SYNTHESIS AND CHARACTERIZATION OF RADIOPAQUE SHAPE MEMORY POLYMER FOAMS

An Undergraduate Research Scholars Thesis

by

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Synthesis and Characterization of Radiopaque Shape Memory Polymer Foams

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Shape memory polymer (SMP) foams have been proposed for a variety of medical applications, including brain aneurysm embolization and occlusion of peripheral vascular malformations. While these devices provide significant advancements in treatment, such as increased volumetric filling and improved healing outcomes, one inherent limitation is a lack of visibility under x-ray fluoroscopy. Medical professionals rely on noninvasive material visualization to enable safe and effective device placement. Although metal markers can assist with SMP device placement, it is difficult to anticipate the interactions between the expanding polymer device and complicated vessel anatomy. Thus, there is a significant clinical need for the development of SMP formulations that can be observed under x-ray during expansion. Using a bulk synthesis method, a contrast agent is incorporated into the polymer composition in various molar ratios to enhance foam visibility under x-ray. This project focuses on the synthesis and characterization of the radiopaque compositions necessary to achieve clinically relevant SMP foams. Foams are characterized in terms of radiopacity, morphology, and thermomechanical properties. Successful synthesis and characterization of the radiopaque foam compositions shows whether or not the properties are within a clinically relevant range for further device development.

DEDICATION

I would like to dedicate this work to my family. They have been there for me throughout my life to provide support and encouragement. I would not be where I am today without them, and I am so grateful for their love.

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NOMENCLATURE

SMP	Shape memory polymer
ATIPA	5-Amino-2,4,6-triiodoisophthalic acid
BEP	2-butyl-2-ethyl-1,3-propanediol
DEG	Diethylene glycol
HDI	Hexamethylene diisocyanate
X_{eq}	Reactive equivalents
NCO	Isocyanate group
T_g	Glass transition temperature
DSC	Differential scanning calorimetry
SEM	Scanning electron microscopy
GDC10	Guglielmi detachable coil
FTIR	Fourier transform infrared spectroscopy

CHAPTER I

INTRODUCTION

An estimated 6 million people in the United States have an unruptured cerebral aneurysm [1]. A cerebral aneurysm is a ballooned area of a blood vessel in the brain resulting from vessel wall weakening. If left untreated, these aneurysms can rupture and cause blood to flood the surrounding tissue. This bleeding may cause stroke, hydrocephalus, nerve damage, or even death.

Current treatments for cerebral aneurysms employ Guglielmi detachable coils and hydrocoils as embolic agents to cut off blood flow to the aneurysm [2]. These treatments achieve aneurysm occlusion, but have issues with aneurysm recanalization requiring re-treatment. Shape memory polymer (SMP) foams have been proposed for use to optimize endovascular embolization of aneurysms in place of current embolization devices [3,4].

SMP foams are capable of being deformed and stored in a secondary geometry, a small crimped form, that enables delivery with minimally-invasive catheters. The polymers subsequently actuate to their expanded primary geometry in response to a stimulus, such as heating to body temperature [5]. The expanded foam geometry provides a better interface for aneurysm embolization to occur; however, treatment with these devices may be difficult due to limited visibility under x-ray fluoroscopy. The SMP foams used in current devices have densities similar to soft tissue and therefore cannot be seen under x-ray.

Previous works by Hasan *et al.,* increased x-ray visibility, or radiopacity, through the incorporation of tungsten nanoparticles. The resultant foams showed x-ray visibility and maintained thermomechanical properties; however, they also had reduced mechanical properties due to disruption of the SMP matrix by the nanoparticles [6].

Alternatively, the incorporation of an x-ray visible agent directly into the foam composition could allow for a higher loading of a radiopaque agent without disrupting the matrix of SMP foam devices. A triodobenzene monomer has been proposed for use as a contrast agent in the foam composition. Specifically, 5-amino-2,4,6-triiodoisophthalic acid (ATIPA), was used because of its triodobenzene monomer motif and functional groups that serve as multiple foaming process components. Preliminary studies showed viability of the radiopaque polymer system. However, minimal loading of the contrast agent, decreased crosslinking, and low glass transition temperature were observed. To address these issues, this work focuses on optimization of the polymer system and characterization of the foam properties to assess clinical relevance of radiopaque foam compositions.

The foam composition was optimized by looking at monomer composition as well as type and concentration of catalysts and surfactants. Further optimization was conducted by focusing on the foaming protocol, which is important for foam morphology. Finally, the optimized system was characterized in terms of radiopacity, mechanical integrity, shape memory capacity, and thermal transitions in relation to clinical specifications for a neurovascular embolization device.

CHAPTER II

METHODS

SMP Foam Synthesis

2-butyl-2-ethyl-1,3-propanediol, (BEP, Sigma-Aldrich Inc., St. Louis, MO), diethylene glycol (DEG, Sigma-Aldrich Inc., St. Louis, MO), hexamethylene diisocyanate (HDI, TCI America Inc., Portland, OR), 5-amino-2,4,6-triiodoisophthalic acid (ATIPA, VWR Scientific, Houston, TX), 5-aminoisophthalic acid (ATIPA analog, Sigma-Aldrich Inc., St. Louis, MO), surfactant (Air Products and Chemicals, Inc., Allentown, PA), amine catalyst (Air Products and Chemicals, Inc. Allentown, PA), tin catalyst (Air Products and Chemicals, Inc, Allentown, PA), and Enovate 245fa Blowing Agent (Honeywell International, Inc., Houston, TX) were used as received.

The radiopaque foams were made using an equal molar ratio of AT, BEP, and DEG total reactive equivalents (Xeq) to total HDI isocyanate (NCO) equivalents. ***Figure 1*** shows a schematic of the overall foaming process. In the initial NCO pre-polymer step, the total NCO mass was added to 60% of the Xeq monomers and reacted at room temp until the premix viscosity achieved approximately 10,000 cps. The balance of Xeq monomers was combined into a polyols mix, which was added to the NCO premix along with surfactant, amine catalyst, and tin catalysts at 4, 1.5, and 0.3 wt%, respectively. The mixture was mixed at 3600 rpm using a Flacktek speed mixer (FlackTek, Inc., Landrum, SC) for 30 s, and subsequently mixed with 0.0625 ml/g of Enovate for another 20 s. The foam was immediately cured at 90 °C for 1 hr. The foams were then cooled and

cubed, then left to post-cure at 90 °C for 24 hr. A fourth foam composition was synthesized with a chemical ATIPA analog using the same method as described above.

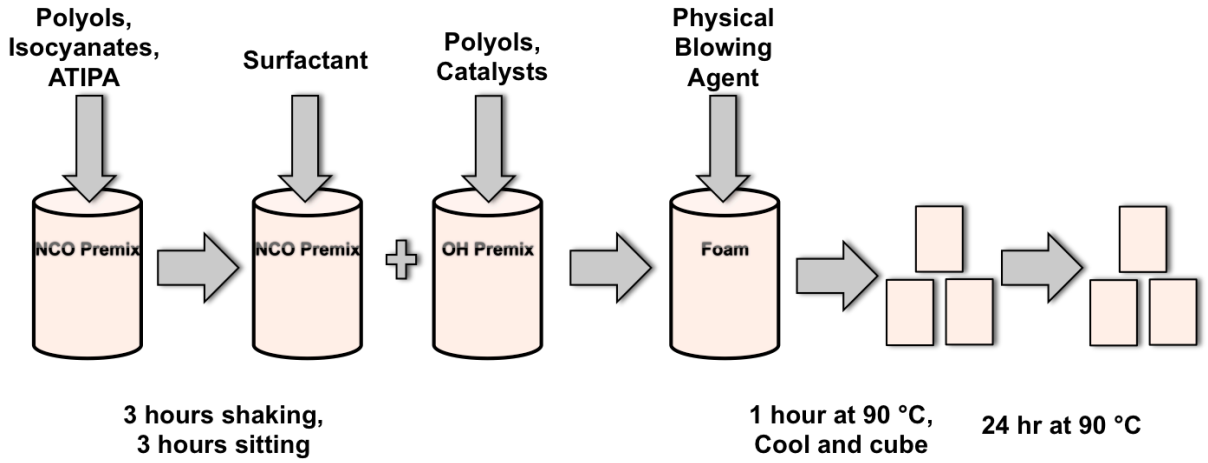


Figure 1. The optimized foam synthesis process wherein the pre-polymer mix is made, the polymer foaming occurs with the added polyols and accessory agents, and the resulting foams are taken through a curing cycle.

Differential Scanning Calorimetry (DSC)

The glass transition temperature (T_g) of the polymer foams was determined for the 15%, 20%, and 25% ATIPA compositions using a Q200 DSC (TA Instruments, New Castle, DE). To quantify the dry T_g, a 4 mg sample was loaded into a vented aluminum pan at room temperature, cooled to -40 °C, and run through a heat/cool/heat cycle from -40 °C to 120 °C at temperature rates of 10 °C/min. T_g was determined to be the transition inflection point during the second heat cycle. The T_g's were measured for an n=3 for each foam composition.

Gel Fraction

Polymer crosslinking can be quantified through gel fraction analysis. Through this method, each foam composition was analyzed at an n=5. The foams were massed, then subject to shaking

and heating at 50 °C under vacuum for 24 hours in tetrahydrofuran (Sigma-Aldrich Inc., St. Louis, MO). After 24 hours the remaining bulk masses of the foams were transferred to previously massed containers and left to dry at 50 °C under vacuum for an additional 24 hours to remove any residual solvent. A final mass of the dry samples was determined and used to calculate gel fraction based on Equation 1:

$$gel\ fraction = \frac{mass\ of\ remaining\ dry\ sample}{mass\ of\ original\ sample} x\ 100 \quad \text{(Equation 1)}$$

Mechanical Testing

The mechanical properties of the foam compositions were tested using an Insight 30 Material Tester (MTS Systems Corporation, Eden Prairie, MN). The foams were cut and prepared for testing by epoxying wood tabs on each end of the samples that could be gripped by the tester. Each sample was subject to a constant strain rate of 5 mm/min at room temperature. Strain at break (%), Young's modulus (MPa), and ultimate stress (kPa) were determined for each sample using the stress–strain curve. An n=8 was used for the 25% ATIPA compositions; however, no data was able to be collected for the 15% ATIPA foam. Comparative analysis of mechanical properties was done using mechanical data for the 6 vol% tungsten foams as well as a control nonradiopaque SMP foam used currently for device development.

Scanning Electron Microscopy

Foam samples were cut into 1 mm slices in the transverse and axial planes. The sample slices were mounted with carbon black tape onto a stage and held under vacuum for 24 hours. The samples were then sputter coated with gold for 90 seconds at 20 mA using a Cressington Sputter Coater (Ted Pella, Inc. Redding, CA). Images of the samples were obtained using a Joel NeoScope

JCM-5000 Scanning Electron Microscope (SEM) (Nikon Instruments, Inc., Melviille, NY). Pore sizes were quantified using ImageJ (https://imagej.nih.gov/ij/), averaging the diameter of 10 foam cells for each image.

Opacity

Material opacity was assessed using a OEC 9800 Plus Mobile C-arm fluoroscope (GE Healthcare) at 62 kVp. Samples of each composition were cut into 1 cm^2 pieces with thicknesses of 9, 3, and 1 mm. Device prototypes consisting of 2 mm diameter 25% ATIPA foam cylinders threaded over 200 μm nitinol wire were included on the frame in both their expanded and axially crimped state. Axial crimps were conducted with an SC250 heated stent crimper (Machine Solutions, Flagstaff, AZ) by heating the material to 70°C in the crimper bore for 15 minutes, radially compressing the material at 50 psi, and constraining the material as it cooled to ambient temperature. Samples were imaged in comparison to an industry accepted control, Guglielmi detachable coils (GDC10) [2]. Samples were adhered to a polypropylene sheet and imaged through a 0.5" aluminum plate as an analog for human skull x-ray attenuation [7].

Quantification of the radiopaque properties of the 25% ATIPA foam composition was done using ImageJ. A histogram of the grayscale value was taken for each sample and then normalized.

Unconstrained Expansions

The 25% ATIPA foam composition was cut into five cylindrical samples with 4 mm diameter and measuring 1 cm in length. The samples were placed onto a nitinol wire to provide

stability. Samples were crimped using SC250 heated stent crimper (Machine Solutions, Flagstaff, AZ) by heating the material to 70 °C, holding it isothermally for 15 min, and compressing the sample at 55 PSI as it cooled to ambient temperature. Images of the crimped foam samples were taken prior to expansion. For the expansions, the samples were placed in reverse osmosis water at 37 °C for 30 minutes and imaged every 30 seconds. ImageJ was used to analyze the diameter of the foam samples through the expansion process.

Fourier Transform Infrared Spectroscopy (FTIR)

Thin foam samples of the 25% ATIPA and a control 25% ATIPA analog composition were cut (2-3 mm) for spectra analysis using Bruker ALPHA Infrared Spectrometer (Bruker, Billerica, MA). The samples were placed between potassium bromide discs and analyzed with a total of 32 scans for each composition. Background spectra were determined with 20 scans of the potassium bromide discs. OPUS software (Bruker, Billerica, MA) was used to remove the background spectra from the measurements and to conduct a baseline correction for IR beam scattering. Each composition spectra was taken three times to confirm reproducibility.

Foam Density

Foam density for samples on the x-ray test frame were determined by obtaining foam volumes and masses of six different cubed samples from each composition. The volumes were quantified by measuring the length, width, and height in millimeters using calipers. Each sample was then massed, and the subsequent densities were averaged for each composition.

CHAPTER III

RESULTS

Foam Composition and Morphology

A primary goal in this project was to determine type and quantity of surfactant and catalysts required to obtain tunable, porous foam morphology. Based on previous work, the development of clinically applicable foam was pursued using BEP, DEG, HDI, and ATIPA. Various compositions were synthesized for scaled radiopacity, as shown in ***Table 1***. The 25% ATIPA composition (i.e., 25% ATIPA, 30% BEP, 45% DEG all in equivalence to 100% HDI and using a premix ratio of 40%) provided superior fluoroscopic and chemical properties and as such was characterized extensively.

Table 1. The various compositions of foams synthesized with the molar equivalence of the polyols and isocyanates given, the weight percentages of surfactant and catalysts, and amount of blowing agent used.

Composition	ATIPA OH Eq%	BEP OH Eq%	DEG OH Eq%	HDI NCO Eq%	Surfactant wt%	Amine Catalyst wt%	Urethane Catalyst wt%	Enovate (mL/g)
25% ATIPA	25	30	45	100	4	1.5	0.3	0.0625
20% ATIPA	20	35	40	100	4	1.5	0.3	0.0625
15% ATIPA	15	40	35	100	4	1.5	0.3	0.0625
25%ATIPA Analog	25	30	45	100	4	1.5	0.3	0.0625

Through several trails, 4 wt% of surfactant yielded the most stability during the foaming process. Amine and urethane catalysts were used in amounts determined from previously established foaming protocols. Previous work has shown success and controlled reactivity using this set of catalysts.

Determining the best pre-mix protocol for the 25% ATIPA foam composition was a major focus of this project. The pre-mixes were mixed at various temperatures (room temperature, 35 °C, and 50 °C) and durations (3 hours, 6 hours, and 12 hours). Testing revealed that the room temperature mixing for 3 hours with a 3 hour sitting period gave the best morphology. Other

variations of the protocol caused premature oligomers to form that altered monomer solubility and/or gave low viscosity pre-polymer mixes that produced undesired morphologies.

The porosity of the foams was qualitatively analyzed using SEM imaging. As seen in ***Figure 2,*** the pore sizes increase with a decrease in ATIPA concentration. This increase in pore size can be explained by taking into account the high molecular weight of the contrast agent itself. As described in the methods, the synthesis involves a pre-polymerization step. This step is important in determining the morphology of the foam-porosity. More viscous the pre-mixes results in reduced pore sizes, due to increased resistance to blowing. With a lower concentration of high molecular weight ATIPA in the pre-mix, the viscosity is decreased, resulting in increased pore sizes. Future work to match the pore sizes for each foam composition could be explored using different amounts of blowing agent and/or by altering the pre-mix ratio to include more ATIPA.

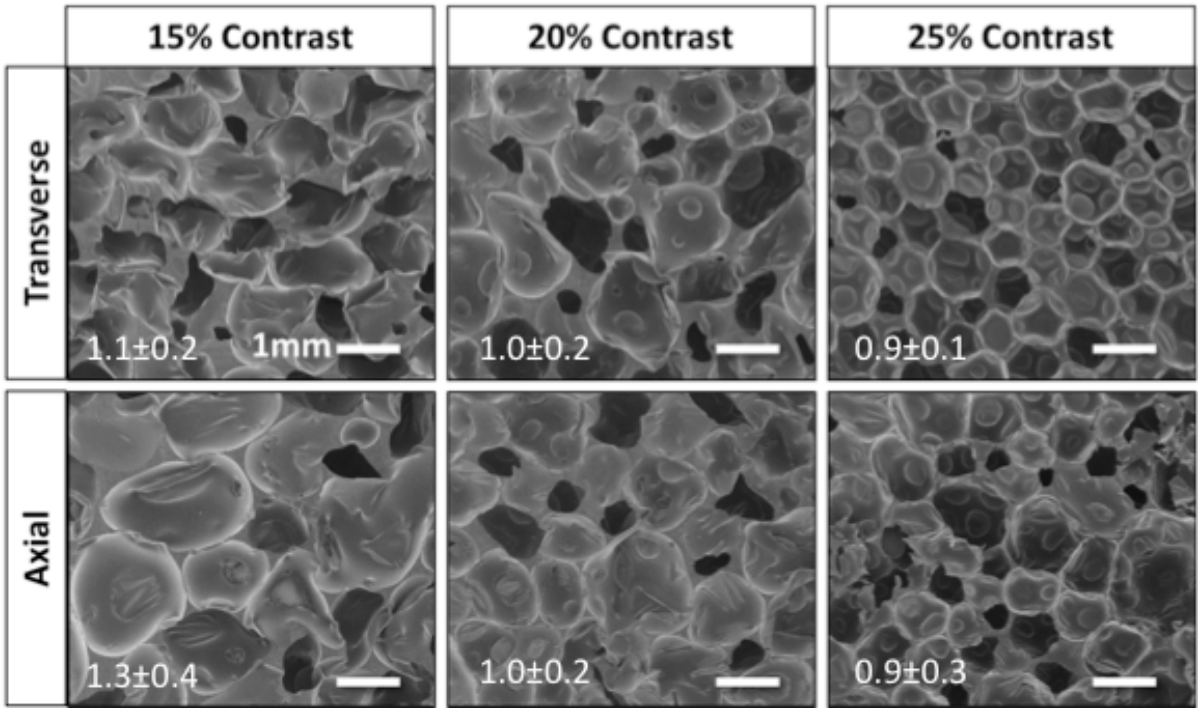


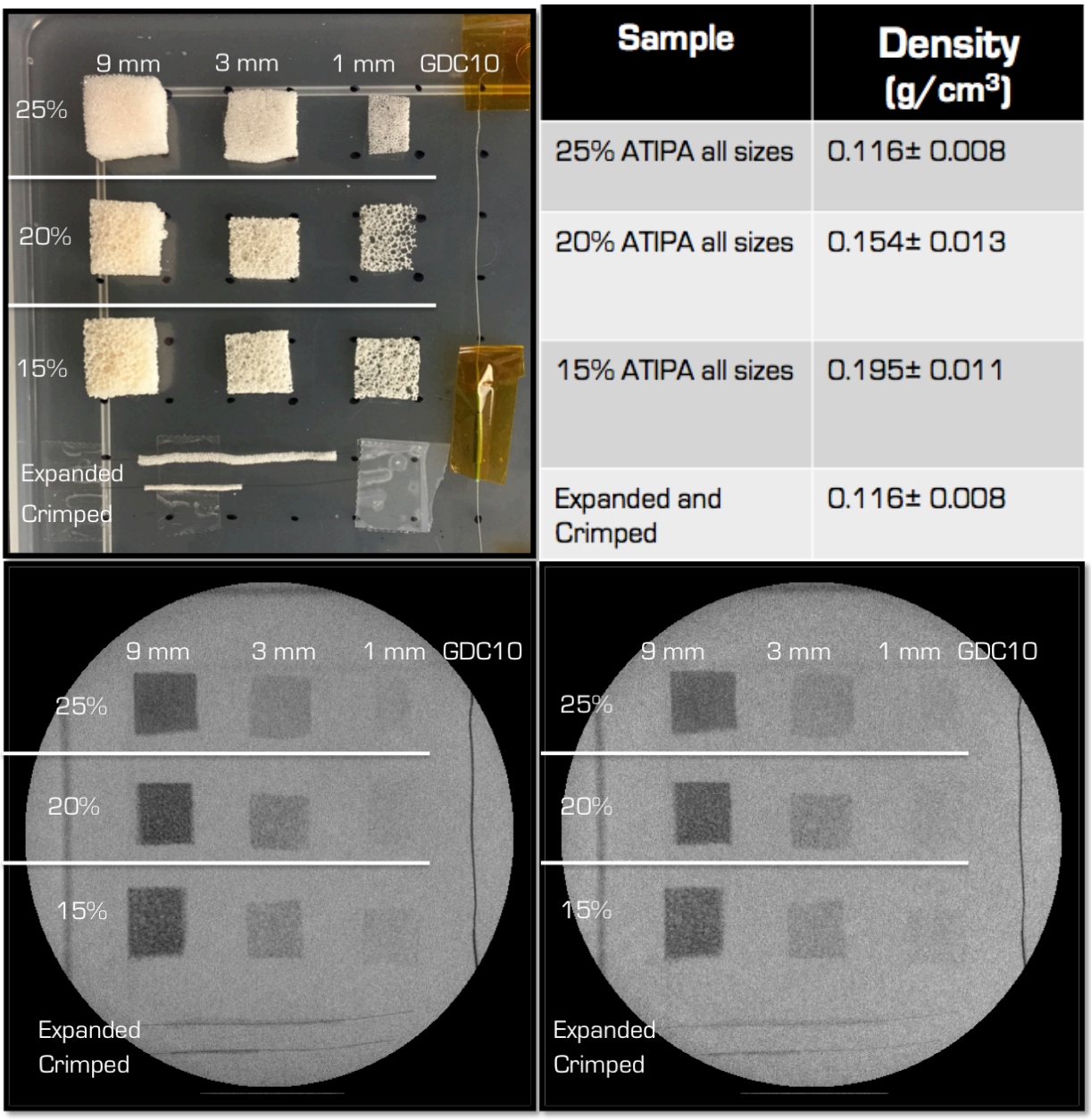
Figure 2. Morphologies of the foam compositions are shown above. Pore sizes are given in the bottom left corner of each with units of mm. Scale bar of 1 mm applies to all images.

Radiopacity

The major goal in the development of this SMP foam is visibility under fluoroscopy. All variations of the foam compositions were visible, as seen in ***Figure 3***. However, the densities of the foam compositions have not been normalized; thus, we did not observe increased radiopacity with increased ATIPA, even though this is a known trend. The density is largely dependent on the foam morphology and the amount of high molecular weight contrast agent present in the foam. The lower percentage foams (15% and 20% ATIPA) had larger pore struts, which increased their densities and contributed to their seemingly greater x-ray visibility. However, all of the samples can be seen at various thicknesses both with and without an aluminum plate barrier. Relevant to the goal of demonstrating clinical applicability, the expanded and crimped device prototypes demonstrated by A and B respectively in ***Figure 3***, were also visible.

The radiopacity of the 25% ATIPA foam was quantified by determining a normalized grayscale value for each thickness under the aluminum plate and for unobstructed imaging ***(Figure 4).*** Visibility increased with increasing thickness, and only slight deterioration in visibility was seen following obstruction with aluminum.

FTIR was performed on the 25% ATIPA foam composition along with a foam with a 25% ATIPA chemical analog, to demonstrate the presence of the radiopaque chemical characteristic in the foams (i.e. iodine). The spectra were similar to each other, as seen in ***Figure 5***. This result indicates that the iodine motif of ATIPA does not greatly affect the polymer chemistry of the foams. However, the expected iodine peaks from incorporation of ATIPA cannot be seen. This result is likely because they are in the fingerprint region (~500-1500 cm^{-1}), in which individual peaks are difficult to discern. Thus, the peaks attributed to other bonds within the polymer could be overshadowing these specific peaks. Although the FTIR spectra does not chemically confirm the presence of the radiopaque functionality of ATIPA, the radiopaque properties of the foam ***(Figure 3)*** provides confirmation of successful incorporation.



Sample	Density (g/cm^3)
25% ATIPA all sizes	0.116± 0.008
20% ATIPA all sizes	0.154± 0.013
15% ATIPA all sizes	0.195± 0.011
Expanded and Crimped	0.116± 0.008

Unobstructed Fluoroscopy

Half-inch Aluminum Plate Barrier

Figure 3. Fluoroscopy images for ATIPA foam compositions. Top left: picture of sample plate preparation. Top right: densities of each sample. Bottom left: Unobstructed fluoroscopy image of samples. Bottom right: Obstructed fluoroscopy using a half-inch aluminum plate barrier. Within each image, from top to bottom: 25%, 20%, and 15% ATIPA. Left to right: thicknesses of 9, 3, and 1 mm. Expanded: Expanded foam over wire prototype. Crimped: crimped foam over wire prototype. GDC10: Control Guglielmi detachable coil (GDC10).

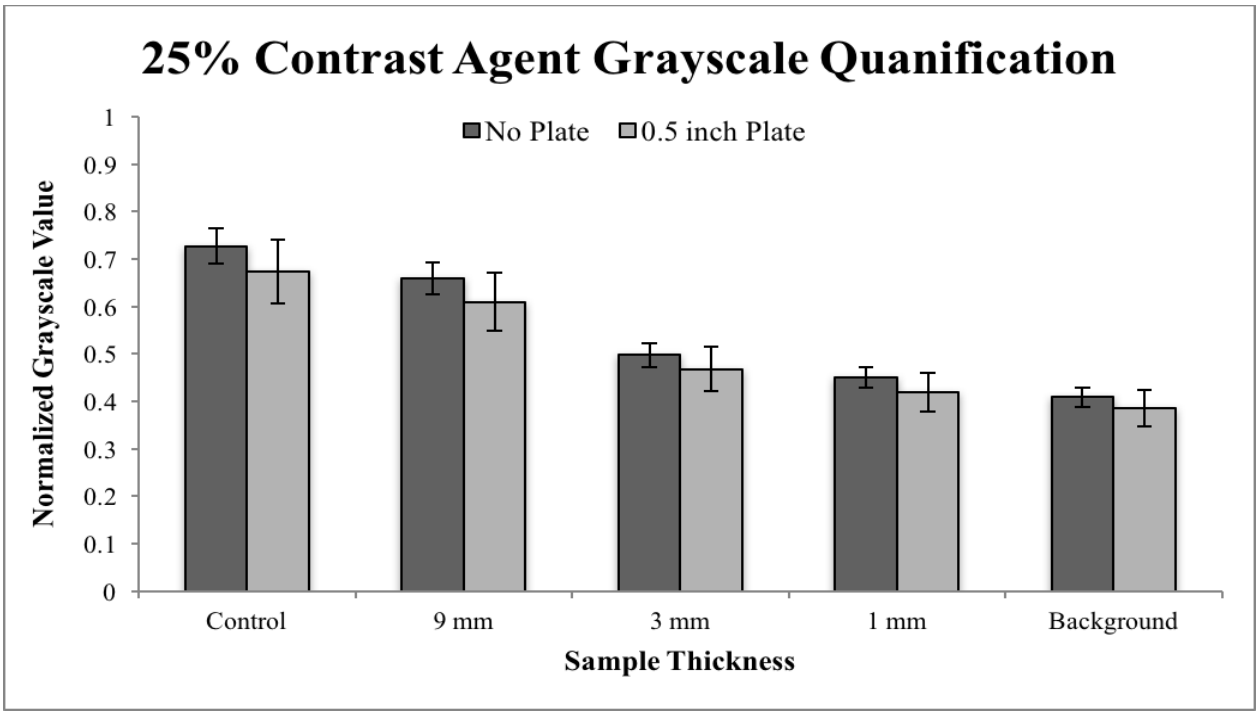


Figure 4. Quantified opacification of the 25% ATIPA foam composition based on normalized grayscale values. Increasing opacity with sample thickness is shown, with little differentiation between the unobstructed images and those with the aluminum plate.

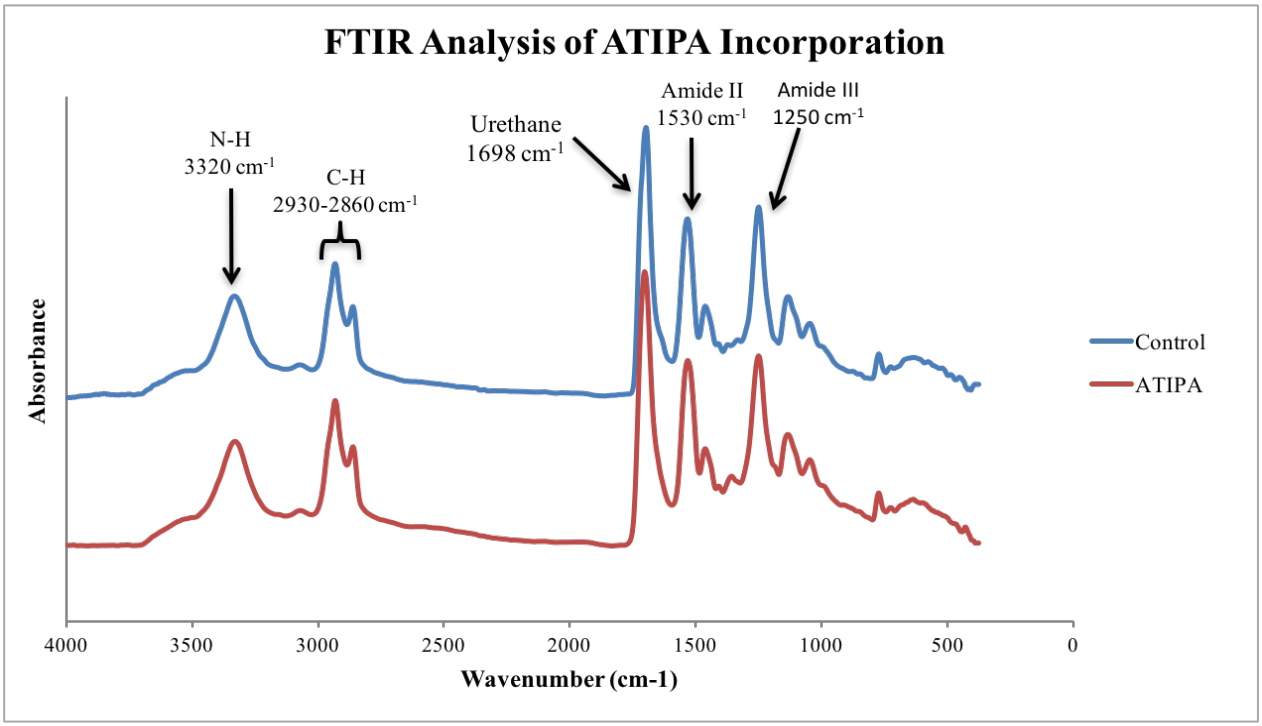


Figure 5. FTIR spectra of the 25% ATIPA contrast agent foam (bottom) and control 25% ATIPA chemical analog foam (top).

Glass Transition Temperature/Gel Fraction

Thermal characterization of the foam compositions showed an increase in glass transition temperature with an increase in ATIPA concentration, as seen in ***Table 2***. This trend can be explained by increased crosslink density that occurs with increased ATIPA. The transition temperatures are still very low for clinical application (at or below body temperature), since they affect foam actuation, which controls the amount of time that a clinician has for delivery. Previous foams for use in embolic applications have transition temperatures between 50 and 70 °C [4].

The gel fractions of the three foam compositions did not demonstrate any significant trends. The gel fractions for the highest percent of ATIPA were relatively low when compared to the current SMP foam formulations with gel fractions of nearly 100% [4]. While the current transition temperatures and gel fractions of these specific compositions are not ideal for clinical application, future directions include incorporating additional crosslinking agents to increase these metrics.

Foam Actuation

Full expansion of crimped 25% ATIPA foam samples took place within 30 seconds of exposure to 37°C water. These results show that the foams exhibit shape memory ***(Figure 6)***. However, such quick response to heat is not clinically applicable, since the clinician would need more time for delivery through the catheter. Further investigations into increasing T_g for the foam need to be conducted to reduce the rate of expansion.

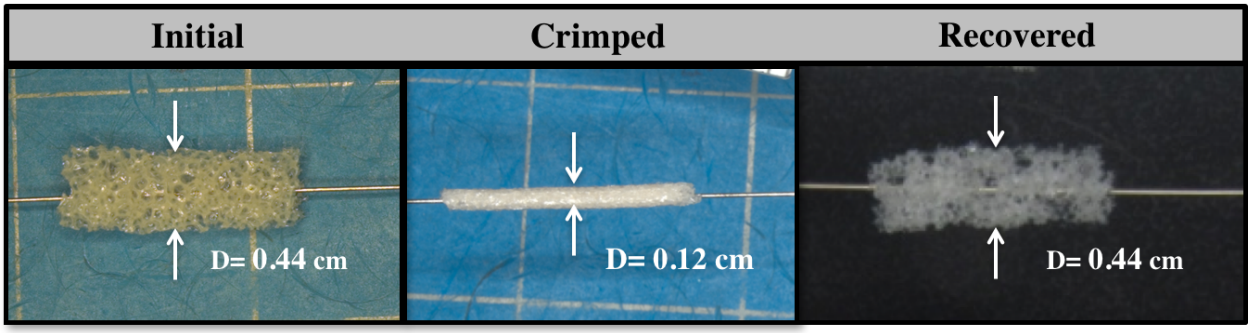


Figure 6. 25% ATIPA foam prior to crimping (left), radially crimped (middle) and after expansion in 37 ^{o}C water (right). Diameters given at bottom right.

Mechanical Properties

Tensile testing showed that the ATIPA foams have increased modulus, strain at break, ultimate tensile stress, and strength relative to non-radiopaque foam formulations and radiopaque tungsten nanoparticle containing foams (***Figure 7***). High tensile strength is promising for embolic device applications, as it indicates a reduced risk for microtears and microfractures that would lead to embolic particles dislodging from the foam. When the concentration of ATIPA increased, an increase in modulus and ultimate stress was seen (***Table 2***). However, no trend for strain at break for the three foam compositions was observed.

Table 2. Quantified glass transition temperatures, gel fractions, and mechanical testing data for each foam composition. Mechanical properties are quantified from stress-strain curves.

	T_g (°C)	Gel Fraction (%)	Strain at break (%)	Modulus (MPa)	Ultimate stress (kPa)
25% ATIPA	38.6±0.1	88.7±2.5	116±14	1.49±0.12	306±31
20% ATIPA	33.5±0.3	89.3±1.0	364±7.9	0.131±0.040	215±28
15% ATIPA	28.6±0.0	85.3±1.9	245±0	0.0851±0	94.4±0

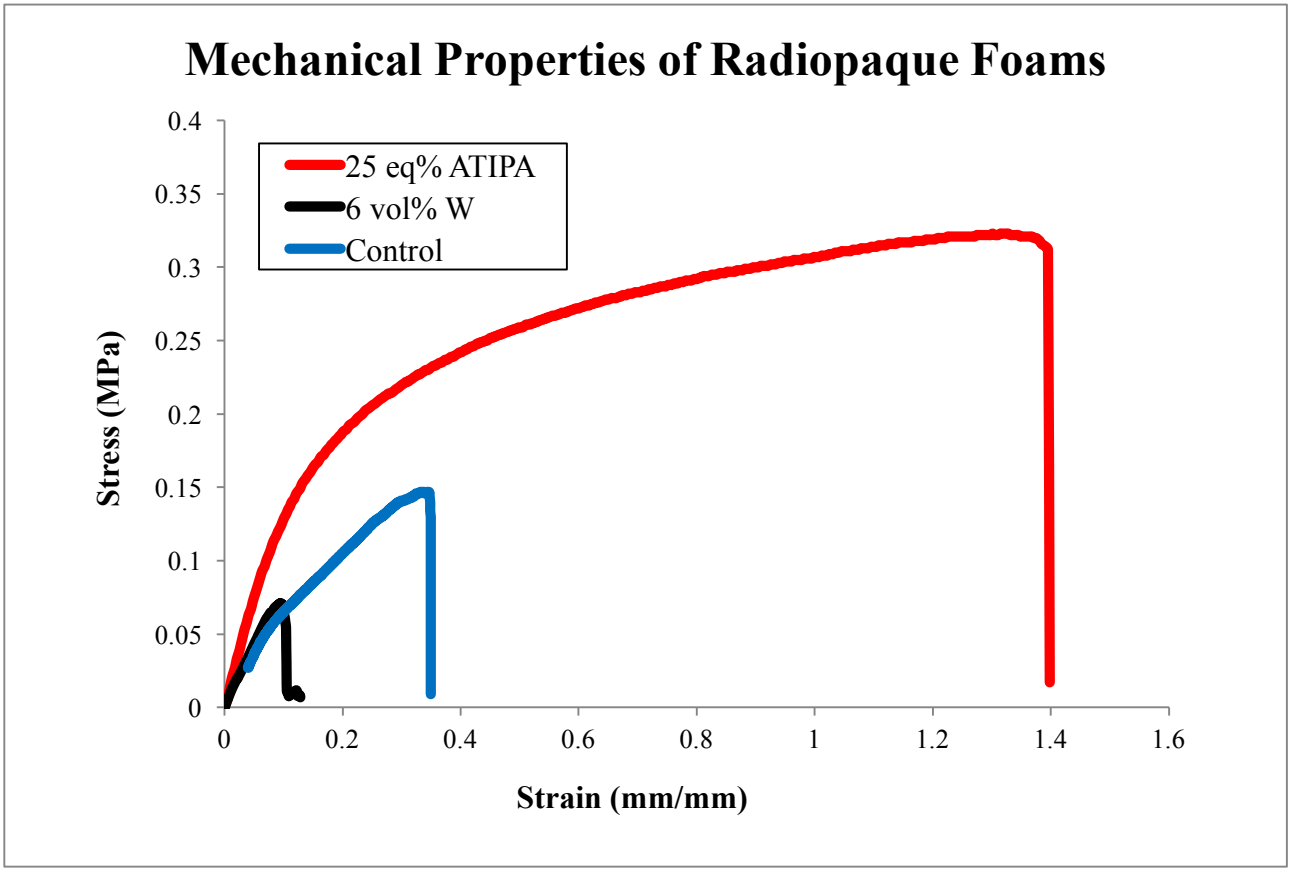


Figure 7. Comparison of the mechanical properties of 6 vol% tungsten nanoparticle incorporated foams and the 25% ATIPA contrast agent incorporated foams versus control nonradiopaque SMP foam currently used for device development [5].

CHAPTER IV

CONCLUSION

An SMP system with a chemically incorporated triodobenzene monomer was developed and proven to be x-ray visible. The results showed clinically relevant morphology and pore sizes in the SMP foams. Additionally, these materials showed significant increases in visibility and toughness compared to previously reported radiopaque SMP systems. This system shows promise for the development of a clinically relevant device; however, further optimization is required to increase polymer crosslinking and glass transition temperatures to enable more clinically relevant medical device designs.

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