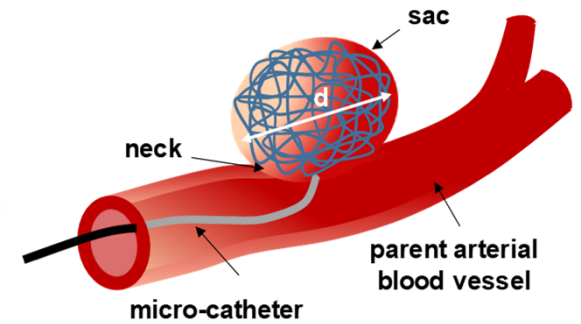
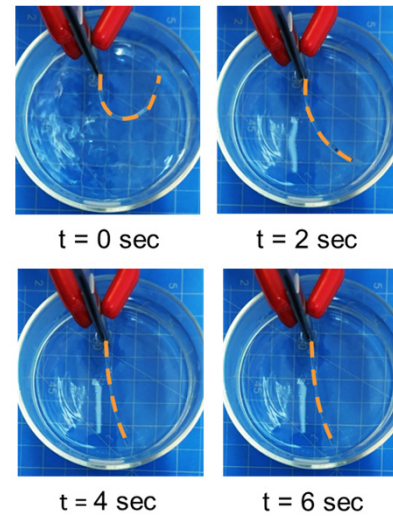
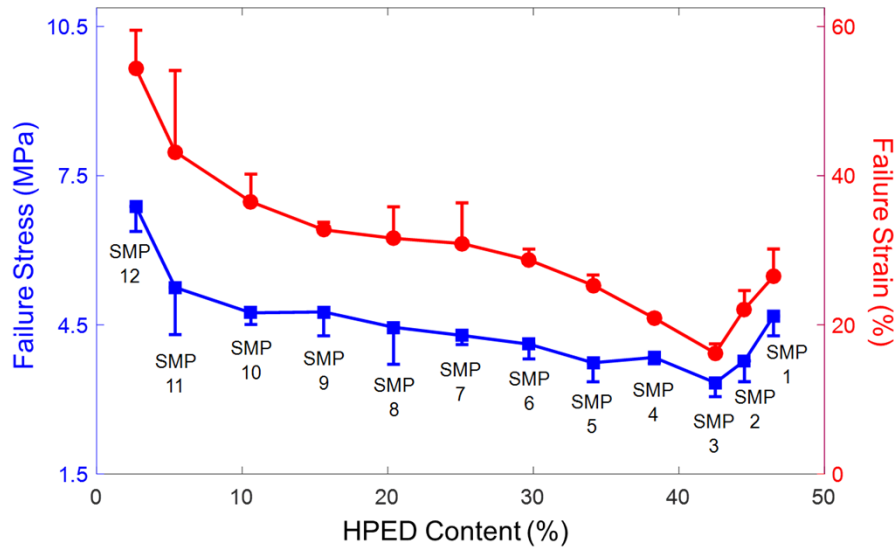
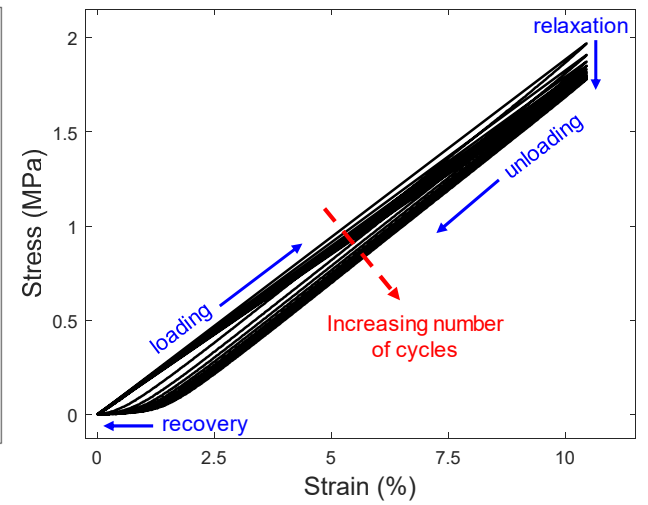
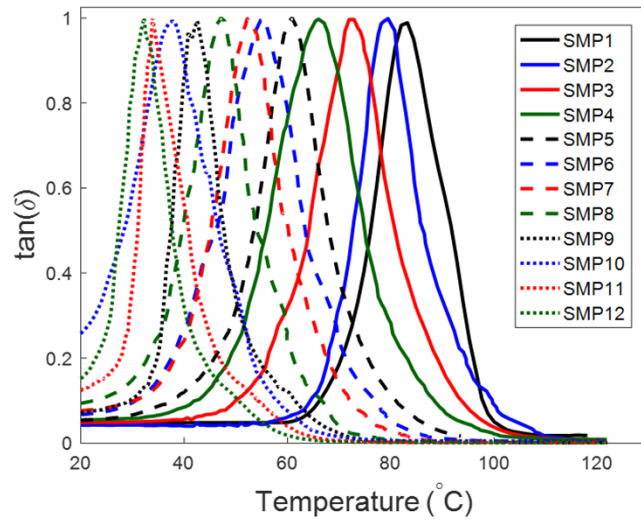
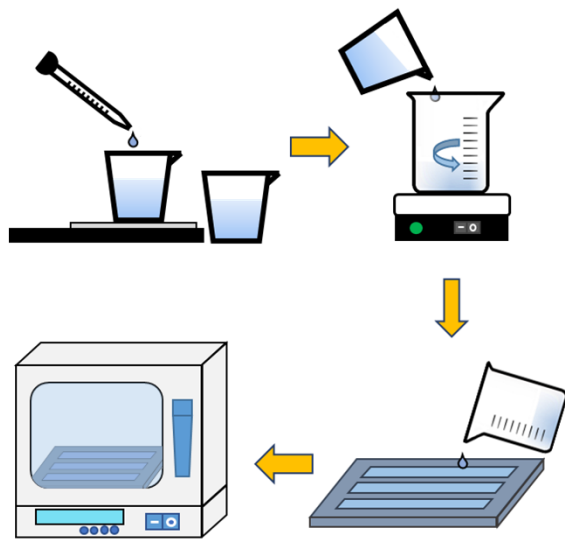


The novelties and research highlights of this work are briefly summarized below:

- A detailed experimental procedure has been developed for the synthesis of aliphatic urethane-based shape memory polymers (SMPs).
- Comprehensive thermomechanical characterizations on a variety of SMP compositions have been performed to investigate the key connections between the polymer's working temperature, thermal stability and their mechanical behavior.
- Recovery tests have also been conducted for demonstrating the superb shape memory and recovering features of the SMPs which is desirable for the endovascular embolization procedure.
- A range of SMP compositions that most accurately meet our criteria have been identified in this study with their great potential for the individualized treatment of intracranial aneurysms, which will be analyzed further in more detail as a part of future studies.



Synthesis and characterization of bio-compatible shape memory polymers with potential applications to endovascular embolization of intracranial aneurysms

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1 **Abstract**

2 Intracranial aneurysms (ICAs) are focal dilations in the brain's arteries. When left
3 untreated, ICAs can grow to the point of rupture, accounting for 50-80% of subarachnoid
4 hemorrhage cases. Current treatments include surgical clipping and endovascular coil
5 embolization to block circulation into the aneurysmal space for preventing aneurysm rupture. As
6 for endovascular embolization, patients could experience aneurysm recurrence due to an
7 incomplete coil filling or compaction over time. The use of shape memory polymers (SMPs) in
8 place of conventional platinum coils could provide more control and predictability for mitigating
9 these complications. This study was focused on characterization of an aliphatic urethane-based
10 SMP to evaluate its potential as a novel biomaterial for endovascular embolization. Twelve
11 compositions of the SMP were synthesized and their thermomechanical properties together with
12 the shape recovery behavior were comprehensively investigated. Our results showed that the
13 SMPs experienced a significant decrease in storage and loss moduli as heated above their glass
14 transition temperatures (32.3°C-83.2°C), and that all SMPs were thermally stable up to 265°C.
15 Moreover, the SMPs exhibited both composition-dependent stress relaxation and a decrease in
16 elastic modulus during cyclic loading. The shape recovery time was less than 11 seconds for all
17 SMP compositions, which is sufficiently short for shape changing during embolization
18 procedures. Several candidate compositions were identified, which possess a glass transition
19 temperature above body temperature (37°C) and below the threshold of causing tissue damage
20 (45°C). They also exhibit high material strength and low stress relaxation behavior, suggesting
21 their potential applicability to endovascular embolization of ICAs.

22 **Keywords:** Shape memory polymers; polyurethane; glass transition temperature; thermo-
23 mechanical properties; endovascular embolization

24 1. Introduction

25 An intracranial aneurysm (ICA), or a cerebral aneurysm, is an abnormal focal dilation and
26 weakening of an arterial blood vessel in the brain with a prevalence of 0.5%-6% in adults (Rinkel
27 et al., 1998; Schievink, 1997). Although most aneurysms are asymptomatic and do not rupture,
28 they can grow unpredictably, and even small aneurysms (size ≤ 5.0 mm) carry a risk of rupture.
29 Incidental rupture of an ICA is most common between age 40 and 65, associated with 50%-80%
30 of the subarachnoid hemorrhage (SAH) cases, which causes individual's death before receiving
31 medical attention associated with a mortality rate as high as 40% within the first week, and
32 accounts for about 5%-8% of all strokes, (Bederson et al., 2009; Connolly et al., 2012; King Jr,
33 1997; Lantigua et al., 2015; Naval et al., 2012; Sacco et al., 1984; Wardlaw and White, 2000).

34 Currently, surgical clipping and endovascular coil embolization are the two most common
35 treatment methods for intracranial aneurysms. Clipping of intracranial aneurysms requires
36 craniotomy and neurosurgeon places a clip across the neck of the treated aneurysm to block it
37 from the normal circulation (Molyneux et al., 2005). In contrast, micro-catheter delivery-based
38 endovascular therapy with Guglielmi detachable coils (GDC) (Guglielmi et al., 1991; Molyneux
39 and Group, 2002; Raymond et al., 2003) is a minimally invasive surgical technique, which aims
40 at excluding the aneurysmal sac and neck from intracranial circulation by means of complete
41 and lasting occlusion. Although GDC-based coil embolization therapy has been considered as
42 an alternative to surgical clip ligation that is associated with higher procedural mortality (Campi
43 et al., 2007; Molyneux et al., 2009; Taha et al., 2006), recent studies (Hope et al., 1999;
44 Tateshima et al., 2000; Vallée et al., 2003; Wehman et al., 2006) have shown that unsatisfying
45 rates of aneurysmal recanalization and incomplete occlusion are still emerging challenges in
46 endovascular coil embolization. Therefore, development of novel biomedical devices for the use
47 in minimally invasive surgical procedures as tailored to patient's complex aneurysm geometry is
48 essential to improve the long-term therapeutic outcomes of current endovascular techniques and
49 to overcome the above-mentioned clinical challenges.

50 As the first logical step towards the attainment of this research objective, we, in this study,
51 comprehensively characterize the thermomechanical properties and the shape recovery
52 capability of aliphatic urethane shape memory polymers (SMPs) and investigate its potential
53 applications to manufacturing individualized embolic devices for treating intracranial aneurysms.
54 Shape memory polymers, such as polyurethane (Gunes et al., 2008; Xu et al., 2006), have
55 aroused great attention from scientists and engineers owing to their excellent shape memory

56 behavior, high biocompatibility, fast shape recovery speed, and low synthesis cost. This type of
57 polymer is synthesized using hexamethylene diisocyanate (HDI), N,N,N',N'-tetrakis
58 (hydroxypropyl) ethylenediamine (HPED), and Triethanolamine (TEA), and consists of two
59 segments at the molecular level: (1) the rigid and glassy segments determining the permanent
60 shape and (2) the amorphous segments controlling the temporary shape. Currently, most of the
61 biocompatible SMPs used for biomedical applications are thermally induced. When heated
62 above its glass transition temperature (T_g), the amorphous segments of the SMP transition from
63 a glassy state to a rubbery state, allowing the polymer to deform under an external load (Huang
64 et al., 2012). After cooling below T_g and subsequent releasing of the external loading, the
65 temporary shape is obtained. The polymer can autonomously return to this programmed shape
66 without external mechanical stimuli when polymer temperature increases above T_g again.

67 Biomedical devices fabricated using SMPs can potentially be introduced into a patient's
68 body in a temporary, compressed shape and then be expanded on demand to their programmed
69 shape as required. Since the shape recovery can be facilitated with a certain triggering
70 mechanism, such as increasing temperature, the release of medical devices can be completed
71 without additional complex surgical operations, but rather through the micro-catheter. Many
72 biomedical devices and applications have been developed for SMPs that allow triggered
73 responses, including self-tightened biodegradable sutures (Lendlein and Langer, 2002), a micro-
74 actuator for blood removal (Maitland et al., 2002), and stents (Wache et al., 2003).

75 In this study, we aim to develop a detailed experimental procedure for the synthesis of
76 aliphatic urethane based SMPs and perform comprehensive thermomechanical characterization
77 on a range of SMP compositions to investigate connections between the working temperature
78 of the polymers and their mechanical behavior. Specifically, we identify the glass transition
79 temperatures of each composition using both dynamic mechanical analysis (DMA) and
80 differential scanning calorimetry (DSC) tests, and we determine the threshold for thermal
81 degradation of each composition using thermogravimetric analysis (TGA). We also report the
82 results of uniaxial cyclic and failure testing and analyze the differences in behavior between
83 different compositions. We conduct this research with the goal of eventually designing an
84 advanced individualized endovascular embolization device using aliphatic urethane SMPs as
85 the primary material. Consequentially, we discuss the results in terms of the desirable physical
86 qualities such an implantable material that would need to possess.

87 2. Methods

88 2.1 Materials and SMP synthesis

89 In this work, (i) hexamethylene diisocyanate (HDI, $\geq 99.0\%$), (ii) N,N,N',N'-tetrakis
90 (hydroxypropyl) ethylenediamine (HPED, $\geq 98.0\%$), and (iii) Triethanolamine (TEA, $\geq 99.0\%$)
91 were purchased from Sigma-Aldrich. All the above materials were used as received for
92 synthesizing aliphatic urethane shape memory polymers. Twelve combinations of these three
93 monomers were synthesized, with their respective SMP formulations given in **Table 1**.

94 2.2 SMP synthesis procedure

95 Various SMPs were synthesized by mixing different ratios of HPED, TEA, and HDI. The
96 molar ratios for each batch were sourced from the previous study by Wilson et al. (Wilson et al.,
97 2007) with modifications to the second and last compositions (**Table 1**). All measurement and
98 mixing procedures occurred within a nitrogen-filled glovebox to avoid moisture contamination of
99 the monomers (**Fig. 1a**). The glovebox received a steady flow of nitrogen through an inlet at the
100 top of the rear panel and vented gas into a fume hood from an outlet at the bottom of the rear
101 panel. This prevented air from entering the work space and removed any undesired moisture
102 prior to the synthesis. Nitrogen flow could be redirected to the vacuum oven used later during
103 synthesis via a set of ball valves.

104 Monomer weighing was performed using a Fisherbrand motorized pipette filler (Thermo
105 Fisher Scientific) and a digital scale (AWS-100, American Weigh Scales). In brief, the HPED and
106 TEA were measured in the same 100 mL glass beaker, while HDI was kept in a separate
107 container until the stirring stage where it was added to the mixture and stirred on a magnetic
108 stirring plate (**Fig. 1b**). The mixture was stirred gently to avoid the introduction of gas bubbles
109 into the liquid. Stirring continued until the mixture showed a sudden transition from translucent
110 to uniformly clear. The time required to produce this transition increased as the ratio of HPED in
111 the mixture decreased and the ratio of HDI increased (**Table 1**).

112 The procedures in Wilson et al. (Wilson et al., 2007) suggested including an excess of
113 1-2% isocyanate (HDI). However, our early synthesis results were unsatisfactory, and the
114 removal of this excess improved the success rate of our syntheses. We also observed a
115 tendency of the mixtures to cure before degassing could take place, leaving large air bubbles in
116 the resulting specimens. Since the mixture of the monomers is an exothermic reaction, we
117 noticed large batches of the mixture could generate adequate heat to act as a catalyst for the
118 curing process. To avoid these scenarios, we limited the size of each batch to 16g-18g, and

119 mixed multiple small batches during a single synthesis procedure, rather than mixing the full
120 volume all at once.

121 Once the mixture had sufficiently reacted, we quickly removed it from the glovebox and
122 poured the contents into a set of silicone rubber molds—rectangular beams (45mm x 8mm x
123 1mm) for glass transition-related characterizations and ASTM D638 Type V dog bones for tensile
124 mechanical testing (c.f. **Sections 2.3 and 2.4**, respectively). Prior to the synthesis, two coats of
125 mold release (Buehler 208186032) were applied to each specimen mold to minimize bubble
126 generations due to any undesired interactions between the mixed monomers and the silicone
127 rubber during curing. Then, specimen molds were placed in a vacuum oven (Being BOV-20) and
128 5 vacuuming (-0.8 bar) and nitrogen purging steps were performed to create a nitrogen protected
129 environment in the oven before degassing. A strong vacuum (-0.925 bar) was next induced using
130 a vacuum pump for 10-12 minutes to remove gas bubbles trapped in the mixture (**Fig. 1a-b**).
131 For cases where multiple batches of mixture were used, we filled each mold half way with mixture
132 and performed an initial degassing step while mixing the other batch. When the first degassing
133 had finished, we filled the rest of the space of the molds and proceeded with the above-
134 mentioned vacuuming-purging and degassing steps. An “overflow” section was included in our
135 specimen molds to trap bubbles as introduced during the degassing procedure. The top few
136 millimeters of each specimen could be polished off to leave a smooth finishing.

137 When curing the SMP specimens, we followed the procedure in Wilson et al. (Wilson et
138 al., 2007) with several modifications. The specimens were kept at room temperature for one
139 hour, then the temperature was increased at a steady rate to 130°C, where it was kept for
140 another hour. The heating rate of temperature was proportional to the glass transition
141 temperature (T_g) of the specimen being cured, to ensure each SMP had an equal curing time
142 before reaching its T_g (**Table 1**). During the curing process, we observed a slow loss of vacuum
143 potentially caused by the pressure increase associated with the heating. To maintain a
144 consistent vacuum, we resealed the oven in intervals of an increase of 7.5°C, by reestablishing
145 the vacuum (-0.4 bar) and quickly purging the system with nitrogen. Upon completion of the
146 curing step, the SMP specimens were carefully removed from the molds and stored in a vacuum
147 desiccator (Bel-Art Lab) to ensure no moisture contamination occurred before subsequent
148 thermomechanical characterization experiments.

149 2.3 Characterization of the synthesized SMPs

150 The mechanical properties of shape memory polymers vary according to temperature,
151 especially in the range of their glass transition temperatures. To characterize these temperature-
152 dependent mechanical properties with various polymer compositions, we conducted a series of
153 thermomechanical tests, including the dynamic mechanical analysis (DMA), thermogravimetric
154 analysis (TGA), differential scanning calorimetry (DSC), and uniaxial tensile tests considering
155 failure and cyclic loading conditions, to pinpoint the glass transition temperature of the SMPs
156 and to better understand their thermally-dependent mechanical behaviors.

157 2.3.1 Dynamic mechanical analysis (DMA)

158 Dynamic mechanical analysis (TA Q800) was used to measure the mechanical properties of
159 synthesized SMPs. The SMP beam specimens were heated under a nitrogen atmosphere from
160 20°C to 120°C at a heating rate of 5°C/min and in the tension mode with a cyclic frequency of 1
161 Hz. DMA studies revealed the significant mechanical and thermal properties of the samples,
162 such as storage modulus, loss modulus and glass transition temperature.

163 2.3.2 Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC)

164 Thermal analysis data were measured by both thermogravimetry (TA Q50, TA Instruments)
165 and differential scanning calorimetry (TA Q20, TA Instruments). All measurements were
166 performed under nitrogen environment. In brief, the thermal degradation behavior of the samples
167 was recorded with heating from room temperature to 600°C at a rate of 10°C/min. An in-house
168 MATLAB (MathWorks) program was used to determine the onset temperature of thermal
169 degradation, which was used as reference for the ensuing DSC measurements. The program
170 performed a linear regression on a section of each specimen's TGA curve below T_g , and another
171 linear regression of the region on the TGA curve between 90% and 85% mass. The intersection
172 of these two lines was determined to be the threshold of thermal stability. DSC measurements
173 were carried out by: (1) heating from 20°C to 160°C at a rate of 5°C/min, (2) cooling to 20°C at
174 50°C/min, (3) maintaining for 3 min at 20°C, and then (4) repeating the above procedures. DSC
175 studies revealed the significant thermal properties of the samples, such as the glass transition
176 temperature. All the DSC data presented in this study were from the second heating cycle.

177 2.4 Mechanical testing for the synthesized SMPs

178 Before performing tensile and cyclic testing on the SMP dog-bone specimens, the overflow
179 region was removed to produce a clean finish on both sides of the specimen and eliminate

180 imperfections. The samples were polished using a custom designed and 3D printed mount on a
181 rotary polishing machine (LaboPol-5, Struers). Once polished, the width and thickness of the
182 testing region were measured thrice each and averaged. Tensile failure testing was conducted
183 using a uniaxial tensile testing system (Instron 5969, Instron). Double-sided padded tape was
184 applied to both sides of each gripping region before mounting to prevent slippage during testing.

185 Failure testing was conducted at 10°C above the T_g of each specimen in a temperature
186 regulated environment on the Instron. The specimens were mounted in three steps. First, the
187 base of the sample was clamped into the bottom set of grips and allowed to heat up to the
188 temperature of the testing environment. Second, the top section was clamped into the top set of
189 grips, and the distance between the two grips was measured with a caliper. After measuring the
190 distance between the grips, the extension reading on the Instron was zeroed, and as the sample
191 returned to testing temperature the grip positions were adjusted to keep the measured load as
192 close to zero as possible. Finally, both sets of grips were tightened to make up for the relaxation
193 of the SMP past its T_g . Once the sample reached testing temperature and the measured load
194 was returned to zero, the extension measured by the Instron testing machine was added to the
195 previously measured length and the extension was zeroed once again. This value was recorded
196 as the initial length of the specimen. Upon starting the test, the specimens were subjected to a
197 displacement of 2 mm/min until failure. Five failure tests were completed per specimen, and the
198 best three were selected for characterization purposes based on relative consistency of the
199 elastic modulus and failure stress values.

200 The procedures for cyclic testing closely resembled those for failure testing. Another set
201 of dog-bone specimens were tested at 10°C above T_g and the same three step mounting
202 procedures were exercised as previously mentioned. For the cyclic tests, each sample
203 underwent three cycles of preconditioning at 25% of the failure strain as determined during
204 failure testing. After the preconditioning step, the samples underwent ten loading and unloading
205 cycles of the previously determined 50% failure strain. Both preconditioning and cycling steps
206 were carried out at the same strain rate of 2 mm/min as the failure tests.

207 2.5 Quantification of shape recovery capability

208 The shape recovery function of the synthesized SMPs was investigated by bending a straight
209 beam sample at a 180° angle, then measuring the time required for full recovery at various
210 temperatures. [We followed a method similar to the recovery tests employed by Lin et al. and](#)
211 [Lan et al. \(Lan et al., 2009; Lin and Chen, 1998a, b\).](#) In brief, the initial bend was achieved using

212 a 3D printed mold. The beam was heated above its glass transition temperature, and then placed
213 into the mold where the specimen could cool and maintain its shape at the desired angle. To
214 measure the recovery time, a video camera was placed directly above a beaker of water on a
215 hot plate. The bent sample was held with forceps on a ring stand and swiftly lowered into the
216 heated water bath, where the SMP specimen was fully recovered. The video was analyzed frame
217 by frame to determine the elapsed time between any two specific angles of 45, 90, 135, 165,
218 and 180 degrees. This procedure was conducted using water baths at T_g , $T_g+5^\circ\text{C}$, and $T_g+10^\circ\text{C}$
219 for each sample. Three repeated recovery tests were conducted at each of the above
220 temperature levels, resulting in a total of 9 recovery time measurements for each SMP
221 composition.

222 3. Results

223 3.1 DMA results

224 All SMP compositions showed a single steep transition in their shear storage modulus, each
225 occurring at a different temperature threshold (**Fig. 2a**). A $\tan(\delta)$ plot (**Fig. 2b**) was used to
226 determine the glass transition temperature of each SMP composition. These values were taken
227 at the peak of the $\tan(\delta)$ plot and decreased monotonically from SMP1 to SMP12, ranging from
228 83.2°C to 32.3°C (**Table 2**). The storage moduli generally increased from SMP1 to SMP12;
229 however, SMP10 exhibited exceptionally large values both above and below its glass transition
230 temperature. Another factor which varied with the SMP composition was the change in the
231 storage modulus from $T_g-5^\circ\text{C}$ to $T_g+15^\circ\text{C}$. With a few exceptions, the storage modulus of each
232 specimen was reduced by a factor of 20-30 times its value at $T_g-5^\circ\text{C}$ when raised to $T_g+15^\circ\text{C}$.
233 Shear modulus values at both temperatures tended to be larger for specimens nearer to SMP12,
234 but there was not a consistent increase from one composition to another. A notable outlier is the
235 shear modulus of SMP10 at $T_g+15^\circ\text{C}$, which is exceptionally large compared to the other
236 compositions.

237 3.2 TGA results

238 The TGA testing results (**Fig. 3**) show two major slopes occurring near 300°C and 400°C .
239 The distinction between these two slopes becomes more pronounced for SMP compositions
240 closer to SMP12 that contain high percentages of the TEA. Values for the onset of thermal
241 degradation were determined for each composition with values, showing no consistent trend,
242 ranging from 268.2°C to 284.7°C (**Table 2**). We determined the temperature at which each SMP
243 composition degraded to 90% of its original weight. This value varied little between specimens,

244 ranging from 275°C to 293°C (**Table 2**). Generally, this value increased from SMP1 to SMP12,
245 but with an appreciable variation between individual compositions. The temperature required to
246 degrade the SMPs to 50% weight varied more than the values for 90% degradation, ranging
247 from 356.6°C to 316.5°C; however, these values showed a more uniform increase from SMP1
248 to SMP12 (**Table 2**).

249 3.3 DSC results

250 The results of the DSC tests were used as a secondary means of determining the T_g of each
251 SMP composition (**Fig. 4** and **Table 2**). To extract these values, we used the local minimum of
252 the resulting heat flow plots (**Fig. 4**), showing a monotonic decrease from SMP1 to SMP12. Such
253 a monotonic decrease is also reflected in the T_g of the SMP compositions, ranging from 87°C to
254 33°C. These T_g values from the DSC testing generally agree with the values determined using
255 the $\tan(\delta)$ plot in the DMA tests (**Fig. 2**). However, the T_g values determined using DSC analysis
256 are consistently higher than those from DMA and $\tan(\delta)$ analysis, but the difference is small
257 enough to attribute to differences arising from the method of determination. The same difference
258 was observed in the analysis performed by Wilson et al. (Wilson et al., 2007).

259 3.4 Uniaxial tensile testing results

260 Under uniaxial tensile failure tests, the SMPs exhibited a sharp decrease in the failure stress
261 and the failure strain from SMP1 to SMP3 and an increase in both failure stress and failure strain
262 from SMP3 to SMP12 (**Fig. 5** and **Table 3**). The trends in the data are nonlinear, with large
263 increases near compositions SMP12 and SMP1 (**Fig. 5**). The maximum failure stress and strain
264 occur at SMP12 with values of 6.88 MPa \pm 0.29 MPa and 54.4% \pm 2.97%, respectively. The
265 minimum stress and strain occur at SMP3 with values of 3.34 MPa \pm 0.16 MPa and 16.2% \pm
266 0.72%, respectively. For most of the specimens, we observed a decrease in both failure stress
267 and strain as the HPED content increased in the SMP composition.

268 As for the uniaxial tensile cyclic tests, the SMPs show a noticeable relaxation behavior under
269 cyclic tensile testing. This can be seen in the representative specimen (**Fig. 6a**). The relaxation
270 behavior is different depending on the specimen composition, and it generally decreases from
271 SMP1 to SMP12. However, this decrease is not uniform and requires more data collection before
272 any concrete trends relating to composition can be identified. Within individual specimens, the
273 relaxation behavior followed a regular pattern (**Fig. 6a**), exhibiting large but decreasing
274 relaxation during the first six cycles and then transitioning to uniform small relaxation during later
275 cycles. The maximum reduction observed at the end of the tenth cycle was 26.9% \pm 3.93% for

276 SMP1, while the minimum was observed to be $1.15\% \pm 0.04\%$ for SMP9. The elastic moduli of
277 the SMPs were also affected by the cyclic loading, decreasing sharply during the first two cycles
278 but remaining nearly constant after the fourth (**Fig. 6c**). The elastic modulus also varies with the
279 SMP composition, with a gradual decrease from SMP1 to SMP12. SMP1 displayed the largest
280 elastic modulus with a value of $22.58 \text{ MPa} \pm 0.08 \text{ MPa}$, while SMP 12 displayed the smallest,
281 with a value of $13.14 \text{ MPa} \pm 0.31 \text{ MPa}$ (**Table 3**).

282 3.5 Shape recovery capability

283 The SMPs showed a consistent temperature dependence in their shape recovery behavior,
284 an example of which is shown in **Figure 7**. Among individual specimens, the SMPs showed a
285 slower recovery response between the initiation of the test and the first 45° of recovery, a fast,
286 linear response between 45° and 135° , and a nonlinear deceleration as it approached a full 180°
287 recovery. The results of the recovery tests indicated no significant trends in the recovery time
288 with relation to the SMP composition. There was a tendency for specimens with a high TEA
289 content (closer to SMP12) to recover faster than those with a high HPED content (closer to
290 SMP1). However, several SMP compositions fell outside of this trend that it cannot be
291 considered significant. **Figure 8** shows a direct comparison of the recovery test results at $T_g + 5^\circ\text{C}$
292 among 3 selected SMP compositions (SMP3, SMP7, and SMP11).

293 4. Discussion

294 4.1 Overall findings and relevance to endovascular embolization treatment for ICAs

295 The thermomechanical characterization of the aliphatic urethane SMPs provided a closer
296 look at the shift in material properties that occurs as each SMP reaches its T_g . The DMA results
297 showed a single sharp transition in the shear storage modulus for all compositions (**Fig. 2a**). We
298 observed that this transition occurs at different temperature levels depending on the SMP
299 composition, with higher glass transition temperatures corresponding to higher concentrations
300 of HPED. In this study, the glass transition temperature of the SMP specimen was determined
301 from these transitions with SMP compositions tested, ranging from 83.2°C to 32.3°C . In the
302 context of implantable embolic devices, the SMP needs to possess a T_g above body temperature
303 (37°C) but below the threshold for tissue damage (45°C) (Wang et al., 2014). If the T_g is below
304 body temperature, then the implant would constantly exist in a malleable state and not hold any
305 one specific shape; however, at temperature levels greater than 45°C , bodily tissues can begin
306 to take damage. This desired threshold falls within our observed T_g values, suggesting that we

307 can synthesize an aliphatic urethane SMP by employing the techniques detailed in this study,
308 which transitions at a temperature suitable for applications in the human body.

309 Moreover, uniaxial mechanical testing was conducted using the SMPs to determine their
310 material strength and investigate how the strengths varied with composition. The failure test
311 results suggested that higher values for both failure stress and strain occur in compositions with
312 lower HPED contents, but the trend is nonlinear with significant variances at SMP3 (**Fig. 5**).
313 Because of its irregular trends, this data will be difficult to use in a predictive manner, but it
314 implies that there may be more complex changes associated with the SMP's composition than
315 we previously expected. With a wider range of compositions and larger sample sizes for each
316 composition, future studies could identify trends which could allow fabrications of SMP-based
317 biomedical devices with specific material strengths.

318 Cyclic tensile testing was performed to investigate changes in the behavior of the SMP
319 under repeated loading. The two major properties that we investigated were the elastic modulus
320 and the peak stress value at 50% failure strain (**Table 3**). GDC-based coils are designed to be
321 left in the body for the remainder of a patient's lifetime, so it is important that the SMP materials
322 used for this endovascular embolization application will not relax over time, resulting in the
323 aneurysm recurrence. One behavior that the cyclic testing revealed was a noticeable reduction
324 in the peak stress, with most of the reduction occurring during the first few cycles. This stress
325 reduction reached a maximum value of $26.9\% \pm 3.93\%$ in SMP1 with respect to the first cycle,
326 and the next highest values fell near the range of 8%-9% for SMPs 2-5. The relaxation behavior,
327 which is not a desirable quality in the context of a permanent embolization device, was more
328 pronounced for SMPs containing more HPED contents. The compositions containing large
329 quantities of TEA contents exhibited less relaxation, reaching values as low as $1.15\% \pm 0.04\%$
330 for SMP9 and $1.92\% \pm 1.36\%$ for SMP11. However, due to a small sample size for our cyclic
331 tests, we were not able to identify any quantitative relationship between the SMP composition
332 and the stress relaxation behavior. In addition, the elastic modulus also varied with cyclic loading,
333 but only during the first few cycles of the test. The elastic modulus values decreased sharply
334 during the first cycle, but quickly reached a constant value around the third or fourth cycle (**Fig.**
335 **6a**). Even though the changes in elastic modulus are small, it is in our interest to minimize any
336 changes in material properties once the SMP is introduced into the body. Since we were able to
337 observe both the stress relaxation and elastic modulus approaching a stable point in the latter
338 cycles of our tests, we expect that it would be necessary to design the embolization devices to

339 undergo pre-cycling before implantation, minimizing the effects of initial relaxation when the
340 device is administered.

341 Another important factor in designing an embolic device made from SMPs is the shape
342 recovery behavior which occurs when the polymer transitions from a deformed state to its un-
343 stressed state. The recovery tests conducted in this study focused on the time required for the
344 SMP to recover its shape. For endovascular embolization of ICAs, short recovery time of the
345 SMP-based device is an important design criterion to avoid the prolonged heating of body tissues
346 during device deployment. We showed the recovery behavior of the SMPs to be temperature
347 dependent, speeding up as temperatures increased past the T_g . At $T_g+10^\circ\text{C}$, with no composition
348 taking more than 10.3 seconds to fully recover from a 180° bend. There was noticeable variation
349 among different compositions, and it is very likely that a more complex relationship exists
350 between the SMP composition and the polymer's recovery behavior. Such relationships are
351 beyond the scope of this study and could be further investigated in the future. The quick recovery
352 time displayed by all compositions is promising for our continued efforts toward the development
353 of an improved aneurysm embolization device. If a device made using this SMP material could
354 be intravenously moved to its target location and then reconfigured in a matter of seconds, it
355 would have the ability to improve a great number of medical procedures.

356 4.2 Study limitations and Future Work

357 This study featured a comprehensive set of thermomechanical characterization
358 experiments, and as a result had a plethora of limiting factors that could have contributed to the
359 variations in our data. The most prominent of these limitations is a relative smaller sample size
360 for our cyclic tensile test, failure test, and recovery test. Two sets of data for each composition
361 were taken during cyclic testing, and three were taken for each composition during failure testing.
362 For the recovery tests, three trials were performed for each temperature point for each
363 composition. The focus of this study was to conduct a broad analysis of aliphatic urethane shape
364 memory polymers with varying SMP compositions. Consequently, we sacrificed the data
365 statistical meaningfulness that comes with a large sample size to instead survey a wide range
366 of compositions for trends and patterns. As future extensions based on the results of this general
367 characterization, we plan to focus on a single composition range and collect more thorough
368 measurements to quantitatively define the trends observed in this study.

369 Within the uniaxial failure and cyclic tensile tests, there are several factors that could have
370 affected our results. The samples that we used were all synthesized at the beginning of our

371 testing period, and so it is possible that the ones that were tested later in the study could have
372 changed over time as they were stored (e.g., absorbing moisture). This could be remedied by
373 testing each composition at the same amount of time after synthesis to ensure age is constant.
374 The sample were attached to the uniaxial tester using double sided tape to avoid slippage.
375 Deformations in this tape layer or slight slippages on the adhesive could have resulted in skewed
376 results. However, since all samples were tested the same way, the error due to this mounting
377 method should be consistent. Small imperfections in the samples, such as bubbles or
378 heterogeneity in the monomer mixtures, could have also resulted in differences between
379 samples in a composition. These errors can be reduced as the synthesis procedure is perfected,
380 and researchers should be careful to select only pristine samples for testing.

381 The recovery tests we conducted had many aspects that can be improved upon. Our
382 measurement method relied on visual inspection to determine the angular position of the sample
383 and the frame at which the position of interest was reached. From the frame analysis, we
384 determined time elapsed. This entire measurement method is subject to human error in multiple
385 places, which is difficult to account for. It would be beneficial to determine a more exact way to
386 measure recovery. Some samples did not return completely to a straight angle, and others began
387 their deformation at an angle other than 180° . While the recovery times were still useful for our
388 analyses, a study looking to definitively quantify the recovery response of these materials would
389 need to better define the start and end conditions for the tests.

390 It is essential that endovascular devices are visible under x-ray based fluoroscopy so that
391 physicians can pinpoint their location and orientation during device deployment. Urethane-based
392 shape memory polymers are typically invisible to radiographic imaging techniques, and,
393 therefore, the addition of radio-opaque additives to the polymer composition is necessary for
394 their use in the endovascular embolization applications. For instance, Wong et al. created
395 composite blends of poly (DL-lactide-co-glycolide) (PLGA) with both tantalum and bismuth (III)
396 oxychloride, which appeared clearly in radiographic images whereas the shape memory effect
397 can be maintained (Wong et al., 2016). While not investigated in this study, we plan to examine
398 different radio-opaque additives in our aliphatic urethane SMP and determine any resulting
399 changes in the SMP material properties.

400 The use of heat as an activation mechanism of SMP shape recovery poses many
401 challenges, especially in an area as sensitive as the brain artery vessel tissues. Although our
402 study has identified a range of SMP compositions that transition at biologically safe temperatures,

403 the challenge of delivering the thermal stimulus remains. There is a wealth of literature
404 discussing diverse activation techniques, many of which are based on the indirect delivery of
405 thermal energy to the material. These methods include, but are not limited to, Joule heating with
406 the addition of conductive inclusions, optical heating achieved using wavelength specific dyes
407 and a matching laser light source, and magnetic stimulation of nanoparticles (Huang et al., 2013;
408 Small et al., 2007). Another activation technique uses chemical interactions to lower the T_g of
409 the SMP below ambient temperature, triggering the shape memory effect. This effect occurs
410 slowly in polyurethane SMPs, and quickly in hydrogels, when the materials are exposed to water
411 (Huang et al., 2005; Lu and Du, 2014; Salvekar et al., 2017; Wong et al., 2016). As part of our
412 future extensions, we plan to test a wide range of activation techniques to determine the method
413 most suitable for the deployment of an endovascular embolization device. Because of the slow
414 reaction to water that has been observed in polyurethane SMPs from the research of Huang et
415 al. and Lu et al., we also intend to study the long-term effects of moisture on our embolic devices
416 after deployment (Huang et al., 2005; Lu et al., 2014).

417 4.3 Conclusion

418 This study aimed to characterize a range of compositions of aliphatic urethane shape
419 memory polymers for their potential use in the treatment of intracranial aneurysms. In specific,
420 we developed a detailed synthesis procedure for the SMPs to provide our study with a variety of
421 compositions and inform future studies seeking to utilize the same material. We have
422 investigated the thermomechanical properties including the glass transition temperature and
423 thermal stability of each composition, and we have also found that compositions between SMP9
424 and SMP11 possess transition temperatures between body temperature and the threshold of
425 tissue damage. This is the optimal T_g range for allowing the polymers to remain functional
426 within the body without causing any tissue damage due to the heating associated with shape
427 change triggering. We have also found that within our desired operating temperatures, all SMP
428 compositions are thermally stable regarding the endovascular embolization procedure. We have
429 also characterized the mechanical properties of the SMPs and identified decreases in both
430 maximum stress and elastic modulus with cyclic loading. Our results showed that in SMPs closer
431 to SMP12, these decreases were not as prominent. Since any changes in material properties
432 during the lifetime of an implanted device are detrimental, the SMP compositions near SMP12
433 are more desirable in the context of endovascular embolization treatment for ICAs. Finally, we
434 have tested the recovery time of each polymer and showed that all the SMP compositions are

435 capable of recovering from a 180° bend within 10.3 seconds. Using knowledge from the broad
436 characterization performed in this study, we have identified a range of compositions between
437 SMP9 and SMP11 that most accurately meet our criteria with their great potential for the
438 individualized treatment of intracranial aneurysms, and they will be analyzed further in more
439 detail as a part of future studies.

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Conflicts of Interest

None of the authors have a conflict of interest with the present work.

Tables

Table 1. Percent monomer content, monomer-mixture stirring time, and the curing heating rate for all the twelve SMP compositions.

	Monomer Content (%)			Stirring Time (seconds)	Heating Rate (°C/hour)
	HDI	HPED	TEA		
SMP1	53.5	46.5	0.0	150	30.0*
SMP2	53.9	44.5	1.6	170	29.6
SMP3	54.3	42.5	3.2	200	29.2
SMP4	55.1	38.4	6.5	225	26.4
SMP5	56.0	34.1	9.9	240	25.2
SMP6	56.9	29.7	13.4	255	23.6
SMP7	57.8	25.1	17.1	270	21.1
SMP8	58.8	20.4	20.8	285	18.5
SMP9	59.7	15.6	24.7	310	15.9
SMP10	60.7	10.6	28.7	330	12.5
SMP11	61.8	5.4	32.8	350	9.6
SMP12	62.3	2.7	35.0	445	8.5

*Suggested same heating rate for SMP curing in Wilson et al. (Wilson et al., 2007).

Table 2. Glass transition temperature (T_g) and storage modulus from the DMA tests (c.f. **Fig. 2**), T_g from the DSC tests (c.f. **Fig. 4**), and the temperature levels associated with 90% and 50% remaining weights of the SMPs from the TGA tests (c.f. **Fig. 3**).

	DMA			DSC	TGA		
	T_g (°C)	Storage modulus at $T_g-5^\circ\text{C}$ (MPa)	Storage modulus at $T_g+15^\circ\text{C}$ (MPa)	T_g (°C)	Temperature (°C) associated with the onset of thermal degradation	Temperature (°C) associated with 90% remaining weight	Temperature (°C) associated with 50% remaining weight
SMP1	83.2	403.3	13.3	87	276.6	289.5	356.6
SMP2	79.5	442.0	13.4	83	278.2	288.7	353.6
SMP3	72.6	459.4	15.7	76	276.6	286.3	351.4
SMP4	65.7	529.6	19.3	73	284.7	293.5	351.0
SMP5	61.1	563.4	22.4	67	277.5	287.1	342.8
SMP6	55.5	589.8	26.8	63	276.8	285.5	341.2
SMP7	52.5	649.9	23.7	56	275.9	284.5	338.1
SMP8	47.5	759.4	46.0	53	278.4	285.8	333.8
SMP9	42.6	706.4	24.6	45	276.7	284.8	331.0
SMP10	37.2	882.7	142.7	39	270.8	279.2	321.2
SMP11	33.9	830.9	43.8	34	268.2	275.5	316.5
SMP12	32.3	867.7	23.9	33	272.8	279.3	318.7

Table 3. Failure stresses and failure strains from the uniaxial tensile failure testing (c.f. **Fig. 5**) and the stress reductions and the calculated elastic modulus from the uniaxial cyclic tensile testing (c.f. **Fig. 6**) for all the twelve SMP compositions. **Tensile tests conducted at Tg+10°C.**

	Uniaxial Tensile Failure Test		Uniaxial Cyclic Tensile Test		
	Failure stress (MPa)	Failure strain (%)	Cumulative stress reduction (%)		Elastic modulus at the 10 th cycle (MPa)
			2 nd cycle w.r.t. 1 st cycle	10 th cycle w.r.t. 1 st cycle	
SMP1	4.68 ± 0.23	26.5 ± 2.11	7.66 ± 0.42	26.9 ± 3.93	22.58 ± 0.08
SMP2	3.78 ± 0.21	22.1 ± 1.24	3.36 ± 0.98	7.88 ± 2.16	20.74 ± 0.52
SMP3	3.34 ± 0.16	16.2 ± 0.72	1.83 ± 0.59	9.08 ± 4.58	18.97 ± 0.33
SMP4	3.84 ± 0.07	20.9 ± 0.32	3.14 ± 0.03	9.06 ± 0.54	19.84 ± 0.04
SMP5	3.74 ± 0.22	25.3 ± 0.76	3.30 ± 0.62	8.39 ± 1.66	18.80 ± 0.82
SMP6	4.11 ± 0.17	28.7 ± 0.83	2.79 ± 0.03	6.64 ± 0.49	20.39 ± 1.48
SMP7	4.29 ± 0.11	30.9 ± 3.14	2.28 ± 0.29	5.68 ± 0.37	18.50 ± 0.18
SMP8	4.45 ± 0.43	31.6 ± 2.44	2.26 ± 0.25	6.70 ± 0.24	19.04 ± 0.77
SMP9	4.76 ± 0.28	32.7 ± 0.58	0.41 ± 0.12	1.15 ± 0.04	18.34 ± 2.12
SMP10	4.74 ± 0.14	36.5 ± 2.14	0.51 ± 0.09	7.42 ± 0.03	16.32 ± 0.52
SMP11	5.25 ± 0.55	43.2 ± 6.29	0.80 ± 0.47	1.92 ± 1.36	15.26 ± 0.25
SMP12	6.88 ± 0.29	54.4 ± 2.97	0.93 ± 0.06	3.34 ± 0.85	13.14 ± 0.31

Figure Captions

Figure 1 – (a) Top-view schematic of the in-house equipment used in the shape memory polymer synthesis. (b) An illustration of the synthesis procedure showing specifically (i) the measurement of each monomer, (ii) the mixture of monomers to form the polymer, (iii) the deposition of the mixture into previously cast molds, and (iv) the curing of the mixture in a vacuum oven.

Figure 2 – (a) Shear storage modulus of all the twelve SMP compositions as directly measured from the DMA tests, and (b) $\tan(\delta)$ curves as derived from the DMA testing results for determining the T_g of each SMP composition.

Figure 3 – TGA results showing the decomposition of the SMP with increasing temperature.

Figure 4 – DSC results used for determinations of the T_g for each SMP composition.

Figure 5 – Mean \pm SEM of the failure stress (blue filled squares) and failure strain (red filled circles) for all the twelve SMP compositions ($n=2$) under uniaxial tension testing ($T_g+10^\circ\text{C}$).

Figure 6 – Representative cyclic mechanical testing results (SMP3) when tested at 50% of the observed failure strain ($T_g+10^\circ\text{C}$) showing: (a) the relaxation trend in the peak stress with an increasing number of cycles, (b) the increase in the cumulative stress reduction and (c) the convergence of the elastic modulus with an increasing number of cycles.

Figure 7 – Mean \pm SEM of the recovery testing time for a representative SMP composition (SMP3, $n=3$) showing the consistent trend of reduced recovery time with an increased temperature.

Figure 8 – Representative experimental photos of the recovery testing for three representative SMP compositions (SMP3, SMP7, and SMP11) at defined time increments ($t = 0$ sec, $t = 2$ sec, $t = 4$ sec, and $t = 6$ sec), showing the observed trend of a decreasing recovery time with an increasing TEA content.

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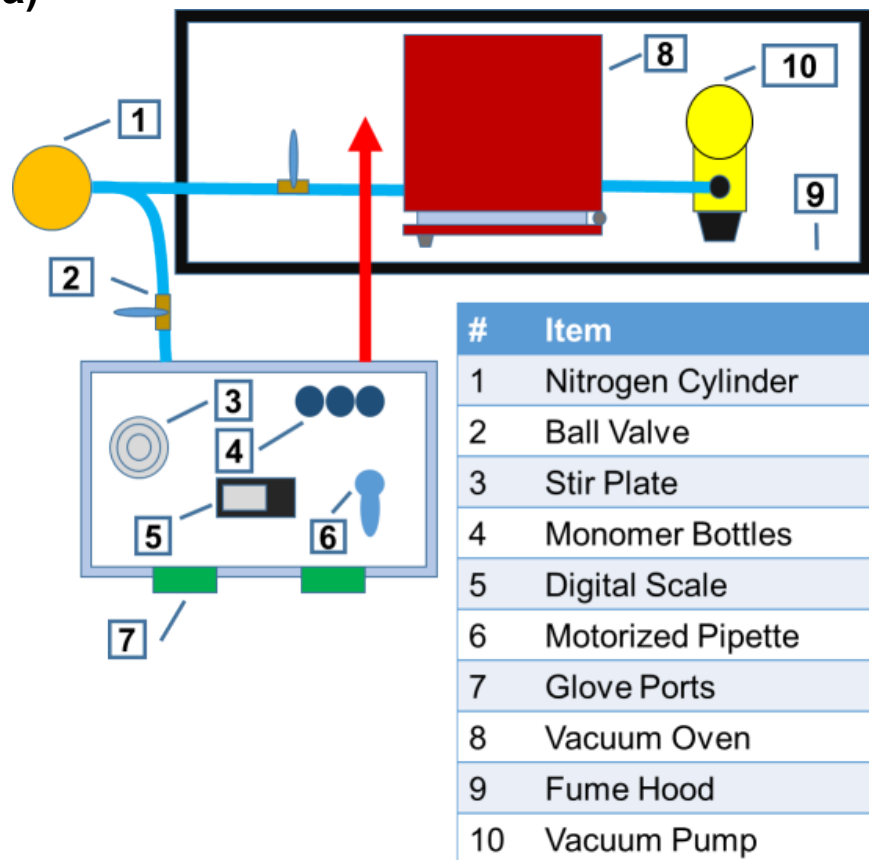
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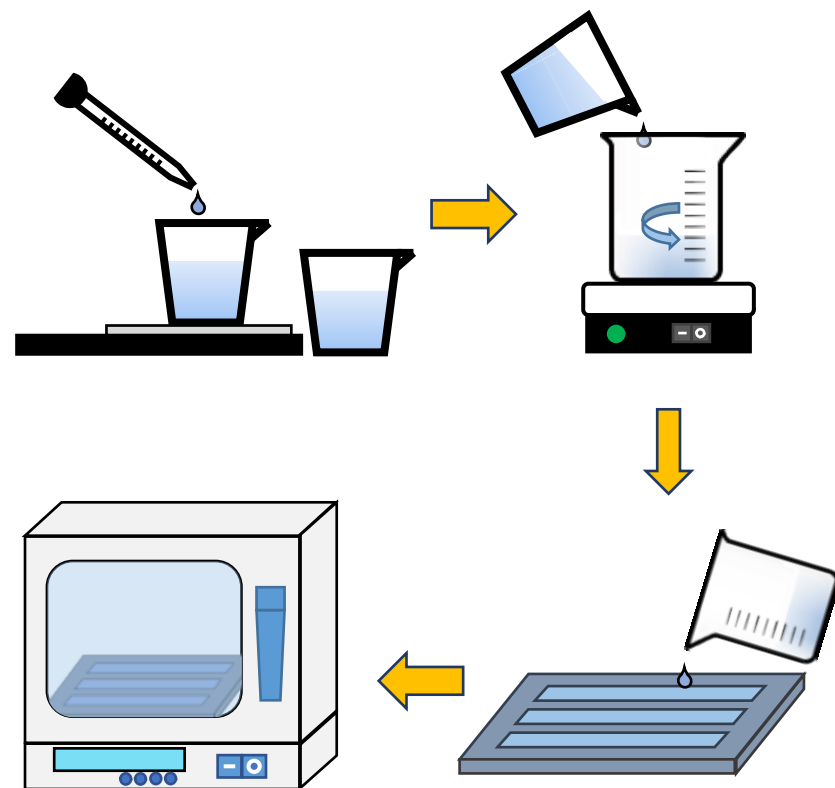
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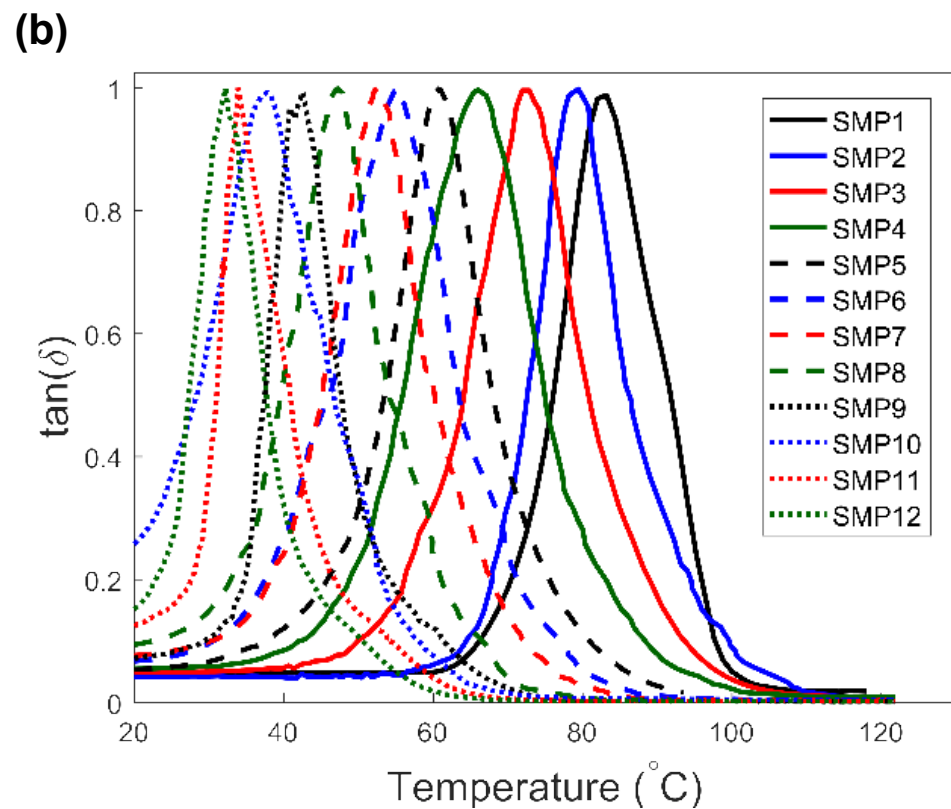
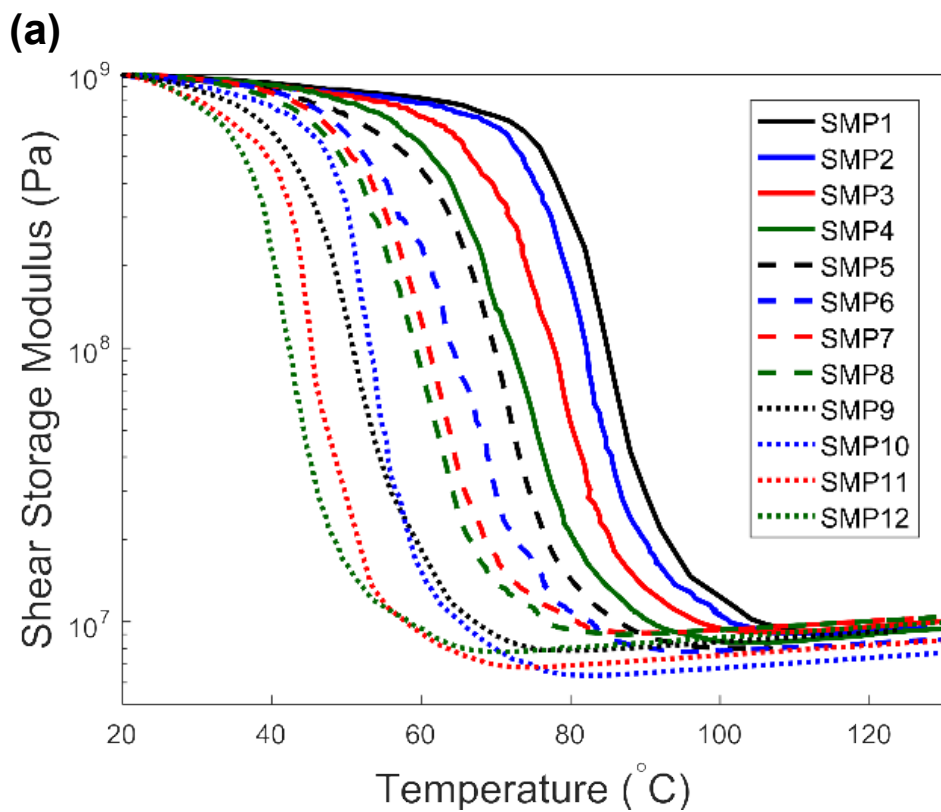
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(a)



(b)





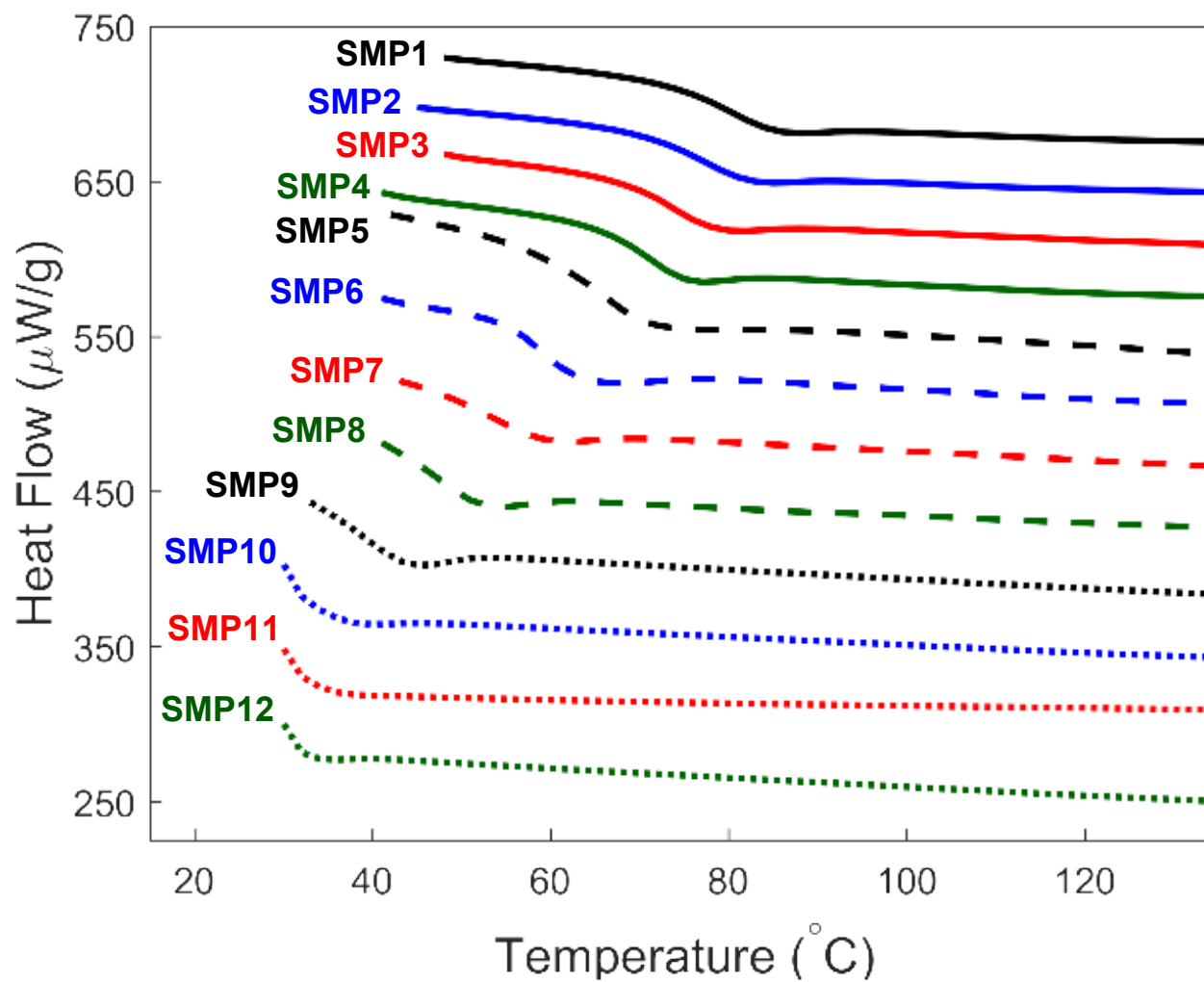


Figure 5

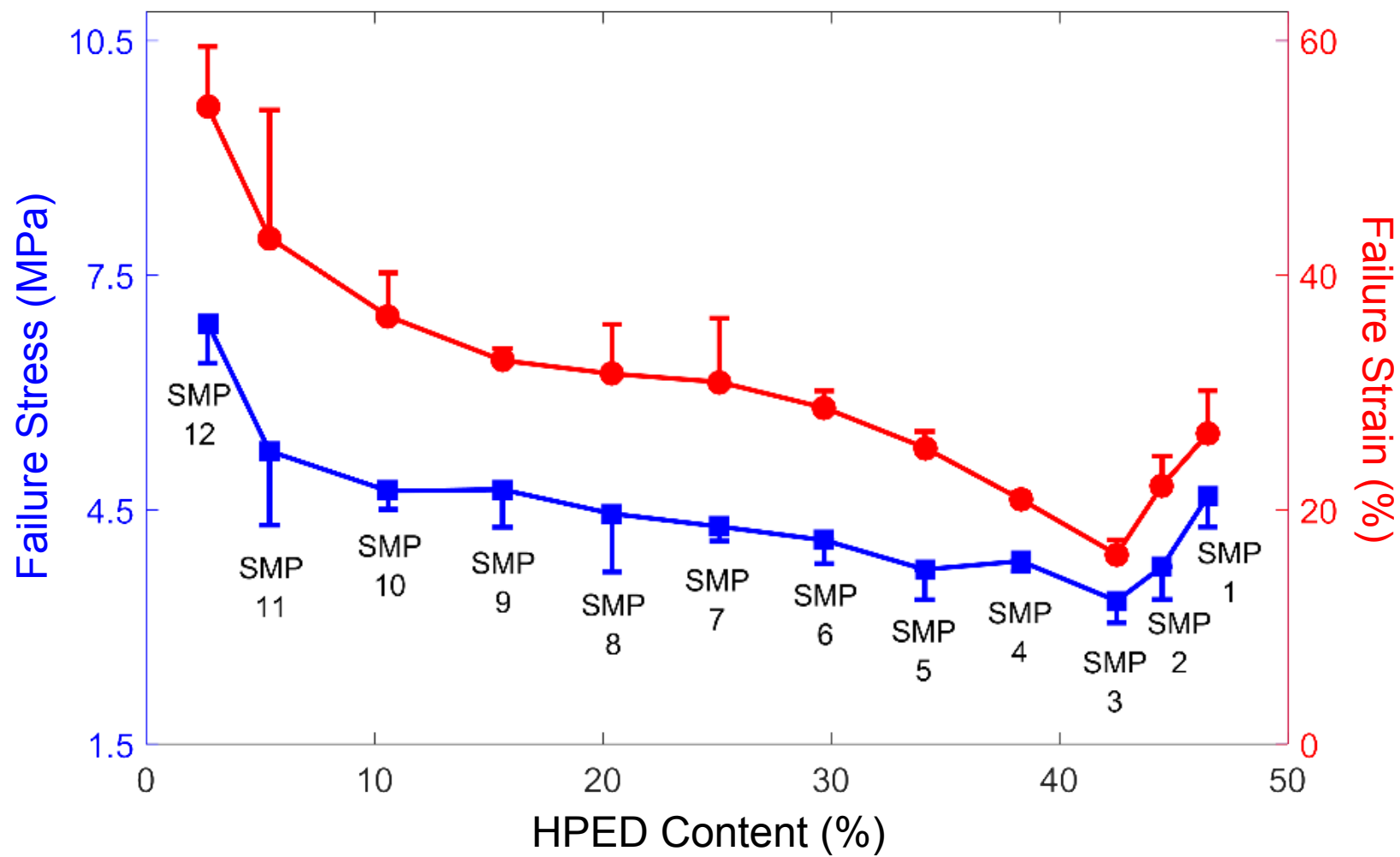


Figure 6

