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Full Paper

Multi-Functional Polyurethane Hydrogel Foams with Tunable Mechanical Properties for Wound Dressing Applications

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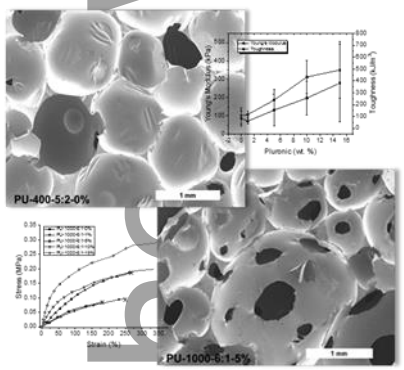
Polyurethane hydrogel foams synthesized through a facile one-pot, solvent-free process are described. The roles of PEG molecular weight, cross-linking density, and foam stabilizer

concentration on polymer properties are evaluated for potential applications as wound dressing materials. Material characterization and wound dressing relevant performance evaluations were performed to understand effects of individual components and identify promising formulations. Surprisingly for a solvent-free reaction, complete polymerization is confirmed by IR and gel fraction analyses. Foam stabilizing agent loading increases mechanical properties including Young's modulus, extensibility, and toughness, while decreasing pore size and drug release rate. Mechanical properties are also dependent on the crystalline melting temperature of the PEG diol. Utilizing caffeine as a drug surrogate, HPLC drug-release analysis identified that polyurethane hydrogel foams exhibit initial burst release kinetics followed by sustained release over 24 h. Antibiotic compatibility and release is demonstrated for all formulations by zone of inhibition testing against gram-positive and -negative bacteria.



[a] **Supporting Information** is available online from the Wiley Online Library or from the author.

1. Introduction

Recent advances in body armor and military medical response have decreased fatality rates in military populations, but increased the severity and frequency of severe limb injury.[1-3] Furthermore, over 30 percent of potentially survivable fatalities in recent combat arenas resulted from hemorrhage due to severe limb trauma.[4] Current acute medical interventions fall short in preserving tissue viability and long-term outcomes of warfighters injured in far-forward settings which require extended evacuation times.[5, 6] The current standard of care dressings were designed from materials for use in civilian settings that allow for frequent dressing replacement, debridement, and intravenous antibiotics, options not readily available to a deployed warfighter that gets injured. Therefore, a need exists to develop improved materials which serve as wound contact materials in composite multi-functional dressings to improve outcomes resulting from traumatically injured limbs. Some of the unique characteristics that a military wound dressing material must exhibit include antibacterial and antifungal activity, hemostatic properties, and robust mechanical properties across a large temperature range, while also performing tasks standard of a wound dressing (adhesion, shelf-life, ease of use, etc.). In addition to performance characteristics, synthetic design and component selection are critical to afford the greatest possible viability for scale-up.

One promising class of hydrogels for wound dressing applications intended for diverse military applications are polyurethane hydrogels. Polyurethane foams have been utilized as scaffolds to provide physical support and elastic properties to acrylate based polymer gels.[7] The addition of a variety of copolymers to polyurethane have been shown to enhance properties across a range of applications.[8] Polyethylene glycol (PEG) is a common component of many polyurethane hydrogel materials for biomedical applications due to its biocompatibility, low toxicity, and resistance to both hydrolytic and enzymatic degradation.[9, 10] Other applications of PEG include tissue engineering

matrices, chronic wound management, stents, catheters, and drug-delivery vehicles.[11, 12] While many materials have been developed for the treatment of chronic wounds,[13] such materials often exhibit undesirable properties for the far-reaching environments where potential military injuries may occur, including thermal instability, sensitivity to light, or limited shelf-lives. Incorporation of poly(lactic acid) has shown to improve physical resilience of polyurethanes foams, although to the detriment of swelling.[14] Polycaprolactone segments have been incorporated into cross-linked poly(ethylene glycol) urethane films to impart biodegradability, temperature dependent swelling characteristics, and sustained drug-release.[15] Likewise, amino acid based monomers have been incorporated into PEG-hexamethylene diisocyanate (HDI) based polyurethanes to impart biodegradable characteristics to polymerized nanoparticles with tunable temperature sensitivity.[16]

Antimicrobial properties of wound dressing can impart bacteriostatic or bacteriocidal conditions to reduce local infection and prevent greater loss of tissue. Several approaches have been taken to incorporate antimicrobial activity into hydrogel materials, including but not limited to silver nanoparticles, antibiotics, and antimicrobial agents.[17] Other materials exhibit inherently antimicrobial characteristics based on structure, which mitigates leaching risks, but diminishes antimicrobial diffusion from the wound dressing.[18]

The goal of this research was to formulate polyurethane hydrogel foams that were mechanically robust, while including additional properties desirable for wound dressing applications: absorption of large amounts of exudate, drug compatibility and delivery, and swelling induced compression. Polyurethane (PU) composition comprised a PEG (M_w varied from 400 – 3000 g/mol), HDI, glycerol ethoxylate (GE), and a foam stabilizing agent. The relative proportions of these reagents were modulated to gain an understanding of how each affects mechanical and bio-relevant properties. It was hypothesized that an inverse relationship between mechanical properties and performance

properties (i.e. absorption and drug-release) exists, from which an ideal formulation that exhibited optimal balance would be identified.

2. Experimental Section

2.1. Materials

Dibutyltin dilaurate (DBTDL), caffeine, and all solvents were obtained from Fisher Scientific and used as received. Ciprofloxacin was obtained from Acros Organics and used as received. Pluronic F-127 (Pluronic), poly(ethylene glycol) (PEG, M_w = 400, 1000, 1500, 3000), glycerol ethoxylate (GE, M_n = 1000), hexamethylene diisocyanate (HDI), and gentamicin were obtained from Sigma-Aldrich and used without further purification. Bacterial strains cultured at Naval Medical Research Center (NMRC) used were *S. aureus* (ATCC 25923), *P. aeruginosa* (ATCC 27853), and *E. coli* (ATCC 25922).

2.2. General Preparation of PEG Hydrogel Foams

Prior to synthesis, PEG, GE, and Pluronic were dried in a vacuum oven at 45 °C for 2 h. Fixed weights of polyols including PEG, GE, and Pluronic were added to a 50 mL conical tube containing a Teflon stir bar submerged in a 60 °C water bath and allowed to equilibrate for at least 30 min prior to addition reagents. Distilled water was then added and allowed to mix. After 5 minutes, DBTDL was added to the mixture. After an additional 1 minute, HDI was added at slight excess (NCO:OH = 1.1) with continued stirring. Foaming due to reaction between diisocyanate and water indicated polymerization initiation typically began within 1 min of the addition of the diisocyanate. A general reaction scheme is shown in **Figure 1** and detailed compositions of each formulation are presented in **Table 1**. Detailed reactant proportions are provided in Supporting Information.

2.3. Material Characterization

Attenuated total reflectance infrared (ATR-IR) spectra were recorded utilizing a Nicolet iS50-FT-IR with iS50 ATR attachment equipped with a Ge crystal from Thermo Scientific (Waltham, MA). 128 scans were compiled for each spectrum. ATR-IR allowed for direct IR analysis and avoided additional sample preparation. Gel fraction analysis was performed, samples were first weighed, then soaked in THF for 24 h, after which the THF was discarded. The samples were dried in vacuum for 24 h and the dried products weighed. Gel fraction was determined by the dividend of the final mass divided by the initial mass. Values are reported as an average of the replicates. Each sample was performed in triplicate.

Glass transition temperature (T_g) and crystalline phase transitions were determined on a TA Instruments Discovery Differential Scanning Calorimeter (DSC). Two successive temperature ramps were performed from -70 °C to 100 °C at a rate of 10 °C min^{-1}. Measurements were recorded from the second ramp. A TA Instruments Discovery TGA was utilized to perform thermogravimetric analysis at a heating rate of 10 °C min^{-1} under N_2 from room temperature to 600 °C. Degradation onset temperature was assigned at the temperature at which 90 % mass remained. DSC and TGA data were processed utilizing TA Instruments Trios software.

Pore size measurements of the polyurethane foams were performed on a JEOL JSM-7600F Field Emission SEM (Peabody, MA, USA) operated at an accelerating voltage of 3 kV. PU foams were cross-sectioned for analysis and were gold sputter coated with at least 5 nm of gold prior to SEM analysis. Image J was employed to determine pore sizes from the SEM micrographs.

Strain-to-break tensile testing was performed using the tensile film geometry on a TA Instruments DMA Q800. Samples of PU foams were cut into rectangular cuboids, measured, and clamped to the DMA geometry. A controlled extension force of 3 N min^{-1} was applied to the sample until the foam

sample broke or the instrument reached maximal extension; experiments were conducted at room temperature. At least three replicate measurements of each PU foam composition were conducted.

2.4. Counterpressure

Counter-pressure was measured with a TA Texture analyzer (Surrey, UK) equipped with a 1 inch diameter stainless steel cylinder probe. PU foams were cut into cylinders with diameter of 25 mm and height of 1 cm and placed in a custom built apparatus to provide lateral constraints. The probe was programmed to compress the foam cylinder 3 mm after a 0.5 g trigger force was achieved. 10 mM PBS buffer solution was poured into the reservoir surrounding the foam to initiate swelling and the probe distance was held constant while applied force was monitored.

2.5. Uptake

PU foams were dried overnight *in vacuo* prior to uptake experiments. Dry foam samples were then cut into cubes, weighed, and placed in 20 mL scintillation vials to which 20 mL of 10 mM PBS buffer solution were added. Samples were prepared in triplicate. Samples were allowed to reside at room temperature for 24 h, after which the swollen samples were removed from the vials and weighed. Absorption was measured in units of grams uptake per gram of material (g/g), which was calculated by dividing the mass gained (final mass – initial mass) by the initial mass of the dry foam.

2.6. Drug-release

PU foams were cut into 100 mg cubes. Each was submerged in 1 mL of chloroform solution containing 1 mg mL^{-1} caffeine. Foams were allowed to swell in sealed vials for 2 h, after which they were dried in vacuum at room temperature. The dry caffeine loaded foams were each placed into 40 mL of PBS buffer at 37 °C. Using a micropipette, 1 mL aliquots were taken and replaced with fresh buffer at time points of 1, 2.5, 5, 7.5, 10, 15, 30, 60, 90, 120, 180, and 1440 min. Aliquots were

analyzed via HPLC. An Agilent 1260 Infinity LC system equipped with an Agilent zobrax SB-C18 column connected to an Agilent Infinity UV-Vis diode array detector monitoring 254 nm (reference at 380 nm) was utilized. A gradient run of 100 % water to 90 % acetonitrile, containing 0.1 % formic acid, at 500 µL min^{-1} was employed. HPLC data was processed using Agilent OpenLAB CDS software. Concentration vs. time data over the first 10 minutes were fit to linear regressions using Origin 2016 software to identify initial release rates.

2.7. Cytotoxicity

The PU foams were tested for cytotoxic effects using a modified version of the ISO 10993-5 "Biological evaluation of medical devices – Part 5: Tests for in vitro cytotoxicity".[19] Extracts were prepared by incubating 5 mg samples of each foam, previously washed in chloroform and thoroughly vacuum-dried, in 1.5 mL of EMEM media supplemented with antibiotics and 10 % FBS for a 24 hour period at 37°C, 5 % CO_2. HeLa cells were cultured in EMEM supplemented with 10 % FBS and antibiotics at 37 °C, 5 % CO_2. Prior to the experiment, HeLa cells were trypsinized, lifted and counted using a hemocytometer. The cells were seeded at 15,000 cells per well in 200 µL of EMEM in a 96-well TCPS plate. After five hours of incubation, the media was removed from the attached cells and promptly replaced with 200 µL of the extract. The cells were cultured in the extract media for 24 hours prior to incubation with 20 µL of PrestoBlue reagent for 45 minutes at 37 °C. The fluorescence was measured at 590 nm. Percent viability was normalized to a negative control of seeded HeLa cells and normal media. A positive control with cells incubated in EMEM media with 1 % Tween-20 for 2 hours prior to addition of PrestoBlue was included; six replicates were conducted for each test condition.

2.8. Antimicrobial Testing

Bacterial cells were statically cultured overnight (14-16 hours) in LB medium at 37 °C. Overnight cultures were then diluted 1/20 into LB and spread over LB agar plates with a cotton applicator. Using sterile forceps PU foams loaded with gentamicin or ciprofloxacin, were placed on the bacterial lawns and incubated for 24 hours at 37 °C. The zone of inhibition diameters were then measured in millimeters.

3. Results and Discussion

The aim of this study was to create robust polymeric hydrogel foams, which could be used for potential wound dressing applications, through a simple synthetic route that can readily be scaled-up. In doing so, the goals were to identify effects of components on physical properties, mechanical behavior, and performance in wound-dressing relevant testing. It was expected that increased cross-linking density would increase mechanical toughness of the materials, to the detriment of uptake and subsequently drug-release. Foam stabilizing agents that were incorporated to facilitate decreased pore size and uniformity were expected to have opposite effects, to increase drug-release rates and uptake capabilities.

3.1. Material Evaluation

Reaction conditions were optimized through several systematic trials, ultimately identifying the procedure aforementioned in the experimental section in which the rate of polyurethane polymerization and cross-linking occurred on the same scale as the water-isocyanate foaming reaction, resulting in a facile, solvent-free, single pot synthesis of a polyurethane foam.

3.1.1. IR Analysis

Absence of -NCO absorbance at 2200 cm^{-1} in the ATR-IR spectra (Supporting Information) of polyurethane foams clearly demonstrated complete reaction and consumption of isocyanate during polymerization of each formulation. This was particularly notable considering that the foaming reaction occurred rapidly, in a single open reaction vessel without solvent. IR spectra across all formulations were nearly identical because of the inherent similarities in the chemical structures among reagents and formulations. The degree of cross-linking did not have any significant effect on the IR spectra of the polymer formulations, since the IR signature of trifunctional GE cross-linker is similar to that of PEG. Increased concentration of Pluronic resulted in increased relative intensities of the ether stretching modes at 1096 cm^{-1} due to the proportionally greater contribution of C-O stretching vibrations from the additional ether moieties introduced from the PPO-PEG-PPO structure of Pluronic. Characteristic absorbance of alkane C-H bonds were observed at 2924 and 2860 cm^{-1} in all formulations from the hexamethylene segment of HDI. Each formulation exhibited peaks at 3550 and 3370 cm^{-1}, which correspond to non-bonded and H-bonded –N-H, respectively.[20] Absorbance from OH hydrogen bonding to N were due to the amide functional group which was generated from the reaction between water and isocyanate that first formed a primary amine, then subsequently reacted with an additional isocyanate to form a urea linkage.

The impact of PEG M_w was observed by comparing the carbonyl region, 1600-1800 cm^{-1} (**Figure 2**). Each composition exhibited a relatively strong absorbance at 1715 cm^{-1} which corresponded to non-bonded amide I C=O stretching that was attributed to urethane linkages. The shoulder peak at 1697 cm^{-1} was attributed to non-bonded urea C=O stretching and decreased with increasing PEG M_w.[21] The additional shoulder at 1662 cm^{-1} was attributed to H-bonded urethane amide I C=O stretching. Use of water as a foaming agent resulted in the formation of urea linkages during polymerization through the mechanism in which water reacted with isocyanate, forming CO_2 and an amine that subsequently reacted with an additional isocyanate to form a urea bond. Reduced absorbance in

the amide II and amide III bands at 1533 cm^{-1} and 1247 cm^{-1}, respectively, further indicated decreased urea linkage content with increased PEG M_w. Therefore, decreased intensity of the urea absorbance of longer PEG lengths indicated fewer amine–isocyanate reactions, likely due to the reduced molecular mobility imparted by the longer chains, especially in a solvent-free reaction. Additional support to this conclusion can be seen in the Supporting Information, as the –N-H stretching absorbance was strongest in the PEG 400 foam, due to the greater degree of urethane linkages. This was further supported upon macroscopic visual observation of the foams, as the longer PEG length PU foams exhibited morphologies of increasing large solid areas dispersed with large dispersion of pores.

3.1.2. Foam Properties

The average pore diameter of the foams were measured via SEM and found to be in the range of 0.6 – 1.2 mm (**Table 2)**. Pore size was inversely affected by cross-linking density and regardless of concentration, presence of Pluronic resulted in reduction of average pore sizes by approximately 35 %. The general appearance of these foams can be seen in representative images shown in **Figure 3**, in which the porous structure is evident. Pluronic loading appeared to impart an open-cell structure with large pores connect through smaller micropores (**Figure 3B**). Overall, spherical pores were dispersed throughout the material, connected through a matrix of solid polyurethane hydrogel. This morphology provided the materials with sponge-like void filling absorption capability coupled with robust physical properties provided by the PU matrix. Results of thermomechanical analyses performed on the series of PU foams are summarized in **Table 2**.

Gel fraction analysis indicated that the polymerization reaction of each formulation was relatively complete as each exhibited a gel fraction greater than 90 %, supporting the absence of isocyanate absorption observed in the previous ATR-IR spectra. Surprisingly, neither degree of cross-linking nor

Pluronic concentration affected gel fraction. In contrast, an inverse relationship existed between PEG M_w and gel fraction that was likely due to decreased molecular motion of the growing polymer chain of PEG of greater M_w which reduced polymerization rates. Thus as polymerization proceeded, each polyol was less likely to be in proximity to an isocyanate group to form urethane linkage, resulting in increased chain terminations and greater soluble fractions.

3.1.3. Thermomechanical Analysis

TGA analyses of the hydrogel foams were performed to assess the environmental stability of the materials (**Supporting Information**). The degradation onset temperatures (**Table 2**) for all foams exceeded 295 °C, indicating significant thermal stability particularly in context of wound dressing materials. In general, PU foams that contained PEG chains of smaller M_w exhibited a lower degradation onset temperatures, i.e. 296 °C for PEG 400 compared to 325 °C for PEG 3000, though a direct relationship was not observed.

DSC analysis indicated that significant endothermic transitions T_m^1 occurred in most formulations, the temperatures of which were dependent on PEG M_w and independent of cross-linking and Pluronic concentration. Increase in temperature of T_m^1 was attributed to the local melting of the PEG segment of the PU foams since the T_m^1 increased with increasing PEG M_w (**Table 2**). The observed temperatures of T_m^1 correspond well with melting behavior of PEGs of comparable M_w in linear polymers.[22] In foams that contained Pluronic, a second endothermic transition T_m^2 occurred at approximately 32 °C due to the localized Pluronic melting, which increased in intensity to the detriment of T_m^1 (**Figure 4**). The decrease in T_m^1 at the expense of T_m^2 suggests that Pluronic was associated with the PEG crystalline regions and contributed a stabilizing effect that increased the T_m for the segment. Additionally, gel fraction did not decrease with increasing Pluronic concentration, indicating that Pluronic was covalently bound into the polymer structure. Since Pluronic is a hydroxy

terminated foaming agent, it likely reacted with available isocyanate during polymerization. Qualitative observation of the hydrogel foams ensured that these melting transitions were only for particular segments of the polymer, as the foams maintained their porous structure and form to temperatures well above T_m^1 and T_m^2.

The mechanical properties of the PU foams were analyzed via strain-to-break tensile testing; Figure 5 and Table 3 illustrate the representative loading curves and a summary of the mechanical properties for the different foam compositions, respectively. In general, the mechanical properties of the PU foams indicated that these were mechanically robust and tough materials, particularly in the context of hydrogels.[23] The stiffness (Young's modulus) of the foams increased with increasing PEG molecular weight: PEG400, PEG1000 and PEG1500 had moduli of 95.3, 195.0 and 872.3 kPa, respectively. This dramatic difference in foam stiffness based on PEG molecular weight could be attributed to PEG crystallization in the higher molecular weight compositions. The T_m^1 provided by DSC illustrates that at room temperature (22-23°C), the PEG1500 would be below its melting point and would therefore, have greater PEG crystallinity which might reinforce the polymer foam network. Unfortunately, the PEG3000 foams were too friable and brittle for tensile experiments and were excluded from analysis.

Adjusting the mole ratio of PEG to glycerol ethoxylate did not substantially change the Young's modulus of the foams, but did impact foam extensibility; the 1:2 and 3:2 PEG to GE compositions broke at 21.5 and 58.4% strain, respectively, while the 6:1 composition had an average strain-to-break of 179.7%. The stoichiometric imbalance in favor of bifunctional PEGs likely contributes to longer networks strands between cross-links and creates a more flexible polymer network. However, the extensibility and toughness of the foams was most improved by the incorporation of Pluronic; in fact, at 10 and 15 wt%, the PU foams did not break (DNB) and were routinely stretched

to greater than 300% strain. The direct relationship between greater Pluronic loading and increased stiffness, toughness, and extensibility of the PU foams appears to results from increased foam stabilization, as indicated by the decreasing average pore size, and the increased melting point, as indicated by DSC.

3.2. Performance Evaluation

3.2.1. PBS Buffer Uptake

The ability of the PU foams to absorb and manage exudate was simulated by uptake of PBS buffer solution. Across the series of formulations uptake of 5 – 12 g/g were achieved, a range comparable to commercial polyurethane foam dressings.[24] The advantage of these foams over existing commercial dressings is that these hydrogel foams have been synthesized and designed from the beginning to withstand a variety of extreme environmental conditions, like those encountered in military settings. Maximum uptake occurred in foams composed of PEG1000, suggesting 1000 M_w as optimal PEG chain length. Reduced uptake in short PEG length PEG400 likely resulted from greater hydrophobic contributions from HDI. Reduced uptake in higher PEG M_w foams were most likely due to increased crystallinity of the PEG segments, since these were below their T_m[1] at room temperature conditions.

3.2.2. Drug-Release

Caffeine loaded PU foams were submerged in PBS buffer at 37 °C and release was monitored via HPLC. Caffeine was used as a surrogate for antimicrobials, such as ciprofloxacin, because of its thermal stability and UV absorption. All PU foams exhibited an initial burst-release of caffeine within the first 2 h in which at least 80 % of drug was released, followed by slower sustained release over the subsequent 22 h (**Supporting Information**). Release of ciprofloxacin from a sub-series of foams

was also performed and demonstrated similar burst-release kinetics at the same rate and degree of caffeine release (**Supporting Information**). Therefore, similarity in release kinetics between the two compounds suggested non-specific binding of drug to polymer. Release of caffeine in the first 10 minutes were fit to linear regressions and the slopes were used to identify initial release rates (**Table 3**), with which a weak correlation with average pore size was identified (**Supporting Information**). It is possible that increased pore size allowed for an increased rate of swelling and penetration of the PU foam samples by the buffer solution. This would effectively increase the initial rate of caffeine release, during which caffeine was released from the PU surface. After 2 h, the similarity in release rates observed across all the samples between 2 – 24 h suggested that during this period caffeine was released from the polymer bulk, as PBS buffer solution swelled the polymer matrix. As approximately 80 % of total caffeine was released in the first 2 h, it was likely that caffeine was concentrated at the polymer-air interface. Such surface concentration of caffeine may have occurred during the drying phase after drug-loading, which allowed caffeine to diffuse to the boundary by internal concentration gradients.

3.2.3. Compression

Mechanical properties were most strongly dependent on Pluronic concentration (**Table 3**), therefore this sub-series of foams was further examined for its effects on the amount of pressure that is able to be applied by the foam as it swells. This was performed to simulate compression capability of the PU foams due to the pressure applied to a wound by a dressing material as it swells with exudate. Both initial pressure and final pressure applied by the swelling foams increased with increasing Pluronic concentration (**Figure 6**). Samples that contained Pluronic each experienced a decrease in applied pressure immediately upon absorption of water, which increased in intensity with increased Pluronic concentration. This was due to the immediate softening of the PU foam upon hydration.

Continued absorption of water by the foams caused swelling and increased volume to the degree that it applied counter-pressure. Since all samples examined in this series exhibited relatively similar uptakes, differences in amount of water absorbed was unlikely to explain the results. By comparison with mechanical properties, applied pressure was found to correspond with Young's modulus of the PU foams. As such, the degree of compression provided by a swollen material can be predicted by the Young's modulus as determined by mechanical testing. These data indicate that modulation of Pluronic concentration to be a facile method through which to tune the capability of the PU foams to provide compression to a wound site.

3.2.3. Biotesting

Zone of inhibition (ZOI) was performed to demonstrate the effect of antibacterial release on bacterial growth. In **Figure 7**, the effect of PEG length in the PU foam on zone of inhibition of three bacterial species are compared. Due to logistical limitations, ZOI analysis was limited to a subset of samples that comprised those of varying PEG length. Zones of inhibition were observed for each formulation loaded with gentamicin and ciprofloxacin and those loaded with ciprofloxacin exhibited, on average, larger zones of inhibition than those containing gentamicin. This was due to the greater efficacy of ciprofloxacin compared to gentamicin,[25] and not due to sample composition. Overall, there were no relationships between the zones of inhibition of and PEG M_w. ZOI results confirmed that the antimicrobial activity of the drugs were maintained while loaded and stored within the PU foam. Further, this test demonstrated the ability of the drugs to leach out of the PU foam into surrounding media to reduce bacterial population, as would occur in an infected wound.

Table 3 presents the results of cytotoxicity testing using an *in vitro* extract-incubation method outlined in ISO 10993-5 "Biological evaluation of medical devices."[19] Interestingly, the PU foams exhibit a varying degree of toxicity with cells incubated in the 0, 1, 5 and 10 wt% Pluronic F-127

extracts exhibiting 76.0, 56.3, 90.0, and 68.0 % viability, respectively. Leached dibutyltin dilaurate catalyst, known to be cytotoxic,[26] was likely responsible for the decreased cell viability; current efforts under investigation are exploring less cytotoxic alternatives.

4. Conclusions

A polyurethane hydrogel foam was synthesized through a facile, one-pot, and solvent-free synthesis that exhibited uptake capabilities comparable to commercial foam dressings. These foams demonstrated thermal stability and compatibility after loading a variety of small molecule antimicrobials. Some of the formulations were cytocompatible, while others were cytotoxic, likely due to the tin-based catalyst employed. Fortunately, the synthetic procedure reported herein can be simply modified to accommodate less toxic catalysts, which future work will explore. This study proved that modulation of both PEG segment length and Pluronic loading concentration were effective means through which mechanical properties can be tuned. Interestingly, rates of drug delivery were relatively similar across all compositions examined, with a minor dependence on pore size. Specifically, each demonstrated a burst-release effect that would be beneficial in infected wound scenarios to quickly reduce infection. As such, depending on specific needs of environment, mechanical and thermal properties can be simply optimized through PEG length selection and Pluronic concentration with negligible effect on drug-delivery, which can then subsequently be optimized through tuning processing conditions that significantly affect pore size. This approach affords a facile pathway to develop robust hydrogel materials that could possibly be employed in a range of potential applications, including wound dressing materials.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author

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Keywords: non-toxic, polyurethane foams, solvent-free synthesis, wound dressing

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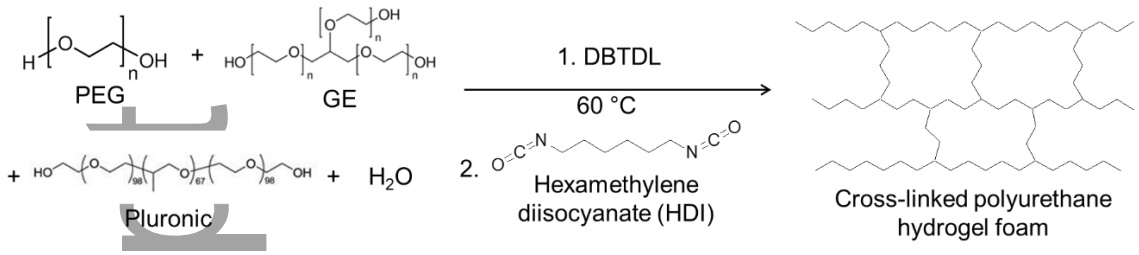

Figure 1. General reaction scheme for polymerization of cross-linked hydrogel polyurethane foams.

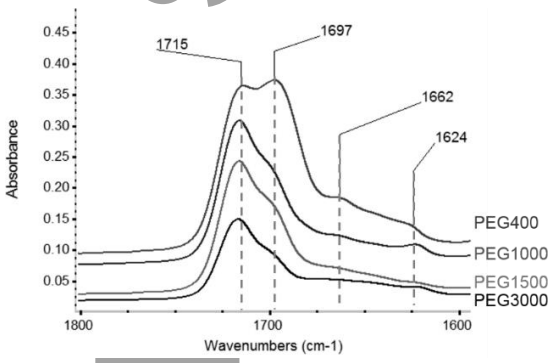

Figure 2. ATR-IR spectra of carboxylate region of PU foams of increasing PEG length.

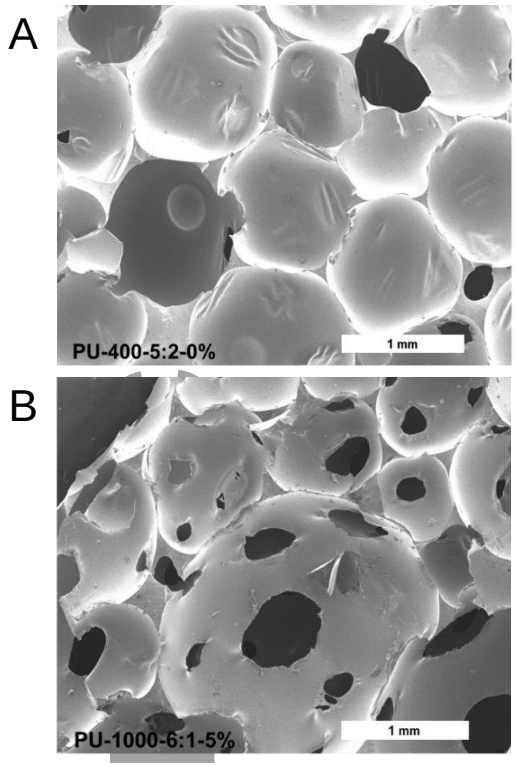

Figure 3. Representative SEM micrographs of A) PU-400-5:2-0% and B) PU-1000-6:1-5%.

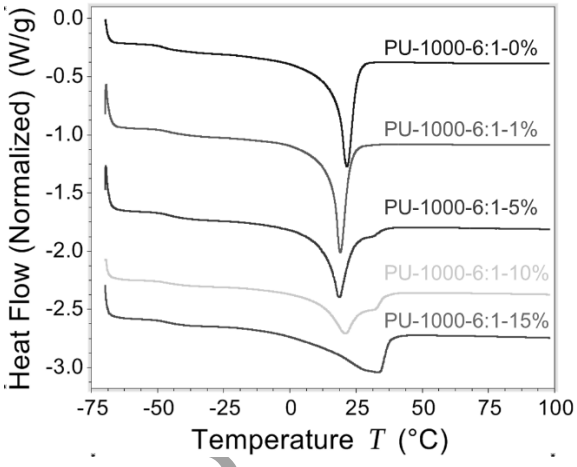

Figure 4. DSC analysis of PU foams as a function of Pluronic concentration. Exo up.

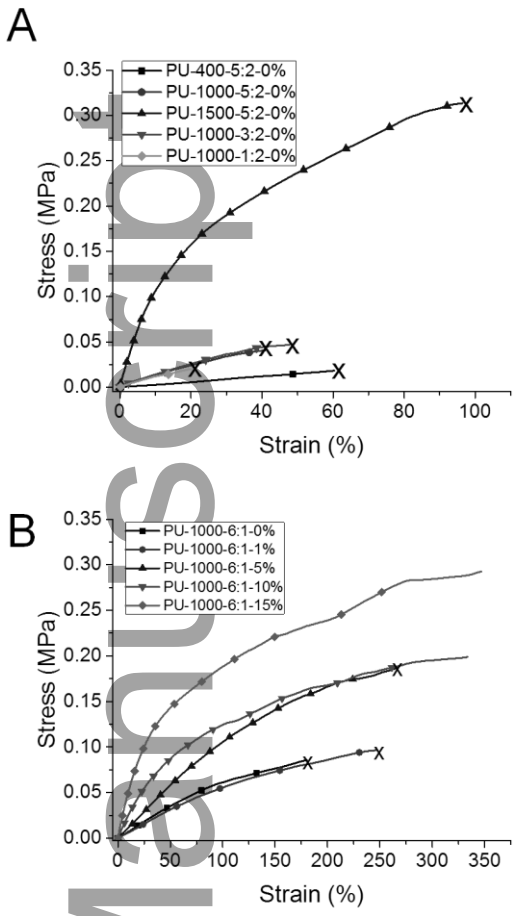

Figure 5. Representative strain-to-break tensile testing experiments for PU foams with A) different cross-linking stoichiometry and PEG molecular weight and B) different concentration of Pluronic F-127. The 'x' denotes the strain at which a sample broke during the test.

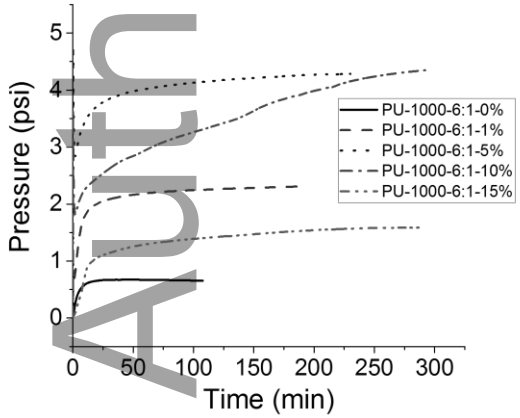

Figure 6. Pressure applied by swelling PU foams as a function of Pluronic concentration.

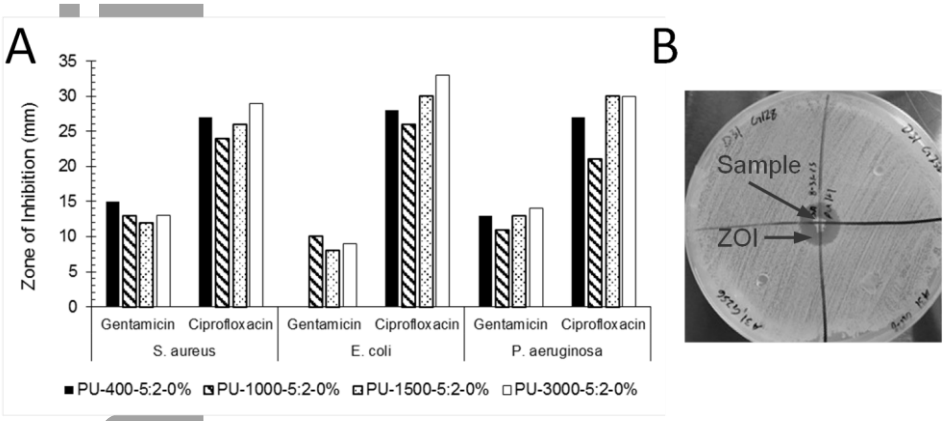

Figure 7. A) Zone of inhibition of *S. aureus*, *E. coli*, and *P. aeruginosa* by PU foams of increasing PEG M_w loaded separately with Gentamicin and Ciprofloxacin and B) representative zone of inhibition on petri dish.

Table 1. Composition of polyurethane hydrogel foams

Sample ID	PEG [M_w]	PEG:GE [Mole Ratio]	Pluronic [wt%]
PU-400-5:2-0%	400	5:2	0
PU-1000-5:2-0%	1000	5:2	0
PU-1500-5:2-0%	1500	5:2	0
PU-3000-5:2-0%	3000	5:2	0
PU-1000-1:2-0%	1000	1:2	0
PU-1000-3:2-0%	1000	3:2	0

PU-1000-6:1-0%	1000	6:1	0
PU-1000-6:1-1%	1000	6:1	1
PU-1000-6:1-5%	1000	6:1	5
PU-1000-6:1-10%	1000	6:1	10
PU-1000-6:1-15%	1000	6:1	15

Table 2. Bulk material properties of polyurethane foam hydrogels.

Sample ID	**Gel Fraction [%]**	**T_g [°C]**	**T_m^1 [°C]**[a)]	**T_m^2 [°C]**[a)]	**Enthalpy T_m^{1+2} [J g^{-1}]**	**Degradation Temperature [°C]**[b)]	**Pore size [µm]**
PU-400-5:2-0%	100.0	-36.2	-	-	-	296.35	927 ± 255
PU-1000-5:2-0%	99.5	-49.5	12.4	-[d)]	40.3	313.86	921 ± 257
PU-1500-5:2-0%	97.2	-46.1	28.2	-	19.5	338.88	997 ± 318
PU-3000-5:2-0%	95.9	-49.7	42.1	-	57.4	325.31	--
PU-1000-1:2-0%	100.0	-45.8	-	-	-	317.73	853 ± 304
PU-1000-3:2-0%	94.1	-47.7	16.6	-	24.7	328.32	906 ± 256
PU-1000-6:1-0%	91.9	-47.8	21.5	-	39.9	322.86	1217 ± 400
PU-1000-6:1-1%	99.7	-44.8	18.1	-[c)]	31.4	304.80	884 ± 218
PU-1000-6:1-5%	99.8	-45.5	18.7	31.6	37.4	301.24	807 ± 418
PU-1000-6:1-10%	94.3	-45.9	20.7	31.7	34.2	312.44	666 ± 248
PU-1000-6:1-15%	98.8	-46.1	-[c)]	33.8	30.2	306.89	764 ± 148

[a] Peak temperature of endothermic transition based on DSC analysis; [b]Temperatures correspond to 10% mass loss based on TGA analysis; [c]Peak obscured as a unresolved shoulder of adjacent peak; [d]Crystallization exotherm was observed at -26.9 °C

Table 3. Performance metrics of PU in wound dressing relevant tests.

Sample ID	Young's Modulus [kPa]	Elongation at Break [%]	Stress at Break [MPa]	Toughness [kJ m^{-3}]	Uptake [g/g][b]	Release Rate [% min^{-1}][c]	Cell Viability [%][d]
PU-400-5:2-0%	95.3 ± 64.3	45.2 ± 13.3	3.4 ± 1.6	7.8 ± 3.4	8.1 ± 0.8	6.3 ± 0.2	n/a
PU-1000-5:2-0%	195.0 ± 88.1	38.0 ± 14.1	3.7 ± 0.4	9.51 ± 3.7	10.5 ± 2.4	5.4 ± 0.4	n/a
PU-1500-5:2-0%	645.3 ± 407.1	102.0 ± 26.3	23.4 ± 7.1	164.2 ± 58.6	9.9 ± 1.6	7.1 ± 0.2	n/a
PU-3000-5:2-0%	n/a	n/a	n/a	n/a	5.6 ± 0.4	5.1 ± 0.3	n/a
PU-1000-1:2-0%	99.3 ± 24.8	21.5 ± 1.6	1.7 ± 0.3	2.1 ± 0.3	7.7 ± 0.9	4.5 ± 0.5	n/a
PU-1000-3:2-0%	122.7 ± 25.7	58.4 ± 9.3	4.1 ± 0.5	15.7 ± 2.4	5.3 ± 1.3	10.7 ± 1.0	n/a
PU-1000-6:1-0%	86.9 ± 41.3	179.7 ± 37.2	8.9 ± 3.9	106.9 ± 66.3	9.5 ± 1.4	9.6 ± 0.6	76.0 ± 5.0
PU-1000-6:1-1%	71.9 ± 13.4	202.4 ± 51.3	9.4 ± 1.2	116.4 ± 28.5	9.2 ± 1.5	4.0 ± 0.2	56.3 ± 14.9
PU-1000-6:1-5%	131.8 ± 87.1	255.8 ± 87.0	14.4 ± 3.8	238.5 ± 87.1	9.2 ± 0.8	3.1 ± 0.3	90.0 ± 13.5
PU-1000-6:1-10%	197.9 ± 92.0	DNB	DNB	433.3 ± 138.7[a]	11.5 ± 0.3	2.7 ± 0.1	68.0 ± 9.5
PU-1000-6:1-15%	278.9 ± 211.2	DNB	DNB	491.7 ± 238.6[a]	9.6 ± 1.2	3.6 ± 0.2	n/a

[a]Estimate based upon maximum strain reached as sample did not break; [b]PBS buffer uptake over 24 h; [c]Based on linear fit of release of caffeine over initial 10 minutes; [d]Negative control was normal EMEM media (100 ± 6.2 % cell viability) and the positive control was EMEM media containing 1 % Tween-20 (12.2 ± 1.8 %); DNB – Sample did not break.

The table of contents entry:

The one-step and solvent-free synthesis of cross-linked polyether urethane foams for the purpose of wound dressing material is reported. This study examines effect linear PEG soft segment, HDI, and glycerol ethoxylate cross-linker have on the mechnical properties and wound-dressing relavent performance of polyurethane foam hydrogels.

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Multi-Functional Polyurethane Hydrogel Foams with Tunable Mechanical Properties for Wound Dressing Applications