. In addition, the onset of thermal degradation in TGA measurements is vital for cleanroom processing, during which...
In part III, the increasing $T_g$ with increasing TCMDA content of the study, shown in Figure 3a, is attributed to the quantity and structure of acrylates in the samples. TCMDA consist of a bridged tricyclic component that may offer less structural freedom than TMTMP, the thiol monomer, and 1,3,5-triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TATATO), the acrylate monomer. As a result of the greater stiffness, it takes more energy or a higher temperature, for the bonds to rotate and let the polymer change shape. In addition, the increase in the curve spread with increase in the TCMDA content is presumably due to the chemical nature of the acrylate. The acrylates have the ability to react with other acrylates, thus causing small regions containing more acrylates than others. The result is less homogeneity with the increasing TCMDA content, which may explain the wider curves. Furthermore, the thiol-ene/acrylate polymer with 50% TCMDA shows promise due to its $T_g$ of 45.9 °C, as shown in Figure 3. This suggests it will be stiff during insertion around 35−36.5 °C while being soft in vivo with a soaked $T_g$ presumably around 25−30 °C. Fine-tuning the $T_g$ of the polymer to be between 50 and 56.5 °C can be achieved by studying the thiol-ene/acrylate polymer with increasing variations of TCMDA above 50%. Likewise, future DMA tests with the polymer soaked in PBS will need to be performed to confirm the degree of softening.

As for the TGA measurements in part III of the study, shown in Figure 3b, the differences between the degradation rate curves are attributed to the quantity of the monomers themselves as well as the bonds between the monomers because each sample has different absolute amounts of each monomer. Furthermore, variations may be attributed to carbon dioxide being randomly released from TMTMP and TCMDA monomers during the degradation process. Additionally, the fact that none of the samples had more than 1.11% water uptake by volume in the swelling tests, shown in Figure 4, is greatly beneficial for the neural electrodes that will be fabricated onto the polymers. Too much swelling in vivo leads to polymer expansion that could potentially destroy the neural devices due to breakage or delamination of the electronics.

**CONCLUSIONS**

Future application for the thiol-ene/acrylate SMP system is directed toward a base substrate for neural electrodes. In other words, neural electronics are fabricated onto the polymer and then inserted into the body. Within the body, these neural electrodes can record, stimulate, or block neural conduction. In this study, we have identified characteristics pertaining to the thiol-ene/acrylate SMP system that could lead to the development of the ideal implant with a $T_g$ between 50 and 56.5 °C. Curing wavelength and time, polymer thickness, monomer composition ratios, and water uptake were all examined with all of the other factors controlled for. An analysis of DMA and TGA results indicate that thin thiol-ene/acrylate polymers cured at 365 nm for at least 1 h with at least 50% TCMDA show promise as polymer substrates for neural devices. This study, in combination of future work, will help pave the path for manipulating nerve conduction that has the potential to treat neurological dysfunction.

**METHODS**

**Materials.** 1,3,5-Triallyl-1,3,5-triazine-2,4,6(1H,3H,5H)-trione (TATATO), trimethylolpropanetriis(3-mercaptopropio-
nate) (TMTMP), tricyclodecanedimethanoldiacylate (TCMDA), and 2,2-dimethoxy-2-phenyl-acetophenone (DMPA) were purchased from Sigma-Aldrich and used without further purification.

**Polymer Synthesis.** Varying the concentration of TCMDA, while keeping the stoichiometric ratios of TATATO and TMTMP equal, has been shown to alter $T_f$. The monomer solution consisted of equal stoichiometric ratios of TATATO and TMTMP, 0.1 wt% DMPA, and TCMDA concentrations at mole percentages of 10, 20, 31, 40, and 50%. The monomers used are depicted in Figure 5a, whereas Table 1 shows which mole percentages were used for the different tests.

First, TATATO, TCMDA, and DMPA were mixed in proportionate amounts to create the appropriate molar ratios of the monomers in each sample. Immediately after the addition of the photoinitiator (DMPA), the vial was wrapped with aluminum foil to prevent polymerization from external light. A vortexing step followed to homogenize the monomer solution at 2000 rpm for 5 min in a speedmixer. TMTMP was subsequently added in the foil-wrapped vial and the solution was vortexed at 2000 rpm for 5 min for a second homogenizing step.

The solution was then either casted between two glass slides to create thick samples or spin-coated, as illustrated in Figure 5b. During the casting process, two glass slides were first cleaned with acetone and sprayed with a hydrophobic spray to allow for later removal of the polymer from the glass slide. Two plastic spacers 0.5 mm thick were placed on the edges between the two glass slides and clamped with a standard binder clip. Monomer solution was poured onto a glass slide. A Laurell WS-650-23B spin-coater spun at 600 rpm with an acceleration of 2000 m/s$^2$ for 25 s to create uniform 30 µm samples.

After either casting or spin-coating the sample, the sample on the glass slide was polymerized by photoinitiating the sample in an UV cross-linker oven with either 365 or 254 nm UV bulbs for desired periods of time as depicted in Table 1. For the casted samples, the top glass slide was removed after 5 min in the oven to prevent it from blocking the UV light from reaching the polymer. Finally, the sample was placed in a postcuring chamber at 120 °C and a 0.17 bar for 24 h. The spin-coated polymer was removed from the glass slide by soaking the sample in deionized water for 5 min and separating the polymer with a razor.

**Dynamic Mechanical Analysis (DMA).** A Mettler Toledo DMA/SDTA861e was used to perform dynamic mechanical analysis on the polymers. The 30 µm thick polymer samples were laser-cut with CO$_2$ using a Gravograph LS100 to create rectangles 10.5 mm in length and 2.8 mm in width. Samples were heated from −10 to 150 °C at a heating rate of 2 °C min$^{-1}$ in a nitrogen environment. The polymers were measured with tension at a frequency of 1 Hz, force amplitude of 2 N, and a displacement amplitude of 20 µm.

**Thermal Gravimetric Analysis (TGA).** A Mettler Toledo TGA/DSC 1 was used to perform thermal gravimetric analysis on the 30 µm spin-coated samples. The polymer samples were heated from 25 to 700 °C at a heating rate of 20 °C min$^{-1}$ and a flow of nitrogen gas of 50 mL min$^{-1}$. Samples were approximately 4 mg each.

**Swelling Tests.** The 0.5 mm casted samples were cut and soaked in a PBS solution and stored at 37 °C for a 4 week period in enclosed glass vials to simulate physiological conditions. The samples were weighed on a balance with 0.01 mg precision before the soaking period. During certain days throughout the soaking process, the samples were removed from the PBS vials and dried using a lint-free cloth. The swollen sample was weighed on the balance with 0.01 mg precision. Polymers consisting of 10, 31, and 50% TCMDA polymerized under UV light for 1 h were tested. Samples were weighed after 1, 3, 4, 5, 7, 14, 21, and 28 days of soaking. The amount of swelling was calculated as a mass change percent from samples when dry using the following formula:

$$\text{mass change percent (\%) = } \frac{m_s - m_i}{m_i} \times 100$$

where $m_s$ is the weight of the swollen samples and $m_i$ is the weight of the samples when dry. The mass change percentage of five samples from the three different polymers were calculated and averaged to determine the final swelling percentage of the respective polymer.

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